Intraspecific chemical communication in vertebrates with special attention to sex pheromones

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Contents

Abbreviations:

ADIO:	androstadienone, a putative male (human) modulator pheromone
AOB:	accessory olfactory bulb
AD:	4-androsten-3, 17-dione
GNG(C):	G_{olf}-cyclic nucleotid-gated (channel)
DAG:	diacylglycerol
DAP:	dog appeasing pheromone
EAP:	equine appeasing pheromone
EOG:	electro-olfactogram
ESP	exocrine gland-secreting peptide
EST:	oestratetraenol, a putative female (human) modulator pheromone
EVG:	electrovomeronasogram
GC-MS:	gas chromatography-mass spectrometry
GnRH:	gonadotropin-releasing hormone
GtH:	gonadotropic hormone
HSD	hydroxy-steroid dehydrogenase
IP3:	inositol-1,4,5-triphosphate
LASP:	*Leptodactylus* aggression-stimulating peptide
LH:	luteinizing hormone
LHRH:	luteinizing-hormone-releasing hormone
MHC:	major histocompatibility complex
MHUSA:	mother-hen uropygial secretion analogue
MOB:	main olfacory bulb
MOS:	main olfactory system
MOE:	epithelium of the main olfactory system
MRI:	magnetic resonance imaging
MUP:	major urinary protein
NO(S):	nitric oxide (synthetase)
NW:	new world
OB:	olfactory bulb
OBP:	odourant binding protein
ORN:	olfactory receptor neuron
OR:	olfactory receptor
OW:	old world
PET	positron emission tomography
PG	prostaglandin
PIP2:	phosphoinsositol-4,5-biphosphate
PLC:	phospholipase C
PMF:	*Plethodon* modulatory factor
PRF:	*Plethodontid* receptivity factor
PRL:	prolactin
PZS:	petromyzonol sulphate
SAL:	salivery protein
SPF:	sodefrin precursor-like factor
TRP2:	transient receptor potential type 2
UG:	urogenital
VEG:	Von Ebner's gland
VNBP:	vomeronasal binding protein
VNE:	vomeronasal epithelium
VNO:	vomeronasal organ
VNS:	vomeronasal system
VR:	vomeronasal receptor
VRN:	vomeronasal receptor neuron
ZDA:	(*Z*)-7-dodecen-1-yl acetate, a urinary female Asian elephant sex pheromone
17,20P:	4-pregnene-17α, 20β-diol-3-one
17,20P-S:	4-pregnene-17α, 20β-diol-3-one sulphate
17,20P-G:	4-pregnene-17α, 20β-diol-3-one glucuronide

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The author thanks Dr. Regiane Santos and Pim van den Hurk for their contribution to the lay-out of tables and figures. Photographs in this review were obtained from Dr. Jan-Willem Resink.

Preface

In this review you will find a survey of pheromonal processes in Vertebrates, the source where they are formed, the chemical nature of pheromones or putative pheromones, the sites where pheromones are perceived, and the way in which they can exert their effects. I hope, in this way, to please researchers at this field and to make many students enthusiastic to start studies on pheromones. Besides, I hope to make clear that this kind of research is important or could be important for application in catching and breeding of fish, husbandry and production of farm animals, housing of companion animals, integrated management of harmful animals (like beavers which, in dense populations, may cause enormous damage to nature), reproduction of endangered animal species, and behaviour of the human.

This 2011 review is an updated edition from the book entitled '*Intraspecific chemical communication in vertebrates with special attention to its role in reproduction*' (Van den Hurk, 2007). This book was sent to many leading figures on the field of vertebrate sex pheromones of which many reacted very praiseworthy. At the internete site 'http://scentoferos.com/ScientificEvidence.html', the book was announced as 'the most recent comprehensive pheromone review available'. Because of the enthousiastic reactions, I decided to make an update of this review and to correct the many typographical errors and a few interpretation mistakes that were made in the book. With the appearance of the 2011 edition, it now becomes the most recent and most comprehensive pheromone review available.

After the publishing of the first edition in February 2007, world-wide attention of pheromone research was particularly directed to odourant/pheromone receptors and signal transduction within odourant/pheromone sensing cells. Therefore, in this 2011-edition of the book, the chapter dealing with olfactory receptor sites, odourant and pheromonal perception, signal transduction, and conduction of evoked action potentials to and within the brain has substantially been changed, while new information published until January 2011 has been incorporated. As a consequence, *Table 15* and the original *Figure 11* (the current *Figure 9*) had to be adapted, while *Table 16* and *Figure 10* were newly added. Furthermore, most tables are extended with new data on pheromones in vertebrate species. To focus more on the term (sex) pheromone and to facilitate tracing of the current book, the original book title has slightly been changed. Please, contact me (r.vandenhurk@planet.nl) if you think some essential things are lacking or incorrectly presented.

Abstract

Sex pheromones in fish can be formed by the liver, the gonads and/or accessory sex organs, excreted through the urogenital efferent duct system, the faeces, the gills or the skin, and may play a role in the development of gonads, the attraction of reproductive partners, reproductive behaviour, sperm production or ovulation induction. In teleost fish, steroid glucuronides, steroid sulphates, free steroids and prostaglandines may function as sex pheromones, while in lampreys, bile acids are used as odourants for successful spawning. In amphibians, abdominal glands and fascial glands may secrete specific peptides or proteins as sex pheromones. In reptiles, the skin, pre-cloacal glands, femoral glands and seminal fluid are possible sources of sex pheromones, while in birds it is the uropygial gland which has this function. A mixture of specific methyl ketones has been indicated as a sex pheromone in snakes, whereas specific fatty acid diesters have been proved to serve as duck pheromones. Many classes of chemical compounds have been found to play or are thought to play a role as (sex) pheromones in mammals. They are produced by the urinary system, the digestive tract and/or all kind of glands. Olfactory signs may be secreted pulsatily in a species-specific mixture of components, of which the concentration and relative proportion is appropriate reproductive information and govern sexual behaviour. Besides olfactory signs, initiation and completion of adequate reproduction behaviour is additionally controlled by other sensory cues, like taste, visual, vibrational, tactile and/or auditory stimuli. Apart from the source, the nature and the role of (sex) pheromones in vertebrates, information is given on the perception of olfactory signals, the subsequent pathways that lead to electric signaling, and the transport of evoked nerve action potentials to and within the brain.

Keywords*:* sex pheromones, pheromone receptors, odourant receptors, vomeronasal organ, main olfactory system, signal transduction, chemosensory amygdala, fishes, amphibians, reptiles, birds, mammals, vertebrates.

Introduction

Physiological processes in the body are regulated by internal and external factors. Hormonal signals or factors resulting from normal or deviant metabolic processes may function as internal factors. Certain cytokines, for example, liberated in deviant metabolic processes may influence the course of certain processes in the body. As examples of external factors photoperiod, temperature, sensory and psycho-emotional factors like stressors may change normal body processes (*Figure 1*). Likewise, environmental odours may influence internal processes that lead to behavioural actions or the development or activity of certain organs. Many external and internal factors are able to affect certain hypothalamic centra which, through their production of releasing hormones, influence the pituitary. On its turn, this latter organ secretes hormones that control the activity of various organs. In this way, gonadotropic releasing hormones control the production of hypophyseal gonadotropic hormones (FSH and LH), which regulate vertebrate reproduction (Ando and Urano, 2005; Senger, 2005). The external factors, which act in this way and are able to influence reproduction processes are presented in *Table 1.* Among them are stimuli that are perceived by olfaction.

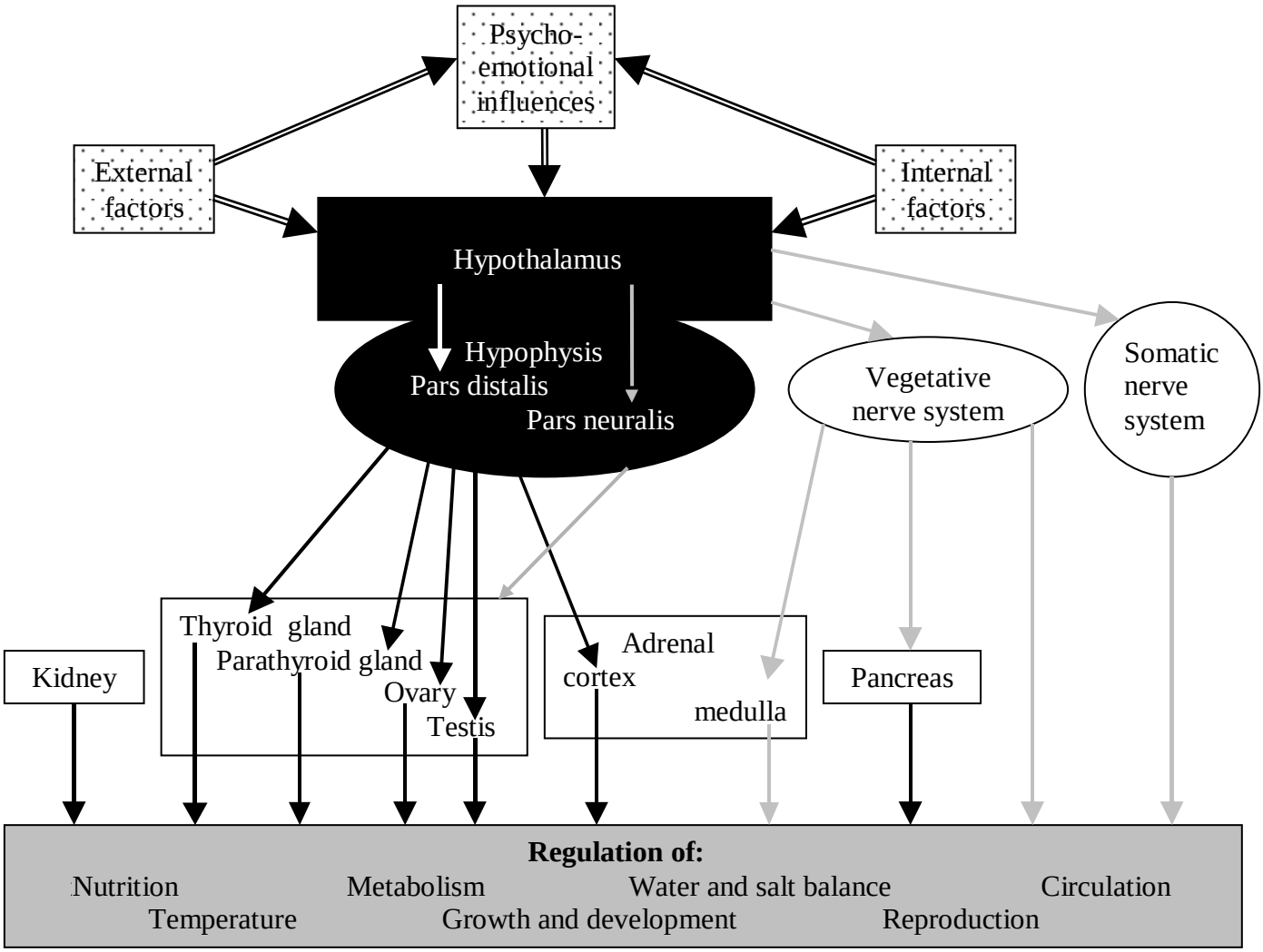


Figure 1: *Regulation of body processes by exogenous and endogenous factors.*

Chemoreception is essential for the survival of a species. It, for example, often allows localisation and evaluation of food, identification of danger and/or gender discrimination. Environmental chemical substances with a signaling function are called semiochemicals (Nordlund and Lewis, 1976) or ecomones (Law and Regnier, 1971; Pasteels, 1982). Five types of semiohemicals can be distinguished (Nordlund and Lewis, 1976): allomones, kairomones, synomones, apneumones and pheromones (*Figure 2A*). Allomones are defensive secretions and beneficial for the emitter of the chemical signal (for example a skunk, whose secretions do chase away enemies). Kairomones localise a prey and are beneficial for the receiver of the chemical signal (for example an antilope whose odour attracts predators). Synomones evoke, when contacting an individual of another species in the natural context, a behavioural or physiological reaction in the receiver, which is adaptively favorable to

Table 1: *Factors affecting reproductive events.*

Modulators of reproduction
age
breed
stress
pathogens or other health-affecting factors
environmental temprature
photoperiod
season
nutrition
lactation
suckling
hormone treatment
experience
socio-sexual interaction
sensory stimuli (tactile, visual, auditory, gustatory, and olfactory signs)

both emitter and receiver (for example a cockroach which for digestion of certain components requires specific protozoa in its gut, that on their turn use the cockroach molting hormone ecdysone for their reproduction). For a recent review on kairomones, allomones and synomones, see Sbarbati and Osculati (2007). Apneumones are emitted by nonliving material and evoke a behavioural or physiological reaction adaptively beneficial for a receiving organism, but detrimental to an organism, of another species, which may be found in or on the nonliving material (for example a parasite that is attracted to the odour of its host's food). Pheromones, in contrast to the mentioned four classes of interspecific acting chemicals (collectively termed allelochemicals), are intraspecific compounds that are beneficial for the emitter and/or the receiver, i.e. a male or female conspecific. Pheromones are able to stimulate general social attraction, species recognition, individual recognition, parent-young interactions, alarm or fright reactions, onset of puberty and reproduction (e.g. cyclicity, pregnancy, milt production, hormone levels and sexual behaviour), and (in some species) enable migration of adults to their spawning grounds. In case chemical compounds stimulate the development or reproductive responses of animals, they are termed sex pheromones.

The original definition for a pheromone was formulated by Karlson and Lüscher (1958) for insects as 'a substance secreted to the outside by an individual and received by a second individual of the same species, in which they release a *specific* reaction, for example, a definite behaviour or a developmental process'. Before the introduction of the term

pheromone the term ectohormone was used (Bethe, 1932; Karlson and Butenant, 1959). A few authors (Rutowski, 1981; Meredith 2001) advocated that the definition of a pheromone should also include mutual benefit to sender and receiver to overcome possible ambiguities and overgeneralisations in usage. However, thus far, this advise has not been widely followed yet in literature. For vertebrates, the definition for a pheromone is too restrictive, and should be extended with the properties that it must possess information about sex, strain or species, and that actions on conspecifics must be meaningful or beneficial for the entire population (Touhara, 2008; Touhara and Vosshall, 2009). Usually, vertebrate pheromones evoke their effect in ultra low concentrations (e.g. 10^{-8} M or lower in fish; see paragraph on 'Sex pheromones in fishes'), while pheromonal communication, in contrast to that of odourants, occurs unconsciousness (Liberles and Buck, 2006). As a consequence, we may have to accept a possible absence of real pheromones in at least certain mammalian species, and to accept a role of odourants in the transfer of social and sexual information. Anyway, it is argued that a precise definition of a pheromone is unimportant, because it is unlikely that any mammalian chemical cues would fit the definition if the definition is too narrow, or any specific chemical cue would fit the definition if it is too broad (Kelliher, 2007). Based on the heuristic value of separating innate responses to olfactory chemical signals from those that are accomplished by learning an animals' chemical profile, it is possible to distinguish pheromones from signature mixtures, respectively (Wyatt, 2010). Thereby, a signature mixture (previously termed a mosaic signal (Johnston 2003; 2005)) is defined as a variable chemical mixture (a subset of the molecules in an animal's chemical profile) learned by other conspecifics and used to recognise an animal as an individual or as a member of a particular social group such as a family, clan or colony. In my opinion, however, a signature mixture can just as well be considered as a pheromone or odourant subdivision and be termed a signature pheromone or signature odourant, depending on the concentration it is working (nanograms to picrograms or milligrams to micrograms, respectively) and the processing within the brain (unconscious or conscious, respectively). Perhaps it is better to distinguish 3 classes of intraspecific semiochemicals or intraspecific odorous chemical substances: odourants (which work conscious in milligrams to nanograms), pheromonal odourants (which also work conscious but in nanograms to picograms) and pheromones (which work unconscious, commonly in nanograms to picograms) (see also chapter '*Concluding remarks and future perspectives*').

In 1963, Wilson and Bosschert distinguished releaser and primer pheromones, the former type of pheromones evoking an often immediate specific behaviour. For example, a silk moth that fly against the wind in search of a reproductive partner can be seen as an animal, using a releaser pheromone mixture for that goal (Regnier and Law, 1968; O'Connell, 1986; Kaissling, 1996). In contrast, primer pheromones need more time to express their presence and often influence (neuro) endocrine systems, which are related to the development of an individual or to physiological processes, which occur during reproduction. Primer pheromones, in contrast to releaser pheromones, act through the neuroendocrine system on the behaviour of an animal and may have physiological effects (*Figure 2B*). A releaser pheromone can be a primer pheromone at the same time or in different context (Wyatt, 2003). 16-Androstene C_{19} steroids, for example, which are secreted by boars (see paragraph on pig pheromones), may act as releaser pheromones which induce the stance in oestrous sows (Reed et al., 1974; Dorries et al., 1997), but are also considered as primer pheromones that stimulate the brain-pituitary-ovarian axis (Stefanczyk-Krzymowska et al., 2000a;b; Stefanczyk-Krzymowska et al., 2002; 2003). Now we understand more about the interactions and feed back loops in the sequence from odour to behavioural and endocrine effects, the distinction beteween primer and releaser pheromones has fainted. In primates, besides primer and releaser pheromones, signaler and modulator pheromones are currently

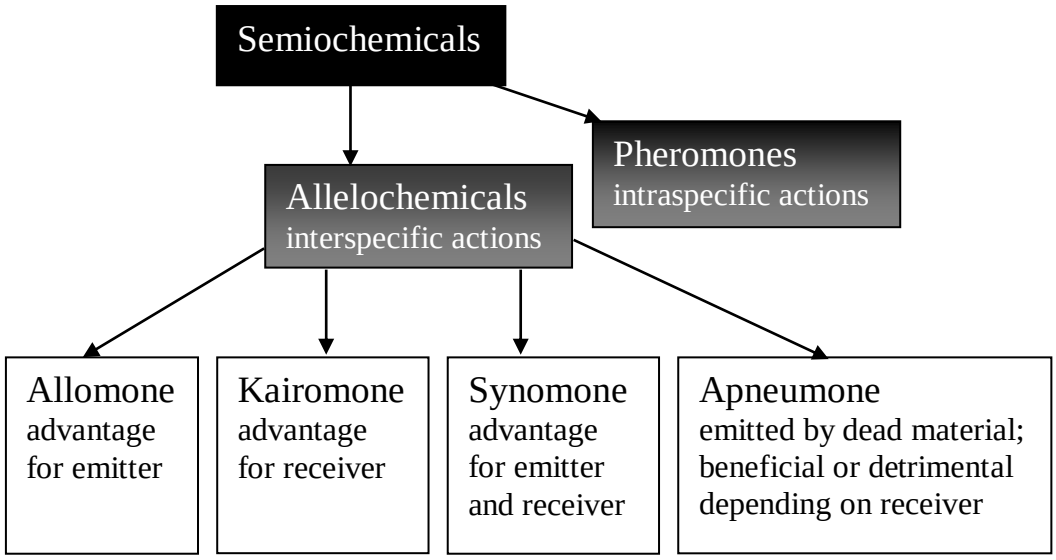


Figure 2A: *Semiochemicals in the surrounding of a vertebrate (classical view).*

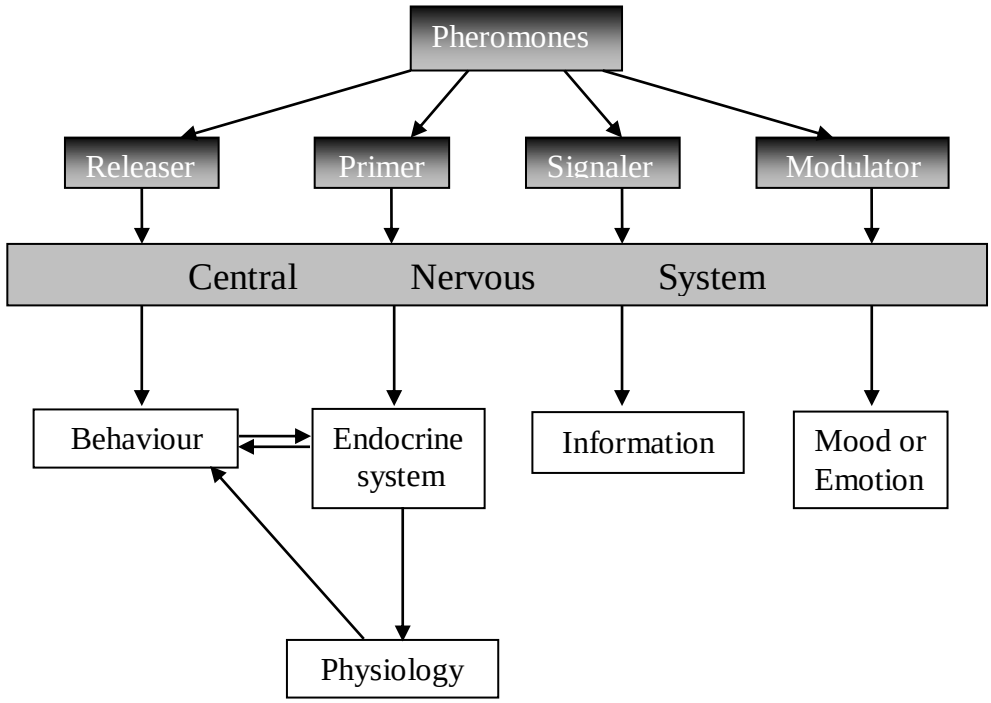


Figure 2B: Types of pheromones and their actions: current categorisation.

distinguished which, respectively, provide information (like recognition of newborn by its mother) and modify emotion and mood, and thus influence the well-being of an animal (Preti et al, 2003; Wysocki and Preti, 2004; Kaminski et al., 2006). All four types of pheromones act through the central nerve system (*Figure 2B*). As has been demonstrated in goldfish, rodents and goats, activation of the central nerve system does not only imply the stimulation of particular brain areas, but also the stimulation of neurogenesis in the brain olfactory system (in particular the olfactory bulb and hippocampus, a site associated with memory formation and emotion), the newly-formed neurons originating from a discrete area of the subventricular zone (Smith et al., 2001; Mak et al., 2007; Chung-Davidson et al., 2008; Larsen et al., 2008; Hawken et al., 2009; Oboti et al., 2009). Pheromone-stimulated neurogenesis in the brain is thought to be important for reproductive success.

Vertebrates may perceive olfactory signs through the main olfactory system (MOS) or both the MOS and the accessory olfactory system, which is also known as vomeronasal system (VNS) or vomeronasal organ (VNO), the latter organ being found in most terrestrial animals but not in birds (Hagelin, 2007). Both systems have an epithelium consisting of microvillous bipolar receptor neurons, sustentacular (supporting) cells and basal cells (stem cells delivering new olfactory neurons throughout life) (Rehorek et al., 2000). Fishes only possess a MOS to detect water-soluble olfactory signals (Hara, 1967; Oshima and Gorbman, 1968; Resink et al., 1989d; Dulka and Stacey, 1991; Sorensen and Sato, 2005). For most terrestrial vertebrates, the MOS is thought to be mainly receptive to volatile cues, whereas the VNO is thought to mainly sense chemicals that are often dissolved in secreted or excreted body fluids and are commonly received by direct contact (Dulac and Torello, 2003; Halpern and Martinez-Marcos, 2003; Luo et al., 2003 Restrepo et al., 2004; Brennan and Keverne, 2004; Witt and Hummel, 2006). These latter nonvolatile molecules carry specific information concerning species, gender, and identity of an animal and are commonly termed pheromones, although, as remarked before, it has recently been proposed to distinguish pheromones from signature mixtures, the former compounds eliciting an innate response, while the latter are learnt by animals, allowing them to distinguish intraspecific individuals or colonies (Wyatt, 2010). Once again, I would prefer introduction of the term signature pheromone in stead of signature mixture.

Besides the MOS and the VNO, two other nasal compartments have recently been identified as olfactory receptor sites in mammals, namely the septal organ (of Masera), an island of chemosensory neuroepithelium located bilaterally at the ventral base of the nasal septum at the entrance to the nasopharynx (Broman, 1921; Rodolfo-Masera, 1943; Breer et al., 2005), and the Grüneberg ganglion, located at the rostrodorsal end of the nasal cavity of various mammals (Grüneberg, 1973). For more detailed information about pheromone/ odour sensing, see the chapter 'Olfactory receptor sites, odourant and pheromonal perception, signal transduction, and conduction of evoked action potentials'.

Most animal pheromones that have been described are insect pheromones. From the many hundreds of insect pheromones currently known, far the most of them are releasers and only few primers. The nature of an insect pheromone generally is a fatty acid, a fatty acid derivative or a ketone, and they are secreted in mixtures (for reviews, see Tillman et al. (1999), Tegoni et al. (2004), Tittiger (2004), Dahanukar et al. (2005), Colette and Waxman (2005), Howard and Blomquist (2005), and Wedell (2005); for convergences and contrasts in insect and vertebrate pheromones, see Sorensen et al. (1998), Wyatt (2005; 2010) and Kaupp (2010)). Further information on insect pheromones is beyond the scope of this review on vertebrate pheromones. Attention will especially be focused on animals, for which released sex pheromones or released chemical compounds with possible sex pheromonal action or

help in sex pheromonal action were isolated and characterised. Besides, some notice is paid to pheromones and odourants that have been implicated in intraspecific behaviours different from those belonging to reproduction (e.g., territory marking, species and individual recognition, parent-young interactions, and alarm reactions), since these behaviours and the potency to recognise the chemical signals involved are important or could be of importance for successful reproduction. As an example, a paragraph is furthermore dedicated to nonolfactory sensory cues in fish which, synchronously with sex pheromones, may elicit reproductive events.

Sex pheromones in fishes

Odours from teleost fish have been found to induce various reproductive processes as the rate of gonadal development, spermiation, ovulation, attraction of a mating partner, courtship behaviour and spawning behaviour (Liley, 1982; Colombo et al., 1982; Stacey et al., 1986; Stacey and Sorensen, 1991; Van den Hurk and Resink, 1992). Initial studies on the characterisation of sex pheromones in fish point to proteinaceaous (Okada et al, 1978: pond smelt, *Hypomesus olidus*) or to water-ether soluble (Honda, 1979: ayu, *Plecoglossus altivelis*; Honda, 1980: rainbow trout, *Oncorhynchus mykiss*) compounds derived from the gonads. In the decade that followed, particularly free steroids, steroid conjugates and prostaglandines have been indicated as sex pheromones in fish. Commercially seen, these pheromones could be used to manage and control certain fish species, for example, by facilitating their trapping, controling their reproductive success, disrupting their movement and migration, repelling them, and assessing their population size and distribution (Sorensen and Stacey, 2004).

Gobies

The first researchers who described the nature of a fish pheromone were Colombo et al. (1980). They discovered that the steroid conjugate etiocholanolon glucuronide (5β-androstane-3α-hydroxy-17-one) is synthesised by the mesorchial gland (a Leydig cell gland) in male *Gobius jozo*. Furthermore, they observed that, after addition of this compound to nests, ovulated females of this species are attracted to these nests and drop their eggs over there in absence of male conspecifics, while oviposition of females normally occurs in the presence of a male (Colombo et al., 1980; 1982). During steroid catabolism all kinds of steroids are formed, which have a hydroxyl group at the third C(arbon)-atom of the steroid skeleton in α-position and a hydrogen atom at the fifth C-atom in α- or β-position. These metabolic products are excreted to the holding water of the fish and then may function as sex pheromones. Etiocholanolon is such a metabolic product of steroidogenesis, which functions as a sex pheromone in *Gobius jozo*.

More than two decades later, the ovarian steroids oestrone (1,3,5(10)-oestratrien-3-ol-17-one) and 17β-oestradiol-3β-glucuronide were found to evoke gill ventilation (a behavioral bioassay of steroid detection) and electro-olfactogram (EOG) responses (i.e. extracellular field potentials, recorded from the surface of the olfactory epithelium) in male but not in female round gobies (*Neogobius melanostomus*; Murphy and Stacey, 2002; Belanger et al., 2006). Although the detected steroids didn't induce reproductive behaviour, such male gobies show a change in ventilation response to oestrone in the sensitivity of the olfactory system to putative pheromones, related to their reproductive status (Belanger et al., 2007). The response threshold for oestrone varied from 10^{-11} M in reproductive males, and rose to 10^{-9} M in non-reproductive males. In contrast to oestrone, confrontation with etiocholanolone increased the ventilation rate in both males and females (Murphy et al., 2001). Furthermore, Belanger (2003), in contrast to Murphy et al (2001), observed EOG responses in round gobies after testing 11-keto(= oxo)testosterone and 11-keto(= oxo)androsterone, which are both formed by the seminal vesicles of these teleosts (Jasra et al., 2007). It has, however, to be remarked that EOG recording is an extracellular measure, which biophysical basis is not well-understood. This technique measures voltage gradients from the surface of the olfactory epithelium, which are thought to reflect multi-unit reflector activity, most likely generator potentials (Ottoson, 1971; Van As et al., 1985). It must still be interpreted cautiously in absence of other assays (Sorensen et al., 1991a), like multi-unit recording from the olfactory tracts, and olfactory tract lesioning studies.

Recently, the release into the water of free and at least four conjugated forms of 11-oxo-etiocholanolone by reproductively mature male round gobies has been described (Katare et al., 2010). Free steroids are mainly released from the gills and conjugated steroids via the urine and/or faeces. In regard the released steroid conjugates, 3α,17β-dihydroxy-5β-androstan-11-one 17-sulphate is the most abundant compound, while a substantial amount of 3α-hydroxy-5β-androstane-11,17-dione 3-glucuronide (= 11-oxo-etiocholanolone 3-glucuronide) and small amounts of 3α-hydroxy-5β-androstane-11,17-dione 3-sulphate (=11-oxo-etiocholanolone 3-sulphate) and 3α,17β-dihydroxy-5β-androstane-11-one 17-glucuronide have been detected. 11-oxo-etiocholanolone and its conjugates may have a pheromonal effect on reproductive female conspecifics. However, reproductive females avoid a blend of free steroids that includes 11-oxo-etiocholanolone and only tend to prefer a blend of synthetic steroid conjugates that includes 3-sulphated and glucuronated 11-oxo etiocholonalone, the attractive effect thus not being significantly different from the effect shown by control females (Corkum et al., 2008). In contrast, nonreproductive females are attracted to the offered blend of synthetic free steroids, but avoid the blend of synthetic comjugated steroids. Consequently, there is no direct evidence yet that 11-oxo-etiocholanolone or any of the detected conjugated steroid derivatives are (sex) pheromones.

Zebrafish

In the eightees, the Utrecht group of comparative endocrinologists studied the behaviour of zebrafish (*Danio rerio)*, and performed (immuno) histochemical studies on the pituitary and enzyme histochemical and steroid biochemical studies on the gonads of fish, which were collected during an sexual encounter between male and female specimens. These studies confirmed the importance of steroid glucuronides as sex pheromones (Van den Hurk et al., 1982; 1983; 1987c; Lambert et al., 1986).

When a male and an non-ovulated female (captive) zebrafish, are taken away from groups of male and female zebrafish kept in 60 L nicely-decorated aquaria, and then are put together in a retangular net hanging in an aquarium filled with 20 L water at 25 ºC, they will show agonistic behaviour, which after a few hours is generally followed by reproductive handlings (*Table 2*). When the prespawning aggressive phase turns into the sexual stage, biting of the male into the female's tail is replaced by his nipping of the female's abdomen. After experiencing that the female has ovulated, the male will show high-speed swimming movements. Hereby, he again and again passes the female, sometimes 'skimming' the net with his belly (skimming), and swimms back to try to block (stopping) her normal straight-forwarded swimming pattern and to lead her to a corner in the aquarium or a fold in the net (leading). The male frequently inspects the female's urogenital opening (nipping), and pushes himself firmly against her and presses her against the net (pushing), while his whole body briefly spasmodically vibrates (quivering). These latter actions are repeated until oviposition. At oviposition, the male fertilises the eggs (sperm ejection), thereby folding his backfin around the back of the female (enlacing). A few minutes after oviposition, the female does not tolerate the male in her close environment and chases him off to a corner or fold of the net. The first 2-3 days the male is not allowed to leave this site (hiding). During this period the male shows a J-posture as a sign of surrender (appeasing). When the male tries to leave his 'hiding' place, he will soon has to flee (fleeing) to escape from her biting actions. For a description of the reproductive behaviour of feral zebrafish in large tanks, see Hutter et al. (2010).

Before an encounter between a male and a female zebrafish and during the prespawning agonistic phase, the (meso) adenohypophysis of the male is loaded with immunofluorescent

Table 2: *Sequence of behavioural actions upon an encounter between a (captive) male zebrafish and a(captive) non-ovulated female conspecific in 20 l-aquaria, after they are separated from their school and placed in a new environment.*

Phase	Stage	Characteristic actions
Pre-spawning agonistic	Threat	Fin stretching ♂♀ Lateral display ♂♀ Frontal display ♂♀ Parallel swimming ♂♀
	Flight	Yielding ♂♀ Fleeing ♂♀
	Aggressive	Approaching ♂♀ Parallel fighting ♂♀ Tail beating ♂♀ Chasing ♂♀ Biting ♂♀
Sexual	Courtship	Belly nipping ♂ Leading ♂ Following ♀ Skimming ♂ Leading ♂
	Spawning	UG-pore nipping ♂ Pushing ♂ Quivering ♂ Enlacing ♂ Egg release ♀ Sperm release ♂
Post-spawning agonistic	Flight/ Fear	Hiding ♂ Appeasing ♂ Approaching ♀ Biting ♀ Fleeing ♂ Chasing ♀

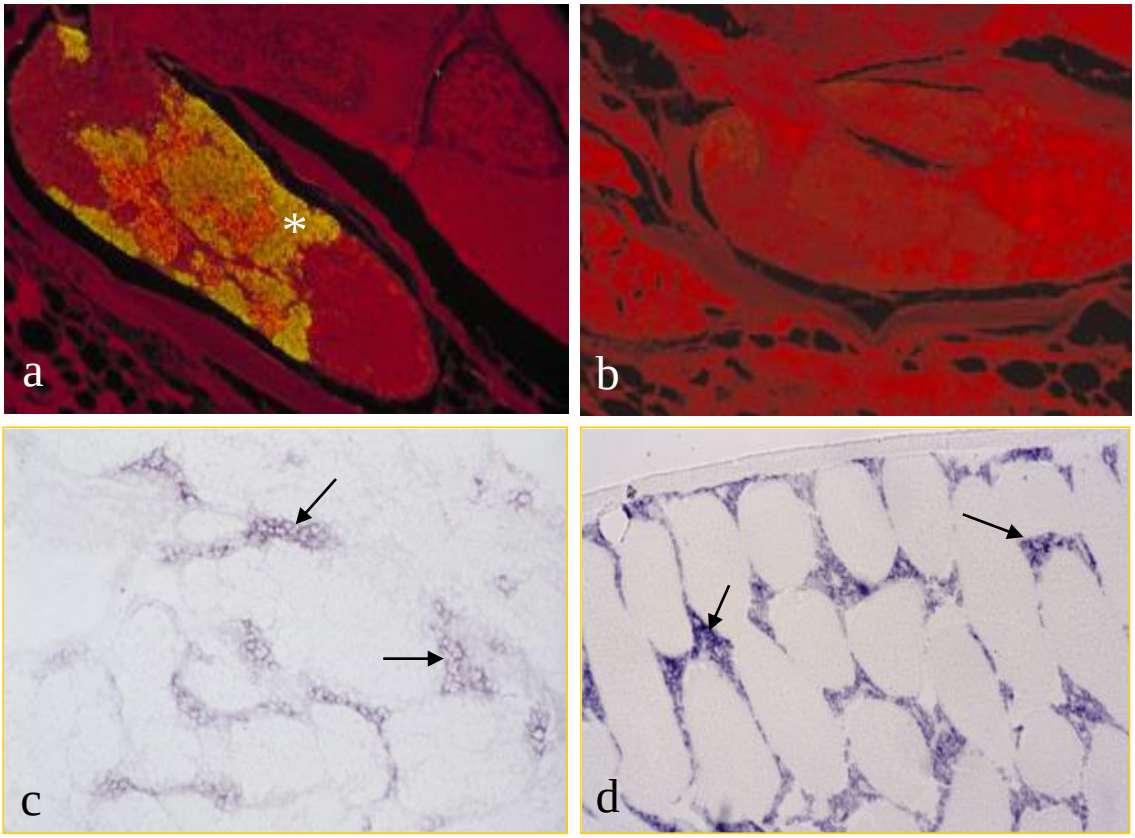


*Figure 3: Changes in immunofluorescent detectable gonadotropic hormone (GtH) in the (meso) adenohypophysis (**a**,**b**) and steroidogenic activity in testicular Leydig cells (**c**,**d**) of male zebrafish during an encounter with a female conspecific. During the pre-spawning agonistic phase, male gonadotropic cells are loaded with immuno-fluorescent GtH (**a**). Asterisk indicates immunofluorescent GtH-cells. Anti-carp-gonadotropic-gamma-globulin (1:50) was used to demonstrate GtH-cells (for method, see Goos et al., 1976). During this pre-spawning agonistic phase, testicular steroidogenic activity, reflected by enzyme histochemically demonstrated 3β-hydroxy-steroid dehydrogenase (3β-HSD), is normal, i.e. moderately developed (**c**, arrows; dehydro-epiandrosterone was used as a substrate for 3β-HSD; for method, see Van den Hurk, 1973). During the sexual phase, gonadotropic cells do not show a positive immunofluorescent reaction, which indicates that all gonadotropic hormone has been secreted at the start of the courtship stage (**b**). In contrast, the 3β-HSD activity in the Leydig cells has strongly increased (**d**), which suggests that testicular steroidogenic activity is firmly enhanced by the hugh output of GtH.*

gonadotropic hormone (*Figure 3a*). At this moment, testicular steroidogenic activity, reflected by enzymehistochemically demonstrated 3β-hydroxy-steroid dehydrogenase (3β-HSD), is normal, i.e. moderately developed (*Figure 3b*). At the start of the sexual phase, all immunofluorescent gonadotropic hormone has been secreted (*Figure 3c*) and the 3β-HSD in the testicular Leydig cells has strongly increased (*Figure 3d*), indicating that the steroidogenic activity is firmly enhanced by the gonadotropic output.
After in vitro incubation of testes with the tritium labelled precursor steroids (pregnenolone or androstenedione), we have demonstrated the biosynthesis of seven labeled glucuronidated steroids in these male sex organs, i.e. the glucuronides of five C_{19} and two C_{21} steroids (for details, see *Table 3*; Van den Hurk et al., 1987c). From these glucuronides only 5α-androstane-3α,17β-diol-glucuronide has been demonstrated in male holding water together with cholesterol-glucuronide, which probably originates from the liver, and other but non-conjugated polar steroids. Addition of male holding water or steroid glucuronide containing

Table 3: *Steroid glucuronides synthesised in the sex organs of zebrafish and African catfish.*

Zebrafish testis	**Zebrafish (postovulatory) ovary**
4-pregnene-17α, 20β-diol-3-one-G	4-pregnene-17α, 20β-diol-3-one-G
5-pregnene-3β,17α, 20β-triol-G	oestradiol-17β-G
4-androsten-17β-ol-3-one (= testosterone)-G	testosterone-G
5α-androstane-3α-ol-17-on-G	5α-androstane-17β-ol-3-one-G
5α-androstane-3α, 17β-diol-G*	5α-androstane-3α, 17β-diol-G
5α-androstane-3β, 17β-diol-G	
5α-androstane-3β-ol-17-on-G	
Catfish seminal vesicles	**Catfish (postovulatory) ovary**
testosterone-G	testosterone-G
etiocholanolone-G*	etiocholanolone-G
5β-dihydrotestosterone-G	5β-dihydrotestosterone-G
5β-pregnane-3α,17α-diol-20-one-G*	5β-pregnene-3α, 17α-diol-20-one-G
5β-androstane-3α, 17β-diol-G*	5β-pregnene-3α, 17α, 20α-triol-G
5β-androstane-3β, 17β-diol-G	5β-pregnene-3α, 17α, 20β-triol-G**
5β-androstane-3α, 17β-diol-11-on-G*	5β-pregnene-3α, 6α, 17α-triol-20-one-G
5β-androstane-3α, 11β-diol-17-on-G	5β-pregnene-3α, 6α, 17α, 20β-tetrol-G
	5β-androstene-3α, 17β-diol-G
	5β-androstene-3α, 17β-diol-11-one-G
	5β-androstane-3α, 11β-diol-17-one-G
	oestradiol-17β-G**

* also demonstrated in holding water of male fish;
** also demonstrated in holding water of female fish.

testicular water fractions to the aquarium water, in which a female zebrafish was kept, induces ovulation in intact *but not* in anosmic female zebrafish, while such an effect is absent when testicular water fractions containing free steroids, other steroid conjugates than steroid glucuronides, or female holding water are administered (Van den Hurk et al., 1987c; Van den Hurk and Resink, 1992). These findings with zebrafish demonstrate a function of male testicular steroid glucuronides as priming pheromone in females.

After *in vitro* incubation of zebrafish ovarian homogenates with tritium labeled testosterone, Van den Hurk and coworkers (1982) have found that, in comparison to water fractions of ovarian homogenates coming from 2- to 5-days postoovulatory females, those from recently ovulated and 1-day postovulatory females are far more radioactive (18-19 % vs 4-7 % of what was offered; *Figure 4*). Further biochemical studies with pregnenolone or androstenedione as labeled steroid precursors have demonstrated the synthesis of five different steroid glucuronides in the ovaries of ovulated zebrafish, i.e. the glucuronides from one C_{18} steroid (oestradiol-17β), three C_{19} steroids (among which 4-androsten-17β-ol-3-one = testosterone), and one C_{21} steroid (4-pregnene-17α,20β-diol-3-one) (Lambert et al., 1986; *Table 3*). From the latter steroid is known that it stimulates oocyte maturation in many teleost fish (Jalabert, 1976; Lambert and van den Hurk, 1982; Nagahama et al., 1983; Scott and Canario, 1987; Milla et al., 2006). Van den Hurk and Lambert (1983) have demonstrated that males are attracted to (i) diluted cell free postovulatory (i.e. between ovulation and oviposition and at 1-2 hours after oviposition) ovarian homogenates, (ii) the steroid glucuronide containing water fraction of these ovarian homogenates, and (iii) a mixture of testosterone glucuronide and oestradiol-17β glucuronide. Mixtures with the other steroid glucuronides that are formed by ovulated females have unfortunately not been tested, because they were not commercially available. Water fractions containing free steroids, steroid sulphates or steroid phosphates nor water fractions from 3 days after oviposition have an attractive effect on male zebrafish.

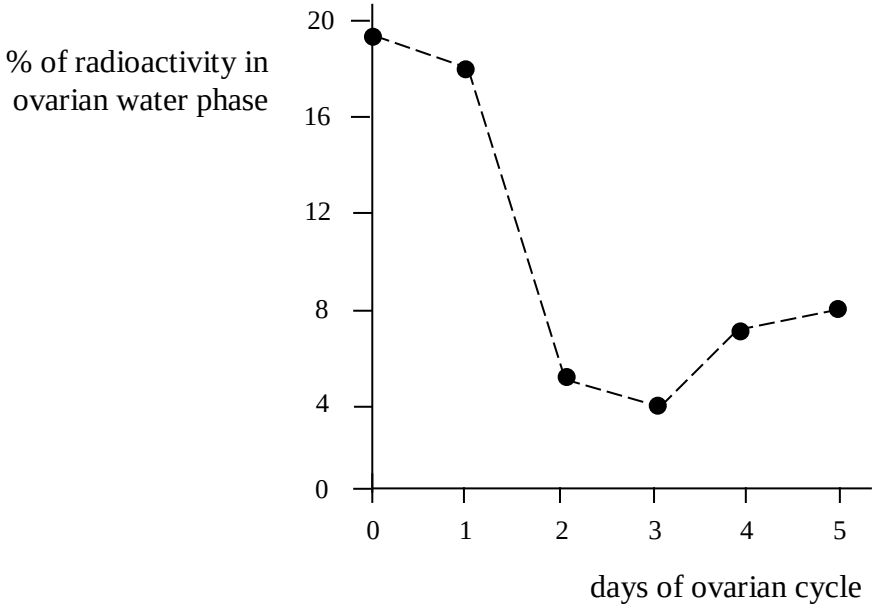


Figure 4: *Percentage of radioactivity found in the waterphase of zebrafish ovarian homogenates at the various days of the (5-day) reproductive cycle (at 25 °C) after incubation with ^{3}H-testosterone. At each day 5 ovaries were pooled and then homogenised. Ovulation has taken place at day 0. The percentage shown for day 5 counts for not yet ovulated females.*

More recently, it has been demonstrated that female zebrafish use waterborne pheromones to suppress reproduction by female conspecifics in terms of the number of spawned viable eggs (Gerlach, 2006). In contrast, male pheromones increased the quality and viability of spawned zebrafish eggs.

Figure 5 shows the presumptive pheromonal regulation of reproduction in zebrafish: released testicular steroid glucuronides most probably prime the pituitary-ovarian system, resulting in enhanced GtH levels in female conspecifics, which induce ovulation (probably by enhanced synthesis of an oocyte maturation inducing steroid like 4-pregnene-17α,20β-diol-3-one). After ovulation, the ovary produces a mixture of steroid glucuronides of which one or more excreted components may cause attraction of male conspecifics (releasing effect), the activation of their pituitary-testicular system and subsequent reproduction behaviour (primer effect).

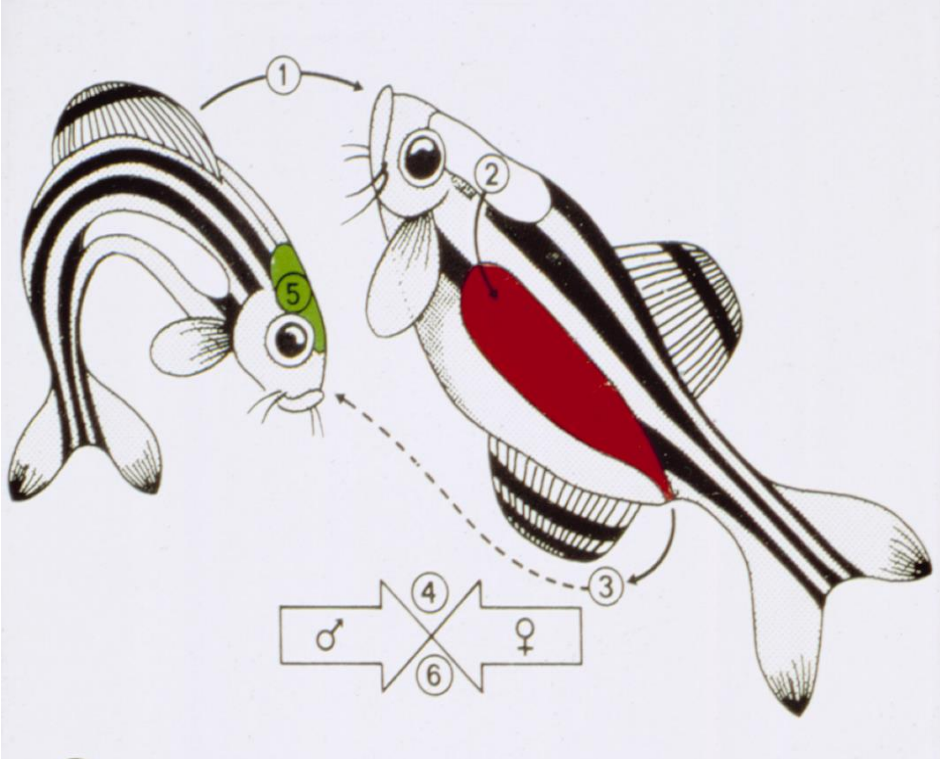


Figure 5: Putative regulation of sexual behaviour in zebrafish: (1) male pheromone release; (2) female GtH-release followed by ovulation induction; (3) synthesis and release of ovarian steroid glucuronides; (4) attraction of males; (5) male GtH-release followed by increased androgen production; (6) male sexual behaviour, resulting in spawning, oviposition and fertlisation of ejected eggs.

African catfish

African catfish, *Clarias gariepinus*, from the Hula Valley Nature Reserve (Israël) spawn when the water level rises to 25 ºC (Van den Hurk et al., 1984-1985) and their spawning grounds are flooded as a result of either direct rainfall, the inflow of water from an upstream source or artificial flooding of dry or shallow habitats (*Figures 6a,b*). At spawning, the male characteristically folds himself in the obtained U-shape (amplexus; *Figure 6c*), the male then slides around the female to induce oviposition (*Figure 6d*), and then fertilises the deposited eggs (Bruton, 1979; Resink, 1988). The fertilised eggs are spread over the inundated plants by tailbeating of the female. The exhibited prespawning, sexual and postspawning behavioural actions of African catfish during the breeding season are listed in *Table 4.*

Table 4: Sequence of African catfish behavioural actions, in their natural habitat, after flooding of their spawning grounds during the breeding season. Modified after Van der Waal (1974) and Bruton (1979). For drawings of characteristic actions, see Bruton (1979).

Phase	**Stage**	**Characteristic actions**
Pre-spawning agonistic	Threat	Approaching ♂♀ Lateral display ♂♀ Tail-slapping ♂♀ Circling ♂♀
	Aggressive	Chasing ♂♀ Mouth fighting ♂♀ Biting ♂♀ Nipping ♂♀ Butting ♂♀
Sexual	Courtship	Body quivering ♂♀ Pushing ♂ Dorsal fin erection ♂ Leading ♂ Following ♀
	Spawning	Amplexus ♂ Sliding ♂ Body stiffening ♀ Body twisting ♂ Egg release ♀ Sperm release ♂

Catfish is a very important source of protein for the African population and is cultivated widespread. The problem, however, is that the fish do not spawn in captivity, since females do no ovulate and male sperm release is blocked (van Oordt et al., 1987). To obtain eggs from captive catfish, females are injected with a mixture of LHRH and the dopamine antagonist pimozide (Richter and van den Hurk, 1982; de Leeuw et al., 1985) or with

gonadotropin, while males are castrated to collect sperm (Viveen et al., 1985). It is of particular economical importance to find a simple and cheap way in which catfish can spontaneously ovulate. The development of a method in which water containing specific pheromones can be used as an ovulation inducing agent, could be of huge significance, as it could be of help for fisherman to catch catfish.

Feral catfish have an annual reproductive cycle, which is controlled by photoperiod and water temperature (van den Hurk et al., 1984-1985). Gonadotropin content in the pituitary of African catfish largely parallels the cyclic changes in the gonads, while prespawning female catfish exhibit a gonadotropin surge (van Oordt et al., 1987). Biochemical (GC-MS) studies with *male* African catfish sex organs have shown that steroids are formed both in testes and seminal vesicles, and that the latter organs additionally are specific sources of steroid glucuronides (*Table 3;* Schoonen and Lambert, 1986a;b; Schoonen et al., 1987; 1988a; Resink et al., 1987b;c; 1989b). The mixture of steroid glucuronides and the concentrations of the components found in seminal vesicle fluid are shown in *Table 5*. Seminal vesicles from spawning catfish are highly active in synthesizing 5β-reduced steroids and contain considerably higher concentrations of 5β-androstane-3α, 17β-diol-, 5β-androstane-3α,17β-diol-11-one- and especially of 5β-pregnane-3α,17α-diol-20-one glucuronide than those from non-spawning feral and captive catfish (Schoonen, 1987; Schoonen et al., 1988a). From the eight steroid glucuronides present in seminal vesicle fluid, four are detected in holding water of one-year old captive catfish, i.e. 5β-pregnane-3α, 17α-diol-20-one-, 5β-androstane-3α,17β-diol-11-one-, etiocholanolone- and 5β-androstane-3α,17β-diol glucuronide (van Weerd et al., 1991b). Enzymehistochemical studies have confirmed the potency of seminal vesicles to produce steroid glucuronides, the Leydig-cell like stromal cells synthesizing the steroids and the epithelium lining the seminal vesicle tubules taking care of the glucuronidation of the formed steroids (van den Hurk et al., 1987a). Thus, in contrast to the 5α-steroid metabolites formed by zebrafish (van den Hurk et al., 1983; 1987b), male African catfish produces 5β-steroid glucuronides, inclusive etiocholanolone glucuronide which has been demonstrated to act as a pheromone in the black goby (Colombo et al., 1980;1982).

Castrated male catfish have enlarged seminal vesicles (Resink et al., 1987a). When kept in Y-maze aquaria, they are more attractive for ovulated female conspecifics than normal intact males. A synthetic mixture, containing the steroid glucuronides in similar concentrations as found in the seminal vesicle fluid of captive castrated catfish, also appears attractive for ovulated female (Resink et al., 1989b). The data show the pheromonal significance of seminal vesicle steroid glucuronides in finding a reproductive partner. Subjection of a male to an ovulated female appears to induce a rise in circulating gonadotropin in both genders of catfish (Resink et al., 1987a). When the artificial partition between them is removed, attraction of an ovulated female to a male is followed by a series of spawning activities, like approaching, butting and chasing, and finally led to oviposition. Apart from their function as sex attractants and possible reproductive behaviour inducers in adult fish, male pubertal (5 months old) catfish pheromones have been demonstrated to stimulate gonadal development in both female and male conspecifics, which were individually kept in flow-through basins (van Weerd et al., 1991a).

Huge production of steroid glucuronides has also been detected in *female* catfish that had recently ovulated (Schoonen, 1987; Schoonen et al., 1989a). The 12 compounds that are found in the ovarian fluid of African catfish between ovulation and oviposition (Schoonen et al., 1988b; 1989b) are presented in *Table 3*. Besides, a few very polar steroid triols and tetrols have been identified. From these compounds, both free and glucuronidated 5β-pregnane-3α-17α-20α- triol, 5β-pregnane-3α, 17α, 20β-triol and oestradiol-17β have been be detected in holding water of one-year old captive catfish (van Weerd et al., 1991b). Apart from that,

Figure 6: Spawning of African catfish in the Hula Valley Nature Reserve (Israël). (a) Habitat of this species before artificial flooding of the spawning grasslands. (b) Presence of catfish at the flooded spawning fields (arrows indicate catfish). (c) Characteristic body folding (amplexus) of a male catfish during spawning. (d) Final spawning actions characterised by female body twisting and oviposition, the latter process being induced by sliding of the male around the female.

oestrone and oestrone glucuronide have been demonstrated in this holding water, despite the inability to identify these compounds in ovarian fluid with spectral analysis and selected ion monitoring (Schoonen et al., 1989a). Enzyme histochemical studies have pointed to postovulatory follicles as sources of steroid glucuronides (van den Hurk et al., 1987b). Addition of ovarian fluid of ovulated females appears to induce ovulation in conspecific females, but only when male pheromones are additionally present (Resink et al., 1989a). Females, in which ovulation is pheromonally induced, have increased plasma gonadotropin levels, indicating the primer effect of the pheromones. It has to be noted that the described

results were only obtained with first generation descendents of feral catfish and not with further generations, indicating that pheromone sensitivity and/or pheromonally primed physiological responses may dramatically alter in catfish descendents which are kept under unnatural conditions.

Table 5: The steroid glucuronide mixture and the concentration of its components in the seminal vesicle fluid of captive castrated African catfish.

Steroid-G*	**Concentration (M x 10^{-8})**
testosterone-G	9.0 ± 2.0
etiocholanolone-G	8.6 ± 2.8
5β-dihydrotestosterone-G	2.7 ± 2.7
5β-pregnane-3α,17α-diol-20-one-G	2.2 ± 0.2
5β-androstane-3α, 17β-diol-G	2.4 ± 1.9
5β-androstane-3β, 17β-diol-G	2.4 ± 1.1
5β-androstane-3α, 17β-diol-11-on-G	2.4 ± 0.3
5β-androstane-3α, 11β-diol-17-on-G	4.2 ± 1.0

* G, glucuronide

The skin of fishes is known to form and secrete alarm pheromones, which are formed in the specialised big club cells, also termed alarm substance cells (Von Frisch, 1941; Pfeiffer, 1977; Smith, 1992). Hypoxanthine-3(N)-oxide has been found to be an active compound in the alarm pheromone blend of the black tetra, *Gymnocorymbus ternetzi*, (Pfeiffer et al., 1985) and several minnow species (Smith, 1992; Brown et al., 2002). Like their gonads and seminal vesicles, the skin of African catfish is able to form various progestins and androgens, among which a few glucuronidated steroids, and in particular 5-androstene-3β, 17β-diol-, 5β-dihydrotestosterone- and testosterone glucuronide (Ali et al., 1987). These glucuronides are formed in skin cells different from the big club cells (Ali et al., 1987), that contain alarm pheromones and which are only released upon damage to the epidermis (Pfeiffer, 1967; Colombo et al., 1982; Smith, 1992; Commens and Mathis, 1999; Mirza and Chivers, 2002). Skin extracts and skin mucus of goldfish furthermore contain various free amino acids, which may have a signaling function (Saglio and Faucanneau, 1985). Previously, the skin was considered as the main source of intraspecific chemical stimuli involved in recognition of conspecific catfish, i.e. the yellow bullhead (*Ictalurus natalis;* Todd et al., 1967) and the channel catfish (*Ictalurus nebulosus;* Richards, 1974). Although, the possibility that water-borne steroid compounds formed by skin play a role as sex pheromones in catfish cannot be ruled out, the thresholds for detection of the demonstrated steroid conjugates are too high (Resink et al., 1989c) for ascribing an important pheromonal function to them.

Among the demonstrated male catfish steroid glucuronides, those with glucuronic acid on the 3α-position are the most potent odourants, evoking EOG responses in concentrations (10^{-11} to 10^{-9} M), with the by feral spawning males highly secreted 5β-pregnane 3α, 17α-diol-

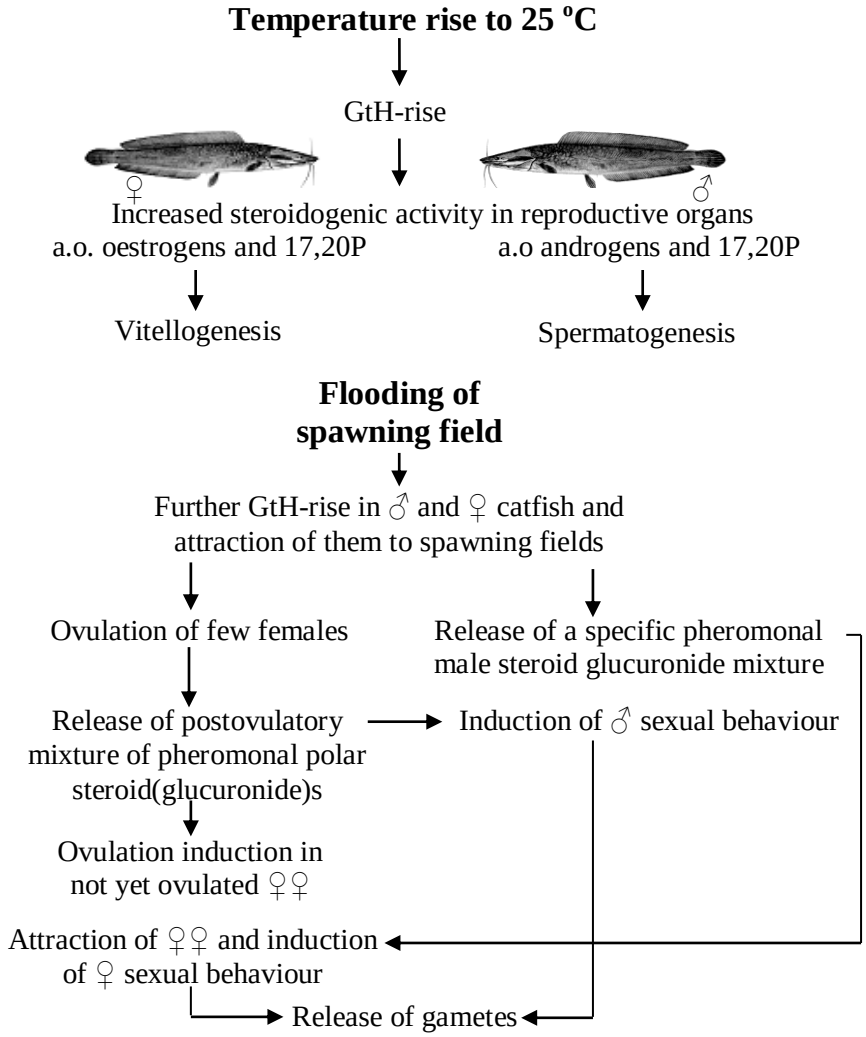


Figure 7: Schematic presentation of the presumptive pheromonal regulation of reproduction in African catfish. The anually returning rise in environmental temperature to 25 °C determines the activity of the hypohyseal-gonadal axis, resulting in a rise in GtH-release, which influences sperm production and steroidogenic potency of the testes and seminal vesicles in males, and steroid production and formation of numerous vitellogenic follicles in females. Flooding of the spawning fields causes the release of an odour that attracts matured catfish to these grounds, and further stimulates GtH-secretion by their pituitary, which on its turn influences steroid glucuronide production by the seminal vesicles in male catfish and triggers ovulation in few female specimens. The released steroid glucuronides by the ovulated female's postovulatory follicles and the male's seminal vesicles then form an adequate pheromone blend, that triggers ovulation in other female conspecifics through adequate stimulation of their hypophyseal gonadotropin output. During their stay at the spawning fields, the released pheromones by male and ovulated female catfish stimulate sexual behaviour in the opposite gender, which finally leads to gamete release and subsequent fertilisation of ejected eggs.

20-one-glucuronide having the lowest detection threshold (Resink et al., 1989c). Unfortunately, the electrophysiological effects of most catfish ovarian steroid glucuronides and those of the synthesised steroid triols and tetrols have not been tested, because they were commmercially inavailable. Olfactory tract lesioning studies have indicated the medial olfactory tract as a functional neuroanatomical pathway, transporting pheromonally induced neural stimuli to the preoptic region in the diencephalon of African catfish to influence the gonadotropin releasing hormone (GnRH) system (Resink et al., 1989d). In doing so, it may lead to behavioural and physiological changes related to spawning.

Figure 7 shows the presumptive pheromonal regulation of reproduction in African catfish: annually returning environmental factors determine the activity of the hypohyseal-gonadal axis and thus production of sperm and steroidogenic potency of the testes and seminal vesicles in males, and steroid production and formation of numerous vitellogenic follicles in females. In rainy periods, the flooding of fields results in the release of an odour that attract matured catfish to the spawning grounds and may trigger ovulation initially in a few female catfish, the enhanced steroid glucuronid production by the female's postovulatory follicles and the male's seminal vesicles then forming an adequate mixture of pheromones, that triggers ovulation in other female conspecifics through further stimulation of their hypophyseal gonadotropin output.

Goldfish

With increasing water temperatures, the nervous system function in goldfish, *Carassius auratus*, is altered (Preuss and Faber, 2003) by the release of β-endorphins, a process which is mediated by the pineal gland (Kavaliers, 1982). As a result, body temperature and behavioural activity levels increase. Spawning of goldfish is induced by rising water temperatures from 12 to 20 ^{o}C (Kobayashi et al., 1986; 1987). Due to this specific rise in temperature, plasma GtH levels in males show a marked increase, which is synchronous with a preovulatory GtH surge in females, and peaks at the onset of spawning. In line with the rise in GtH levels, plasma testosterone and 4-pregnene-17α, 20β-diol-3-one levels increase in both male and female goldfish. These hormonal changes are followed by the formation of large amounts of milt in males and oocyte maturation and ovulation in females. The presence of ovulated females further enhances male GtH levels.

Like zebrafish (van den Hurk and Lambert, 1983), anosmic goldfish, *Carassius auratus*, do not spawn (Sorensen et al., 1992). To enable spawning they thus rely on pheromones. *Female* goldfish produces at least three pheromonal signals that are released in concentrations varying from 10 to 100 ng/h, and that synchronise male behaviour and physiology with those of the female conspecific releasing the signals (Scott and Sorensen, 1994). The 3 signals are successively produced (i) days to weeks before spawning, (ii) approximately 12h prior to ovulation to immediately prior to ovulation, and (iii) immediately after ovulation. The first signal is produced by vitellogenic females, is associated with elevated plasma oestradiol levels, and is attractive for males (Kobayashi et al, 2002). Previously, etiocholanolon glucuronide has been found to attract male goldfish (Colombo et al., 1982). The second signal is a mixture of at least twelve steroids of which three, 4-androsten-3, 17-dione (AD), 4-pregnene-17α, 20β-diol-3-one (17,20P) and its 20-sulphate (17,20P-S), are considered as primary components, because they are detected with high specificity and sensitivity. Gradually, there is a shift from AD dominancy (which probably prevents males to respond too early to 17,20P) to 17,20P and subsequently to 17,20P-S dominancy, which stimulates the sexual motivation of males, their GtH (type II = LH) release and their milt (sperm + seminal fluid) production (Sorensen et al., 1995; Stacey, 1991; Poling et al., 2001; Stacey and Sorensen, 2002). When administered to tanks in which goldfish were

kept, 17,20P and especially 17,20P-S elicit the courtship behaviours chasing (high-speed movements around a tank initiated by a male) and nudging (male inspection of males or females near the vent and gills) (Poling et al., 2001).

Immediately after ovulation, female goldfish secretes a third pheromone, i.e. prostaglandin F2α and one of its metabolites, 15-keto-prostaglandin F2α (Sorensen and Goetz, 1993). Water-borne PGFs stimulate the olfactory system and trigger male spawning behaviour (Sorensen et al, 1988; 1989). This behavioural effect is probably brought about through the modulating effect of PGF2α on male brain plasticity (Chung-Davidson et al., 2008), since exposure to waterborne PGF2α increases the number of dividing diencephalon cells and elevates GnRH transcripts in the brain's telencephalon and cerebellum and choline acyltransferase in the vagal lobe and the brainstem underneath this lobe. In females, exposure to waterborne 17,20P increased the transcripts of androgen receptor and GnRH-II in the female cerebellum (Chung-Davidson et al., 2008). In males, exposure to waterborne 17,20P increases circulatory levels of immunoreactive AD). Male goldfish releases approximately 50 ng/h AD and up to 1 µg/h of this androgen, when they are sexually aroused (Sorensen et al., 2005). Nanomolar concentrations of AD have been shown to stimulate aggressive interactions between male goldfish (Poling et al., 2001) while, in a mixture with the female pheromone 17,20P, it suppresses the responsiveness of males to the latter steroid (Stacey, 1991). Under the influence of large concentrations of pheromonal androstenedione released by male conspecifics, females become motivated to exhibit sexual behaviour. Sexual behaviour of both goldfish sexes finally culminates in gamete release and subsequent fertilisation of ejected eggs. The putative pheromonal prostaglandin and steroidal compounds all evoke EOG responses in goldfish, in concentrations (10^{-10} to 10^{-12} M), which can be expected for a (sex) pheromone (Sorensen et al., 1992). In this regard several tested steroid glucuronides (testosterone-, oestradiol-, and ethiocholanolon glucuronide) appeared ineffective (Sorensen et al., 1987) or relatively poorly effective ((17,20P-glucuronide; Sorensen et al., 1991a). Except ethiocholanolon glucuronide, the mentioned steroids and their conjugates are all demonstrated in aquarium water in which goldfish were kept (Sorensen and Scott, 1994). Besides, a few pregnene triols, 11-keto kestosterone and their respective sulphates and glucuronides have been detected with C_{20} sulphated or glucuronidated 4-pregnene-17α, 20β, 21-triol-3-one in the largest concentrations (5.5 and 7 nM, respectively) in water containing ovulatory females. As a free steroid, this latter triol may act as a hormone, which induces oocyte maturation in many fish species (Thomas and Trant, 1989).

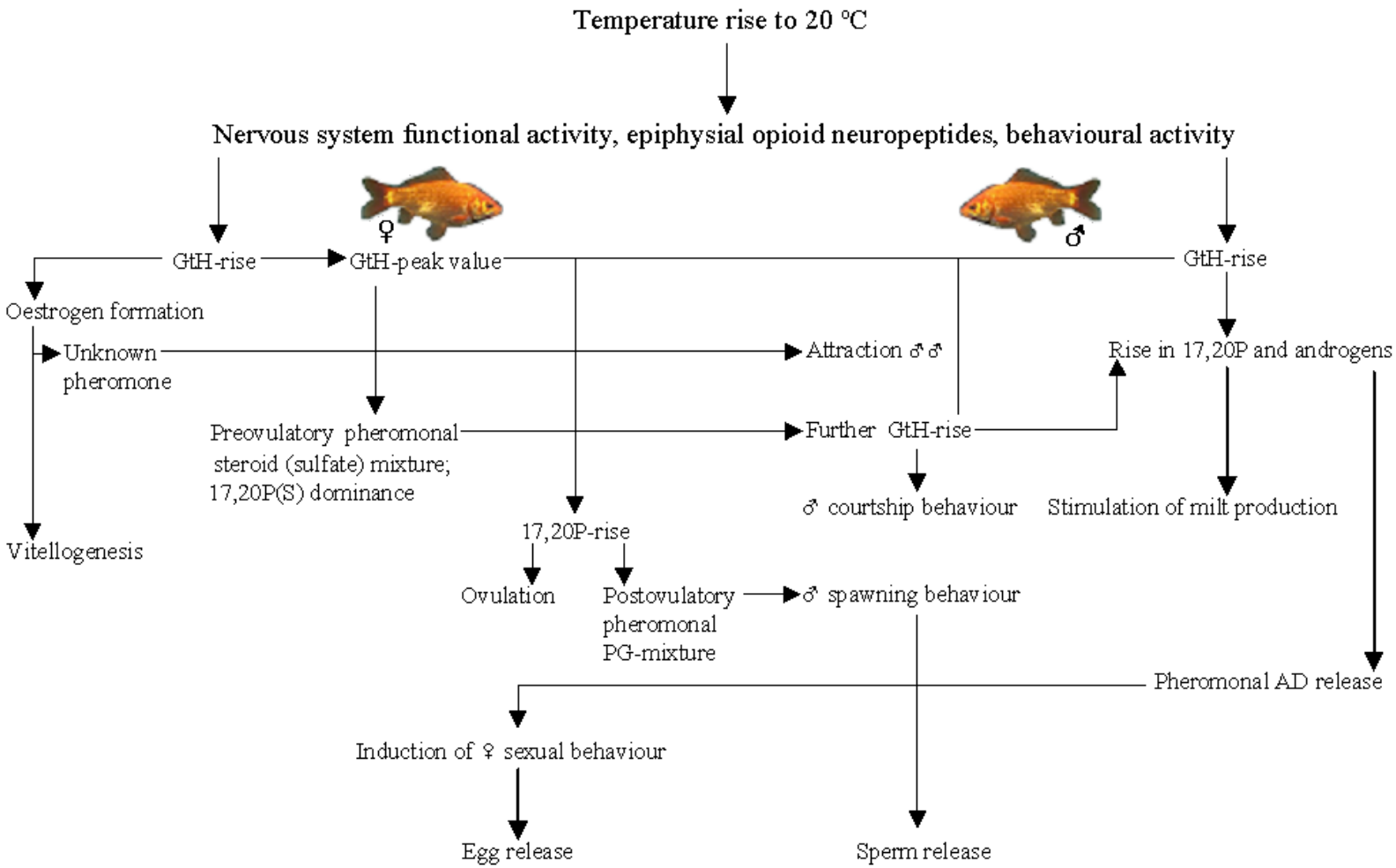
The olfactory sensitivity of goldfish to water-borne steroids is extremely specific and restricted to a few compounds. Among eight C-19 steroids tested, only AD is detected with notable sensitivity by non-ovulatory vitellogenic female and spermiated male goldfish. From thirteen C_{21} steroids tested, only three have been detected with notable sensititvity: 17,20P, 17,20P-S and 4-pregnene-17α,20β,21-triol-3-one (17,20,21P; Sorensen and Scott, 1994). The sulphated form of the latter pregnene triol evokes an EOG response in non-ovulatory vitellogenic female and spermiated male goldfish, while its glucuronide has not been tested. Thus, apart from free and sulphated 17,20P (Poling et al., 2001), free and conjugated 17,20,21P could be other steroidal sex pheromones which are secreted by ovulated female goldfish. However, cross-adaptation experiments have shown that olfactory responsiveness to 17,20,21P is attributable to non-specificity of the 17,20P receptor (Sorensen et al., 1990), which may indicate that there are only three steroidal stimuli that are specifically detected by goldfish. Sorensen and Scott (1994) were unable to procure seven water-borne steroidal compounds for EOG testing, among which were 4-androstene-17β-ol-11,17-dione glucuronide, 4-androstene-17β-ol-11,17-dione sulphate and 17,20,21P-glucuronide. Their opinion, that a sex pheromonal function of any of them is unlikely, is only based on their findings that closely related compounds are unable to electrically stimulate the nasal

epithelium of goldfish, even when tested at a concentration of 10^{-7} M. In goldfish and a few other cyprinid species, in contrast to pheromonal steroids, olfactory responsiveness to prostaglandins is androgen-dependent (Belanger et al., 2010).

In goldfish, steroid conjugates are preferentially excreted in the urine, and free steroids by way of the gills (Sorensen et al., 1995). Urinary release can be pulsed (Curtis and Wood, 1991; Applet and Sorensen, 1999) and male goldfish must be within several body lenghts of an ovulatory female in order to detect 17,20P (Sorensen and Stacey, 1990). A thus created small and transient effective space around the pheromone emitter is only likely to be encountered by an interested conspecific.

Goldfish detect AD, 17,20P and 17,20P-S with different olfactory receptor neurons, giving them the ability to make fine distinctions (Sorensen et al., 1995; 2000; Sato and Sorensen, 2003). Apart from electrical stimulation of the nasal epithelium, exogenous sex steroids also alter the spontaneous and evoked electrical activity of the olfactory bulb in goldfish (Hara, 1967; Oshima and Gorbman, 1968). Neurons in the central part of the ventral olfactory bulb are especially sensitive to pulses evoked by sex pheromones (Lastein et al., 2006). These authors have furthermore shown a remarkable gender difference in the responses of the bulbar neurons torward 17,20P, 17,20P-S, AD and PGF2a, goldfish males being far more sensitive than females. As in African catfish (Resink et al., 1989d), steroidal sex pheromones selectively stimulate the medial olfactory tracts (MOTs) of male goldfish (Dulka and Stacey, 1991; Sorensen et al., 1991b) to innervate various regions in the forebrain. Central projections of the MOTs terminate in the midline regions of the ventral telecephalon (Von Bartheld et al., 1984; Levine and Dethier, 1985), which have been implicated in the control of a variety of reproductive functions in goldfish and other fish (Demsky and Hornby, 1982; Kyle et al., 1987). These regions include those that control male reproductive behaviour (Kyle et al., 1982; Koyama et al., 1984), sperm release (Demski and Hornby, 1982) and regions in the preoptic area that produce GnRH and dopamine. GnRH stimulates and dopamine inhibits gonadotropin release (Peter et al., 1986) through neurons which project to the pituitary (Kah et al., 1986; 1987). In male goldfish, the preovulatory sex pheromone 17,20P exerts its effect through this anatomical pathway to inhibit dopamine turnover, resulting in an abatement of dopamine release to the pituitary, which neuro-endocrinally promotes the release of gonadotropin (Dulka et al., 1991; Dulka and Stacey, 1991). *Figure 8* shows the putative hormonal and pheromonal regulation of reproduction in goldfish triggered by yearly water temperature rising.

Figure 8: Schematic presentation of the presumptive pheromonal regulation of reproduction in goldfish. The annual rise in water temperature to 20 °C determines the activity of the hypohyseal-gonadal axis, resulting in a rise in GtH release, which stimulates steroidogenesis and spermatogenesis in males and follicular oestrogen production in females. On their turn, the formed oestrogens stimulate the formation and secretion of vitellogenic proteins in the liver resulting in the formation of vitellogenic ooytes. The ovary then produces an unknown pheromone, which attracts males. Before ovulation, the ovaries form a second pheromonal mixture consisting of steroid(sulphate)s, which evokes in males a further rise in GtH-output, followed by further stimulation of milt production, exhibition of courtship behaviour, and release of large amounts of androstenedione (AD). After ovulation, the females release a prostaglandin (PG)-mixture, which induces male sexual behaviour. Under the influence of large concentrations of pheromonal androstenedione released by male conspecifics, females become motivated to exhibit sexual behaviour. Sexual behaviour of both goldfish sexes finally culminates in gamete release and subsequent fertilisation of ejected eggs.


Temperature rise to 20 °C
Nervous system functional activity, epiphysial opioid neuropeptides, behavioural activity
♀
♂
GtH-rise
GtH-peak value
GtH-rise
Oestrogen formation
Unknown pheromone
Attraction ♂♂
Rise in 17,20P and androgens
Preovulatory pheromonal steroid (sulfate) mixture; 17,20P(S) dominance
Further GtH-rise
♂ courtship behaviour
Stimulation of milt production
Vitellogenesis
17,20P-rise
Ovulation
Postovulatory pheromonal PG-mixture
♂ spawning behaviour
Pheromonal AD release
Induction of ♀ sexual behaviour
Egg release
Sperm release

Other fish species

Besides goldfish and African catfish, male and female Burton's mouthbreeder (*Haplochromis burtoni*, also referred to as *Astatotilapia burton*, an African mouthbrooding cichlid) give EOG-responses to 17 tested glucuronated and sulphated steroids at concentrations from 10^{-11} to 10^{-8} M (Cole and Stacey, 2006). Although there is no evidence that specimens of this species release, or exhibit biological responses to, the detected steroid conjugates, the findings suggest that this teleost species utilises pheromonal cues, consisting of a complex mixture of steroid conjugates.

Apart from gobies, zebrafish, African catfish and goldfish, biochemical, behavioural and/or semen analysis either or not followed by electrophysiological studies have thus far demonstrated the identity of sex pheromones in eight other teleost species and in lampreys (*Table 6*). This table furthermore shows the source and function of the detected pheromones. In this table, findings with for example Mozambique tilapia (*Oreochromis mossambicus*; also called the blue kurper or mud bream) are omited, since the exact nature of the male urinary sterol-like pheromone, that likely signals social dominance to females ready to spawn and thus influences female spawning, is unknown (Barata et al., 2008). For this reason, anal glands and accessory organs of the male peacock blenny (*Salario pavo*) are not mentioned as sources of a putative multicompenent pheromone (Serrano et al., 2008a,b), attractive for female conspecifics.

Male yellowfin Baikal sculpins *(Cottocomephorus grewingki)* produces 4-androsten steroids, e.g. testosterone and AD, which induce spawning behaviour in ovulated females, and 11-ketotestosterone, which induces ovulation of attracted females (Dmitrieva and Ostroumov, 1986; Dmitrieva et al., 1988; Katsel et al., 1992). Furthermore, these authors have suggested that a polyenic alcohol, 2*Z*,6*E*-farnesol, functions as a male pheromone in this teleost species, which attracts female conspecifics. Male silver barbs, *Punctius schwanenfeldi*, detect 11-ketotestosterone down to concentrations of 10^{-11} M (Cardwell et al., 1995), which suggests that this C-19 steroid may also functions as a male-derived pheromone in fish. Females of the cyprinid genus *Barilius bendelesis* secrete a preovulatory steroid sulphate and postovulatory 15-keto-PGF2α, which promote the male's spawning success by stimulating its milt production and sexual activity, respectively (Bhatt and Sajwan, 2001; Bhatt et al., 2002). Ovulated female cobitid loaches (*Misgurnus anguillicaudatus)* produce F prostaglandins, which stimulate male courtship (Kitamura and Ogata, 1990; Ogata et al., 1994). In the perciform Chinese black sleeper (*Bostrichthys sinensis*), ovaries, testes and seminal vesicles show different 17α-P, 17,20P and PGE_2 levels (Hong et al., 2006). These compounds attract both male and female conspecifics to spawning sites, while PGE_2 is the most effective pheromone in inducing spawning.

Male arctic chars (*Salvellinus alpinus)* release PGF2α into the water that attracts ovulated females and elicit spawning behaviour (Sveinsson and Hara, 1995; 2000). Urine from ovulated female atlantic salmon (*Salmo salar)* contains large quantities (18 ng/mL) of PGFs, while urine from non-ovulated females or males contains significantly smaller amounts (<1 ng/mL; Moore and Waring, 1996). EOG-studies from these authors show 'pheromonal' sensitivity of the olfactory epithelium of male atlantic salmon to PGF1α and PGF2α (threshold concentrations 10^{-11} M), and to 15-keto PGF2α (threshold concentration 10^{-8} M), the sensitivity increasing as the reproductive season progresses. Exposure of males to waterborne PGF1α and PGF2α (10^{-8} M) results in increase in milt and in plasma concentrations of 17,20P, testosterone and 11-ketotestosterone. The olfactory epithelium of male brown trout (*Salmo trutta*) is sensitive to urine and ovarian fluid from ovulated female conspecifics as well as to PGF1α and PGF2α (threshold concentration 10^{-11} M; Moore et al., 2002). Exposure of male brown trout to ovarian fluid results in an increase in the 17,20P

plasma levels, whereas exposure to urine stimulated the milt production. PGF2α is present within both urine and ovarian fluid of female brown trout. As in atlantic salmon, exposure of male brown trout to waterborne PGF1α and PGF2α (10^{-8} M) results in milt increase and in plasma concentrations (10^{-8} M) of 17,20P, testosterone and 11-keto-testosterone. In experiments of Laberge and Hara (2003), exposure to PGF2α and 13,14-dihydro-PGF2α does increase the swimming activity in brown trout, whereas the prespawning behaviours digging and nest probing are induced in female trout, which have been exposed to PGF2α. Ovulated female masu salmon (*Oncorhynchus masou*) contains a major metabolite of tryptophan, the amino acid (2S)-2-amino-4-(2-aminophenyl)-4-oxo-butanoic acid (termed *L*-kynurenine) in their urine. This male-attracting amino acid has an electrophysiological response threshold of 10^{-14} M in spermiating males, and advertises the female's readiness for mating (Yambe et al., 2006). Like the brown trout, lake whitefish (*Coregonus clupeaformis*) increase their locomotion, when exposed to 10^{-8} M PGF2α and 15-keto-PGF2α (Laberge and Hara, 2003). This fish, however, differ from brown trout in not showing increased prespawning activity after being confrontated to these prostaglandins, and in being most sensitive in EOG measurements to both 15-keto-PGF2α and 13,14-dihydro-PGF2α in stead of PGF2α. The data show that PGF2α and/or its metabolites function as sex pheromones not only in cyprinids and cobitids, but also in salmonids.

Male sticklebacks (*Gasterosteus acculeatus*) produce and excrete major histocompatibility complex (MHC) peptide ligands, that provide information about their immunological system, that is used by the female to choose among males in order to achieve an optimal diversity of MHC genes (Reusch et al., 2001; Aeschlimann et al., 2003; Kurtz et al., 2004; Milinski et al., 2005). Hence, MHC peptide ligands have been shown to play a role in social recognition of stickleback, particularly in their mate choice. Whether these proteins may function as carrier proteins for other excreted pheromonal compounds as they do for mammalian communication is unknown (for further details, see the chapter 'Introductory information on MHC peptides, lipocalins, MUPs and vomeronasal binding proteins' in this book). Although, apart from sticklebacks, MHC genes were also demonstrated in channel catfish (*Ictalurus punctatus*; Godwin et al., 2000), zebrafish (Sambrook et al., 2005) and salmonids (Aguilar and Garza, 2006; Kjoglum et al., 2006), it is yet unknown whether MHC peptides have a role in pheromone signaling in these latter fish species.

In sea lampreys (*Petromyzon marinus)*, the spermiating adult male produces a mixture of the bile acid derivatives 3-keto-petromyzonol sulphate (5α-cholan-7α,12α,24-trihydroxy-3-one-24 sulphate) and 3-keto-allocholic acid (5α-cholan-7α,12α-diol-3-one-24oic acid) as sex pheromone plume, that attracts ovulating females for reproduction (Li and Siefkes, 2004; Venkatachalam, 2005) and which components are potent stimulants of the adult olfactory system (Li and Sorensen, 1997; Li et al., 1995; Siefkes et al., 2003). In these adult lampreys, bile compounds are produced by the liver and released through the gills (Siefkes et al., 2003). A mixture of three sulphated steroids (petromyzonamine disulphate, petromyzosterol disulphate and petromyzonol sulphate), released by stream-resident conspecific larval sea lampreys, functions as migratory pheromone for adult conspecifics to locate spawning sites (Sorensen et al., 2005; Hoye et al., 2007; Sorensen and Hoye, 2007; Fine and Sorensen, 2008). In laboratory mazes, the mixture is as attractive as larval water to adult sea lampreys (Fine and Sorensen, 2008). Each of the three steroids is released in picomolar concentrations in river waters and their half-lives is about 3 days, i.e. sufficiently slow for the entire pheromone to persist in river mouths (Fine and Sorensen, 2010). This makes the authors conclude that it appears highly likely that a mixture of petromyzonamine disulphate, petromyzosterol disulphate and petromyzonol sulphate is present at biologically relevant concentrations and ratios in many Great Lakes streams where it functions as a pheromonal attractant. Similarly to sea lampreys, adult migrating Pacific lampreys (*Lampetra tridentata*)

Table 6: Identified sex pheromones and their source and function in fish. Apart from the mentioned sex pheromones, certain amino acids and bile acids are important (teleost) odourants, which have a function in food detection, migration to spawning sites (Hara, 1976; Hara et al., 1984; Sorensen et al., 2005; Fine and Sorensen, 2005) or ovulation signaling (Yambe et al., 2006).

Species	**Pheromone**			**Author**
	Source	**Structure**	**Function**	
Gobius jozo	mesorchial gland	C_{19}-steroid glucuronide	♀-attractive	a,b
Neogobius melanostomus	testis	etiocholanolone	increases ♂/♀ gill ventilation rate*	c
	ovary	oestrone	increases ♂ gill ventilation rate**	d-f
Danio rerio	testis	C_{19}/C_{21}-steroid glucuronide mixture	ovulation induction	g
	ovary	C_{18}/ C_{19}/C_{21}-steroid glucuronide mixture	♂-attractive	h,i
Clarias gariepinus	seminal vesicle	C_{19}/C_{21}-steroid glucoronide mixture	♀-attractive ovulation induction	j-o
	ovary	mixture of C_{18}/C_{19}/C_{21}-steroid glucuronides and polar steroids	ovulation induction	p-s
Carassius auratus	testis	C_{19}-steroids	induce ♂-aggressive interaction	t,u
	ovary	mixture of C_{21}-steroids and C_{21}-steroid sulphates; PGFs	stimulates ♂-courtship and milk production induces ♂-sexual behaviour	v-bb
	♂♂/♀♀	PGF, C21-steroid	modulate brain plasticity	cc
Cottocomephorus grewingki	♂♂	C_{19}-steroids	induces ♀-spawning behaviour and ovulation	dd-ff
		2*Z*,6*E*-farnesol	♀-attractive	
Barilius bendelesis	♀♀	C_{21}-steroid sulphate	stimulates milk production	gg,hh
		15-PGF	stimulates ♂-sexual activity	
Misgurnus anguillicaudatus	♀♀	PGF mixture	elicits ♂-courtship behaviour	ii,jj

Species	Pheromone			Author
	Source	Structure	Function	
Bostrichthys sinensis	♂♂/♀♀	mixture of C_{21}- steroids and PGE_2	♂♂/♀♀-attractive elicits spawning	kk
Salvellinus alpinus	♂♂	PGF2α	♀-attractive induces ♀-prespawning behaviour (digging)	ll,mm
Salmo salar	ovulated ♀♀-urine	PGF1α, PGF2α	increase milt increase ♂ plasma hormone levels	nn
Salmo trutta	♂♂	PGF2α	induces ♀-prespawning behaviour (digging, nest probing)	oo
		13,14-dihydro-15-keto-PGF	increases locomotor activity in ♂♂ and ♀♀	
	urine, ovarian fluid	PGF1α, PGF2α	increase milt increase ♂ plasma hormone levels	pp
Oncorhynchus masou	♀♀	*L*-kynurenine	♂-attractive	qq
Coregonus clupeaformis	♂♂	PGF2α, 13,14-dihydro-15-keto-PGF	increases locomotor activity in ♂♂ and ♀♀	oo
Petromyzon marinus	♂-liver	bile acid mixture	♀-attractive	rr-tt

Legend belonging to Table 6: * marker of the male's reproductive status; ** marker of the female's reproductive status; a,b: Colombo et al., 1980;1982; c: Murphy et al., 2001; d: Moore and Stacey, 2002; e: Belanger et al., 2006; f: Belanger et al., 2007; g: Van den Hurk et al., 1987c; h: Van den Hurk et al., 1982; i: Van den Hurk and Lambert, 1983; j,k: Schoonen and Lambert, 1986a;b; l,m: Schoonen et al., 1987; 1988a; n,o: Resink et al., 1987a; 1989a; p: Schoonen, 1987; q: Schoonen et al., 1989a; r: Van den Hurk et al., 1987b; s: Resink et al., 1989a; t: Poling et al., 2001; u: Sorensen et al., 2005; v: Sorensen et al., 1995; w: Stacey, 1991; x: Poling et al., 2001; y: Stacey and Sorensen, 2002 z: Sorensen and Goetz, 1993; aa,bb: Sorensen et al, 1988; 1989; cc: Chung-Davidson et al., 2008; dd: Dmitrieva and Ostroumov, 1986; ee: Dmitrieva et al., 1988; ff: Katsel et al., 1992; gg: Bhatt and Sajwan, 2001; hh: Bhatt et al., 2002; ii: Kitamura and Ogata, 1990; jj: Ogata et al., 1994; kk: Hong et al., 2006; ll: Svensson and Hara, 1995; mm: Sveinsson and Hara, 2000; nn: Moore and Waring, 1996; oo: Laberge and Hara, 2003; pp: Moore et al., 2002; qq: Yambe et al., 2006; rr: Li and Siefkes, 2004; ss: Venkatachalam, 2005; tt: Siefkes et al., 2003.

are highly sensitivity to petromyzon sulphate and 3-keto petromyzonol sulphate (3kPZS), but differ in having a longer period of sensitivity to those bile acids (Robinson et al., 2009). Synthesised 3kPZS induces upstream movement in ovulated female sea lampreys, redirects them away from a natural pheromone source and lure them into traps (Johnson et al., 2009). EOG data from the olfactory epithelium of adult rainbow trout (*Oncorhynchus mykiss*) suggests, but does not yet prove, a pheromonal function of bile acids (Giaquinto and Hara, 2008) in this teleost species. Bile acids are more water-soluble than steroidal pheromones, which makes these acids detectable from a greater range (up to 65 m) than steroids are traceable (Li et al, 2002).

Salmonoids are well-known for their accurate homing migration in order to return to their spawning grounds. It is widely accepted that certain specific odourant factors in the natal stream are imprinted on the olfactory system of juvenile salmon, and that adult salmon evoke these factors to recognise their natal stream during homing migration (Dittman & Quinn, 1996; Quinn, 2005; Ueda et al., 2007). Various findings support the possibility that olfactory imprinting and homing in salmon is controlled at the gene level, and that the genes related to both processes are expressed in the olfactory system of salmon (for more detailed information, see Hino et al., 2009). This current review will not further deal with homing migration, since imprinted olfactory factors cannot be considered as (sex) pheromones.

In over 40 teleost species, EOG recording of various prostaglandins, steroids and a few steroid conjugates has been carried out. Several tested compounds are perceived by the olfactory epithelium in nanomol to picomol concentrations (for detailed information, see Cardwell et al., 1991; Sorensen and Scott, 1994; Stacey et al., 1994; Kitamura et al., 1994; Sveinsson and Hara, 2000; Murphy et al., 2001; Sorensen et al., 2004), which may indicate their possible pheromonal function. Among the tested fish species, most cypriniform species respond to prostaglandins (PGF2α, 15-keto-PGF2α or 13,14-dihydro-15-keto- PGF2α), steroids (17,20P, 17,20,21P or AD) and steroid conjugates (20P-G and 17,20P-S), especially to the free or glucuronated form of 17,20P, the conjugated steroid being the most potent (lower minimum effective dose) odourant (except in goldfish). In contrast, many non-cypriniform species appear anosmic to prostaglandins and steroid/steroid conjugates.

Despite the exhibition of a similar response to some chemical compounds, fish can discriminate between specific chemical mixtures (Poling et al., 2001) and slight variations in it (Sorensen and Scott, 1994). This discriminative potency makes fish capable to recognise conspecifics and heterospecifics, and avoids hybridisation between closely related species (Sorensen and Scott, 1994; Stacey and Cardwell, 1995).Although putative pheromones may play a role in family or sub-family identification, there is little evidence that olfactory sensitivity to these compounds is species-specific, even in species that spawn sympatrically. In such cases additional information from other sensory modalities or unknown substances is necessary to ensure an appropriate response.

Among chemical communication signals, school-specific pheromones emitted by the school members may play a role in the recognition of the school to which fish belong to. In the striped eel catfish (*Plotosus lineatus*) a familiar complex mixture of phosphatidcholines functions as recognition of school-specific odour (Matsumura et al., 2004; 2007). Human-induced eutrophication changes the chemical environment and the pH of water and is a serious environmental problem that restricts visual communication (Utne-Palm, 2002) and may influence the mate choice process in fish (Candolin, 2004; Candolin et al., 2007). Indeed, an increase in pH enhances the use of male olfactory cues in mate choice of three-spined sticklebacks (*Gasterosteus aculeatus*; Heuschele and Gandolin, 2007): gravid females appear more attracted to male olfactory cues when pH is raised. The authors conclude from their observations that pH increase in eutrophied waters could compensate for impaired visual communication in eutrophied waters and facilitate adaptive mate choice by influencing (i) the

binding or transportation of olfactory cues to olfactory receptors or (ii) the chemical cues themselves. Human activity may also lead to elevated humic acid (a pervasive, naturally occurring organic derivative found in aquatic and terrestrial environments) levels. High humic levels (200 mg/L) impair the ability to differentiate between conspecifics from heterospecifics, thus hinder chemical communication between fish by disturbing their sensory environment (Fabian et al., 2007).

Studies on the projection of the sensory neurons onto the olfactory bulb have revealed a clear subdivision into spatially different areas that each responds specifically to different classes of odourants. Amino acids induce activity in the lateral part, bile salts induce activity in the medial part, and alarm substances induce activity in the posterior part of the medial olfactory bulb of the crucian carp (*Carassius carassius*) (Hamdani et al. 2000; 2001b; Hamdani and Døving, 2006).

Reproduction and nonolfactory sensory cues

Apart from pheromonal signals, reproductive behaviour in fish is also thought to be influenced by other sensory cues, i.e. by taste, visual, vibrational, tactile, electrical and auditory stimuli. Taste compounds for fish are aminoacids, organic acids, nucleotides and bile salts. They are perceived by taste cells in taste buds, which are distributed in the oropharyngeal wall and throughout the entire body surface, where after nerve signals are transported to the CNS through brain nerves VII, IX and X. For further information, see Hara (1994).

Once individuals have been able to gain proximity, visual or tactile cues would become useful as a means of species recognition. Male cichlids, labyrinthfishes, poecillids, gourami's, cyprinids and sticklebacks are well-known examples of fish species, that use colour language or other body marks to show other males to stay away and females their readiness to spawn (Stolk, 1978; Tinbergen, 1974). On their turn, females of various species alert conspecific males their reproductive status with their tensed, shining and egg-filled belly. These body marks thus are clear examples for the role of visual cues in reproductive behaviour of fish. Female sticklebacks, *Gasterosteus acculeatus*, select their mating partners according to visual and olfactory cues (Milinski et al., 2003). These females prefer bright-red males as mates. It has been shown that red reflects physical condition and the state of parasitisation (Milinski et al., 1990). Hence, the red colour represents a surrogate for the state of the male's immune system. As described above, the MHC peptides-containing male stickleback odour is another source of information about their immunological status. Female fish thus may use both visual and olfactory cues for mate choice to extrapolate immune function in prospective offspring. In a series of experiments with zebrafish, we also made plausible that both visual and olfactory cues are of importance for the display of sexual behaviour and that ovulated females need only 2 minutes to stimulate a suddenly confronted male to express his reproductive actions, inclusive the fertilisation of ejected eggs (Van den Hurk, 2007).

Intersexual vibrational communication has been observed in many fish (sticklebacks, salmonids and tropical fish): males heavily vibrate in the close surrounding of a female without touching her (Stolk, 1978; Liley et al., 1991). Body vibrational signals cause pressure changes which stimulate egg deposition, thus acting as cues to synchronise the gamete release. These signals are supposed to be processed through the lateral line system, and to be integrated with the visual information to elicit spawning behaviour (Satou et al., 1991). Such a phenomenon can also be seen during parental care (labyrinthfishes, sticklebacks, cichlids), school formation (anchovies, dogfishes), and when a nesting site has to be chosen (sunperches) (Stolk, 1978).

Tactile stimulation can serve to provide the excitation required before a female submits copulation, i.e. fertilisation of her ejected eggs. At least in sticklebacks (Tinbergen, 1974), zebrafish and catfish (see above), spawning actions depend on tactile stimili, whereas the foregoing courtship actions are shown upon adequate chemical and visual signs. Furthermore, in pubertal African catfish, males stimulate ovarian development of females by both olfactory and tactile cues, while pubertal female catfish tend to inhibit male gonadal development especially through tactile cues (Van Weerd et al., 1991b).

Electric fish, like the electric eel (*Electrophorus electrus*) and the mormyrid fish (*Brienomyrus brachyistius*) use their electric sense for communication and navigation (von der Emde, 1999; Wong and Hopkins, 2007). The waveform of the electric organ discharge is highly stereotyped and contains information about species, sex and social status, while the sequence of pulse intervals varies with the behavioural state and motivation for aggression and courtship (Stoddard, 1999; Carlson, 2002; Arnegard et al., 2006; Silva et al., 2007; Wong and Hopkins, 2007).

Sound production in fish is variable, but common, and alarm signals, starvation cries, war songs, mating calls, and courtship songs can be distinguished (Stolk, 1978; Mann and Lobel, 1997; Crawford and Huang, 1999; Kishlinger and Klimley, 2002, Lugli et al., 2003). Various studies on hearing in fishes reported that the hearing bandwith generally extends from below 100 Hz to approximately 7000 Hz (e.g. Fay, 1988; Popper and Fay, 1999; Mann et al., 2001). However, certain fish species, like the blueback herring (*Alosa aestivalis*, Nestler et al., 1992), the alewife (*Alosa pseudoharengus*, Ross et al., 1996) the Atlantic cod (*Gadus morhua*, Astrup, 1999) and the gulf menhaden (*Brevoortia patronus*, Mann et al., 2001), are able to detect high frequency (ultrasound) signals (i.e. > 20 kHz), the American shad (*Alosa sapidosomma*) even to as high as 180 kHz (Mann et al., 1997; 1998). Low frequency sounds are produced by drumming with specialised tendons, muscles or bones on the swimbladder or by using the tendons, which are stretched over their swimbladder, as strings of a stringed instrument (Stolk, 1978; Sargent et al., 1998; Crawford and Huang, 1999). High frequency sounds are produced, for example by soldierfishes and moonfishes, through their mouth by scraping of their pharyngeal teeth or, for example by catfishes and cyprinids, through bony attachments to their pectoral fin (Sargent et al., 1998). In water, low frequency sounds travel farther and are more easily localised than high frequency sounds (Dusenbery, 1992). This could indicate, that low frequency sounds are used to communicate at a distance, whereas high frequency sounds are used during interactions that involve close contact between individuals. The acoustic signals are perceived by the inner ear or the lateral line system of fishes (Webb, 1989; 2000; Mann et al., 1997; 2001; Weeg et al., 2005).

Sex pheromones in amphibians

In most urodeles, glandular chemical signals play an important role in sex recognition and courtship behaviour (Salthe and Mecham, 1974; Houck, 1986; Kikuyama &Toyoda, 1999). In contrast, anurans depend primarily on auditory signals to accomplish this (Holliday and Tejedo, 1995; Sullivan et al., 1995). Frogs and toads use a few stereotyped vocularisations to communicate with conspecifics. Regarding sexual encounters, there are (i) 'advertisement calls' produced by males to attract females and/or to main territorities, (ii) 'release calls' emitted by males and sexually unreceptive females when clasped by other individuals, and (iii) aggressive calls during interactions between two males (Moore et al., 2005). As in fishes, relatively little is known about the identity of sex pheromones produced by amphibians. There are various amphibian species from which the nature of sex pheromones is known, i.e., 5 urodele (the red-bellied newt, *Cynops pyrrhogaster*, the sword-tailed newt, *Cynops ensicauda*, the terrestrial Jordan's salamander, *Plethodon jordani*, the (lungless) Ocoee salamander (*Desmognathus ocoee)*, and the crested newt (*Triturus cristatus*), as well as 2 anuran species (the magnificent tree frog, *Litoria splendida*, and the mountain chicken frog, *Leptodactylus fallax*). The isolated and characterised amphibian sex pheromones are found to be either small peptides or larger proteins (*Table 7*).

Red-bellied newt (Cynops pyrrhogaster)

Gel-filtration chromatography and two steps of reverse-phase HPLC have revealed that the cloacal abdominal gland of male red-bellied newts secretes a decapeptide, named sodefrin, with an amino acid sequence SIPSKDALLK (Kikuyama et al., 1995; Kikuyama and Toyoda, 1999). This peptide attracts female conspecifics and appears species-specific, since it is not attractive for females of related sword-tailed newts. Synthesis of sodefrin is induced by prolactin and testosterone (Moore et al., 2005), while the neuropeptide arginine vasotocin enhances its release (Kikuyama et al, 2001).

Compared to sodefrin derived from newts from two other regions in Japan, an active sodefrin variant, [Val8] sodefrin (also called aonirin) with the amino acid sequence SIPSKDAVLK, is exclusively expressed in the abdominal glands of specimens from the Nara area (Iwata et al., 2005) and potently attracts females particularly from this area (Nakada et al., 2007). The data indicate the occurrence of geographic variation in newt pheromones. Electro-olfactography has indicated the responsiveness of the female vomeronasal epithelial cells to sodefrin, while those of undeveloped females and males hardly respond (Toyoda et al., 1999; Toyoda and Kikuyama, 2000). Furthermore, the population of the sodefrin-responsive cells increases during the breeding period and according to the sodefrin concentration (Iwata et al., 2003). The axons of vomeronasal receptor cells project to the accessory olfactory bulb, which is located dorsocaudally to the main olfactory bulb (Toyoda et al., 1999).

The sexually developed male newt recognises a sexually responsive female newt by a yet unidentified substance released from the oviduct (Kikuyama et al., 2009). Secretion of this substance is stimulated by prolactin (PRL) and oestrogen.

Sword-tailed newt (Cynops ensicauda)

Biochemical analysis of sword-tailed newt abdominal glands has demonstrated a variant type of sodefrin peptide, designated as silefrin, with the aminosequence SILSKDAQLP, thus with 2 amino acid residues having substitutions Leu for Pro and Gln for Leu at positions 3 and 8,

respectively (Yamamoto et al., 2000). Like sodefrin, silefrin exhibits species-specific bioactivity in regard to attraction of female newts.

Plethodontid salamanders

Plethodontid salamanders use slapping behaviour to convey pheromones from the male mental gland to the female nasal cavity and scratching and pulling behaviour to apply pheromones to the dorsal skin of females, from where the pheromonal substances likely diffuse into the female's peripheral circulation system (Houck and Sever, 1994). Exposure to male mental gland exract evokes a priming effect in male (but not in female) red-legged salamanders (*Plethodon shermani*) by elevating their plasma levels of corticosterone, a metabolic and stress hormone (Schubert et al., 2009), while levels of testosterone in males and oestradiol in females were not influenced.

Anion exchange HPLC and gel-filtration chromatography have identified a 22-kDa protein, termed plethodontid receptivity factor (PRF), which structurally resembles interleukin-6, and a 7-kDa protein pheromone, termed plethodon modulatory factor (PMF), in the mental gland of male Jordan's salamander, *Plethodon jordani* (Rollmann et al., 1999; Palmer et al., 2007a). These factors are also highly expressed in the mental gland of *P. shermani* (Fontana et al., 2007) and activate female VNO neurons in this latter salamander species (Wirsig-Wiechmann et al., 2006). PRF enhances female receptivity and shortens the time for courtship, while PMF lengthens female courtship behaviour. In conjunction with PRF, however, PMF decreases courtship behaviour (Houck et al., 2007). Each of the two components of the male pheromone mixture appears to activate specific populations of female vomeronasal neurons, in this way transmitting different information to the brain (Wirsig-Wiechmann et al., 2006). As for red-bellied newt populations, occurrence of geographic variation in courtship pheromones has been reported for this urodele species. In all eastern Plethodontid species, multiple PRF and PMF transcripts have been found with genetic sequence variation within many of these species (Watts et al., 2004; Palmer et al., 2005). Analysis of mental glands of four different populations showed four isoforms of PRF with significant differences in the presence or absence of each isoform among the populations (Rollmann et al., 2000). For more detailed information on within-species variation in courtship pheromone protein isoforms and transcript sequences, and on mating and pheromone delivery in *Plethodon* species, see Houck (2009) and Woodley et al. (2010). A synthesised recombinant PRF isoform has been demonstrated to mimic the activity of a mixture of PRF isoforms (Houck et al., 2008). Although PMF is hyperexpressed in male mental gland, it is also expressed in different isoforms at low levels in the skin, liver, intestine and kidneys of both sexes (Palmer et al., 2007a). In plethodontid salamanders, PMF evolution is rapid, incessant and driven by positive selection, and more extreme in these aspects than both PRF and sodefrin precursor-like factor (SPF) (Palmer et al., 2010).

Ocoee salamander (Desmognathus ocoee)

SPF is highly expressed in mental glands of Ocoee salamanders (Palmer et al., 2007b). The amino acid sequence of the SPF protein is for approximately 22% homologous to that of the sodefrin precursor, which has been found in the red-bellied newt (Kikuyama and Toyoda, 1999). This peptide significantly decreases time to insemination when applied during courtship (Watts et al., 2007). Data on mental gland SPF nucleotide and amino acid sequences of 28 species from four genera of plethodontid salamanders (*Aneides, Eurycea, Desmognathus* and *Plethodon*) are presented by Palmer et al. (2007b). Analysis of expressed sequence tags derived from unamplified primary cDNA libraries constructed from mental

glands shows marked differences in transcript frequency for PRF, PMF and SPF among Ocee salamander, Jordan's salamander and three-lined salamander (*Eurycea guttolineata*), PRF being absent and SPF being predominantly encoded in Ocee and three-spined salamanders (Kiemnec-Tyburczy et al., 2009). In contrast, PMF appears predominantly encoded in Jordan's salamanders.

Korean salamander (Hynobius leechi)

Like in goldfish, F-prostagandins have been demonstrated to function as sex pheromones in the Korean salamander (Eom et al., 2009): holding water from ovulated females contains higher concentrations of PGF2α, 15-epi-PGF2α, and 13,14-dihydro-15-keto PGF2α compared to those from males or oviposited females, and these prostaglandins are the only three among 19 prostaglandins tested, that induce EOG responses in concentrations as low as 10^{-8} to 10^{-10} M in males and/or ovulated females. Furthermore, like ovulated female holding water, 15-epi-PGF2α appears to significantly induce male reproductive behaviour (i.e., snout contact), when 4 x 10^{-6} M prostaglandin was added to 10 mL water containing a salamander. Body undulation, another characteristic courtship action displayed by male Korean salamanders, was also significantly stimulated after their exposure to female holding water, but not when 15-epi-PGF2α was added to the water in which they were kept. It is still unclear whether F-prostaglandins, like in several fish species (Sorensen et al., 1988; Moore and Waring, 1996; Yambe et al., 1999; Applet and Sorensen, 2007), are released into the (holding) water via urine.

Magnificent tree frog (Litoria splendida) and mountain chicken frog (Leptodactylus fallax)

Although acoustical communication is very important in sex recognition and mating of anurans, the involvement of sex pheromones in these aspects becomes more and more manifest. For example, in the Australian magnificent tree frog, the existence of the sex pheromone splendipherin has been demonstrated, which is produced by male parotid and rostral chin glands (Wabnitz et al., 2000). This pheromone is a peptide comprising 25 amino acid residues with the sequence GLVSSIGKALGGLLADVVKSKGQPA-OH and has a female-attracting activity. Its content becomes elevated during the breeding season. Surface pressure and X-ray refectometry measurements demonstrate that splendipherin moves across the surface of water to reach the female (Perriman et al., 2008). From these studies it appeared thar the sex pheromone has an ordened structure, whereby the peptide's hydrophilic portion interacts with the underlying water and the hydrophobic region is adjacent to the vapour phase. Movement of splendipherin over the water surface is caused by a surface pressure gradient.

Males of the mountain chicken frog, secrete a skin pheromone termed *Leptodactylus* aggression-stimulating peptide (LASP), which has a chemoattractive effect on males and stimulated aggressive behaviours, such as rearing and leaping, and which may play a role in initiating competetive male-male interactions that are associated with the onset of reproductive behaviour (King et al., 2005). Like the magnificent tree frog, the peptide pheromone of male mountain chicken frogs comprises 25 amino acid residues, but with the sequence GLTAALLAAALLVVSSLASAAIGLL-NH2.

Other amphibian species

A pheromonal substance from male abdominal skin glands, that attracts females and evokes an electrophysiological response, has been demonstrated in the crested newt (Malacarne et al., 1984). Females of this species are attracted by newt holding water containing a mixture of

glycoproteins and steroids (Andreoletti et al., 1994). A cDNA, comparable to cDNAs encoding for female-attracting pheromones produced by male *Cynops,* has been obtained from a cDNA library of *T. cristatus* abdominal gland (Cardinali et al., 2000). Whether this cDNA encodes for a pheromone molecule is unclear.

In the abdominal glands of male smooth newts (*Lissotriton vulgaris*) and Montandon's newt (*L. montandoni*), two sister species which differ in male secondary sexual traits but hybridise and produce fertile hybrids, five and three unique pheromone-encoding genes are expressed, respectively (Osikowski et al., 2008).

Male African dwarf clawed frogs, *Hymenochirus* sp. probably release a female-attracting substance through their sexually dimorphic postaxillary skin glands (= breeding glands; Thomas et al., 1993; Pearl et al., 2000). The identity of this putative sex pheromone is, however, unknown. The same counts for the whole-body chemical cues originating from male axolotls (*Ambystoma mexicanum*), which evoke courtship displays in conspecific females (Park et al., 2004).

The tailed frog (*Ascaphus truei*) is another Anuran, that is likely to use intraspecific chemical communication. Results from experiments, in which collected conditioned water from reproductive males and females was used to examine behavioral responses, reveal that both males and females jumped more frequently toward conditioned water from the opposite sex than toward water from their own sex or toward control water (Asay et al., 2005). Although the signal for mate attraction is most likely a waterborne chemical, its source and its chemical composition are still unknown.

In various *Triturus* and other newt species the production of male-attracting pheromones by sexually developed female conspecifics has been noted (Twitty, 1955; Dawley, 1984; Belvedere et al., 1988; Toyoda et al., 1994). In all these cases, the involved sex pheromones have not yet been isolated and charaterised. The same can also be said from the repellent pheromone that is produced by the red-spotted newt, *Notophthalmus viridescens.* This pheromone repels competing males and may act to increase both the sender's and receiver's mating success when the operational sex ratio is male biased (Park and Propper, 2001).

Table 7: Identified sex pheromones and their source and function in amphibians, reptiles and birds.

Species	Pheromone				Author
	Source	Name	Structure	Function	
Urodeles					
Cynops pyrrhogaster	♂-abdominal gland	sodefrin	decapeptide	♀-attractive	a
		aonirin	decapeptide	♀-attractive	b
Cynops ensicauda	♂-abdominal gland	silefrin	decapeptide	♀-attractive	c
Plethodon jordani/shermani	♂-mental gland	PRF	22kDa protein	enhances ♀-receptivity; shortens time for courtship	d-f
		PMF	7 kDa protein	lengthens time for courtship*	d-f
Desmognathus ocoee	♂-mental gland	SPF	23kDa protein**	decreases time to insemination	g-h
Triturus cristatus	♂-abdominal gland		glycoprotein-steroid mixture	♀-attractive	i
Hynobius leechi	ovulated ♀	15-epi-PGF2α	prostaglandin	induces ♂-reproductive behaviour	j
Anurans					
Litoria splendida	♂-skin glands	splendipherin	peptide (25 amino acids)	♀-attractive	k
Leptodactylus fallax	♂-skin glands	LASP	peptide (25 amino acids)	♀-attractive; elicits mating	l
Lizards					
Iberolacerta cyreni	♂-femoral gland		oleic acid	♀-attractive	m
Snakes					
Thamnophis sirt. par	skin		methylketone mixture	♀-attractive; elicits mating	n
Birds					
Anas platyrhynchos	♂-uropygial gland		fatty acid diesters	♀-attractive	o-q
Melopsittacus undulatus	♂-uropygial gland		alkanol mixture	♀-attractive	r

Legend belonging to Table 7: PRF, *Plethodon* receptivity factor; PMF, *Plethodon* modulatory factor; SPF, sodefrin precursor-like factor; LASP, *Leptodactylus* aggression-stimulating peptide; *, In conjuction with PMF, time of courtship decreases (Houck et al., 2007); **, data on nucleotide and amino acid sequences of mental gland SPF's of 28 species from four genera of plethodontid salamanders (*Aneides, Eurycea, Desmognathus and Plethodon*) are presented by Palmer et al. (2007b). a, Kikuyama et al. (1995); b, Iwata et al. (2005); c, Yamamoto et al. (2000); d, Rollmann et al. (1999); e, Palmer et al., 2007a; f, Fontana et al., 2007; g, Palmer et al., 2007b; h, Watts et al., 2007; i, Andreoletti et al. (1994); j, Eom et al., 2009; k,Wabnitz et al. (2000); l, King et al. (2005); m, Martin and Lopez, 2010; n, Mason (1993); o, Jacob et al. (1979); p, Balthazart and Schoffeniels (1979); q, Bohnet et al. (1991); r, Zhang et al. (2010).

Sex pheromones in reptiles

Chemical cues also play an important role in the production and perception of intraspecific sex pheromones for the coordination of reproductive behaviour of reptiles, like lizards (Halpern, 1992; Mason, 1992; Cooper, 1994; Martin and López, 2000; Martin et al., 2007; Martin and López, 2007), turtles (Munoz, 2004; Lewis et al., 2007) and snakes (Mason, 1992; Mason et al., 1998; LeMaster and Mason, 2003; Parker and Mason, 2009). Studies with different lizard species have shown pheromonal secretion of pre-cloacal and femoral glands (Cooper and Vitt, 1984; Alberts, 1990; López et al., 1998). The presence and relative concentrations of the glandular pheromone components vary between sexes and individuals (Alberts, 1990;1992;1993).

Lizards

Males of a lacertid lizard *Podarcis muralis*, are capable of sophisticated pheromonal discrimination of and differential response to surface chemical cues from conspecific males and females, from gravid and nongravid females, and from males and females of the closely related sympatric congener, *P. bocagei carbonelli* (Cooper and Pèrez-Mellado, 2002). Unfortunately, the chemical composition of produced lizard pheromones is unknown. In lizards, pheromonally induced responses are mediated by the highly-developed tongue-vomeronasal system (Kubie et al., 1978; Schwenk, 1993a; Cooper, 1997). Female Iberian wall lizards (*Podarcis hispanica*) prefer scent marks of males with high proportions of cholesta-5,7-dien-3-ol (= provitamin D_3) in their femoral gland secretions, which may signal a better cell-mediated immune response (López and Martin, 2005; López et al., 2009).

GC-MS analysis of femoral gland secretions from the giant girdled lizard or sungazer (*Cordylus giganteus*) has revealed 53 involatile compounds, including casrboxylic acids, alcohols, ketones, esters and steroids of both sexes, among which are probable pheromones (Louw et al., 2007).

GC-MS analysis of preclocal gland secretions from the fossorial, almost blind, Iberian worm lizard, *Blanus cinereus*, has shown 29 major lipid compounds, including several steroids (mainly cholesterol and cholesterol methyl ether), carboxylic acids, and waxy esters, along with squalene (López et al., 2005). Most likely, there are sex pheromones among these chemical substances, since there are clear differences between males and females in the presence or absence of sex-specific compounds and in the relative proportion of some compounds expressed in both sexes. In particular, squalene is much more abundant in males than in females (López and Martin, 2005). This compound has been demonstrated to elicit in males chemosensory and aggressive responses similar to those that has been elicited by precloacal secretions (López and Martin, 2009). It is likely, that squalene allows male discrimination by male Iberian worm lizards. It also may signal dominance status or aggressiveness of these male lizards, because higher concentrations of squalene elicit higher levels of aggression in males.

Female Iberian rock lizards, *Lacerta monticola cyreni* (= *Iberolacerta cyreni*), prefer the scents from males with low fluctuating asymmetry in their femoral pores and from those with higher number of femoral pores, which suggests that the females are able to discriminate males by the quality and/or the amount of their pheromones cues and that they prefer to be in areas marked by males of high quality, thus increasing their chance to produce high quality offspring (Martin and López, 2000). Besides the number of femoral pores and their level of fluctuating asymmetry, some other secondary sexual traits (such as body size and number of blue spots) have been related to variability in the relative proportions of some lipophylic compounds in their femoral gland secretions of male Iberian rock lizards (López et al., 2006).

Males with relatively higher concentrations of hexadecanol and octadecanol in their femoral glands have a higher dominance status, the dominance signaling effect of these compounds being confirmed by increased male tongue-flicking, when they are confronted to these isolated synthetic compounds (Martin et al., 2007). Furthermore, males with a greater T-cell immune response have higher proportions of two steroids (ergosterol and dehydrocholesterol) in their femoral gland secretions. These steroids thus signal the health status of Iberian rock lizard males, which could be an important aspect in the mate choice of female conspecifics. Besides, oleic acid in the femoral gland secretion of these male rock lizards appears an attractant for female conspecifics, the higher its concentration, the more attractive it is (Martin and López, 2010). In *Lacerta monticola cyreni* males (which lacks hexadecanol in their femoral gland secretions), but not in males from *L. monticola monticola*, cholesterol levels in femoral gland fluid are well-correlated with male body size (Martin and Lopez, 2007). Males of this variety are able to discrimnate cholesterol from other compounds with increased tongue-flicking and become more aggressive.

In the femoral gland secretions of male Hungarian green lizards (*Lacerta viridis*) 40 lipophilic compounds have been detected, including several steroids, a-tocopherol, esters of n-C16 to n-C20 carboxylic acids, C12-C20 alcohols, squalene, three lactones and a ketone (Kopena et al., 2009).

The MHC peptide mixture in the released odour of male Swedish sand lizards (*Lacerta agilis*) is a determinant for making them favoured by some females as a mating partner and disfavoured by others (Olsson et al., 2003; 2004). The possible reproductive significance and working mechanism of MHC peptides is discussed below in the chapter on mammalian pheromones.

Turtles

Unknown sex pheromones have been found to be important in chemo-orientation of the stripe-necked terrapin, *Mauremys leprosa* (Munoz, 2004). Outside the mating season, both males and females of this turtle species avoid water that contains chemical cues from conspecifics of the opposite sex. However, during the mating season, male turtles prefer water with chemical cues from females, while females choose water with chemical cues from other conspecific females. Similar results have been described for the common musk turtle, *Sternotherus odorantus* (Lewis et al., 2007). Male European pond turtles, *Emys orbicularis*, also prefer water with female cues, preferably from the largest females, which usually produce more eggs than smaller ones (Poschadel et al., 2006).

Snakes

The majority of studies concerning snake reproductive pheromones have been conducted with northern temperate species, with particular emphasis on the gartner snakes of the genus *Tamnophis* (Ford, 1986; Mason, 1992; Mason et al., 1989). Little is known, however, about the identity of snake sex pheromones. During the breeding season, female Canadian red-rider gartner snakes (*Thamnophis sirtalis parietalis)* produce a pheromone blend, which is sequestered in skin lipids and which is primarily responsible for eliciting male trailing behaviour, courtship behaviour and subsequent mating (Noble, 1937; Gartska and Crews, 1981*;* Garstka et al., 1982. Chemical analysis showed that this sexual attractiveness pheromone mixture was composed of a homologues series of (17) nonvolatile, nonpolar, long-chain saturated and mono(ώ-9 *cis*-)unsaturated methyl ketones (*Table 7*; Mason, 1993; Mason et al., 1989; 1990; Mason and Parker 2010).

Male red-sided gartner snakes (*Thamnophis sirtalis parietalis*) display a courtship preference for larger females (Hawley and Aleksiuk, 1976; Shine et al., 2001). Larger females express pheromone profiles dominated by nonvolatile unsaturated methylketones, whereas smaller females express pheromone profiles higher in saturated methyl ketones (LeMaster and Mason, 2002). This indicates that male red-sided gartner snakes utilise compositional variation in the female sexual attractiveness pheromone to differentiate among potential mates of varying size. The methylketones elicit EOG responses from sensory VNO neurons (Huang et al., 2006), and both their quantity and quality change during the annual reproductive cycle of these snakes (LeMaster and Mason 2001b; Parker and Mason, 2009) . Two sexually isolated populations of red-sided gartner snakes show significant population-specific variation in the composition of the female sexual attractiveness pheromone, causing courtship preference for females from the own den over females from another den (LeMaster and Mason, 2003). In these females, variation is specifically observed in the expressed relative concentrations of individual unsaturated methyl ketones. Although sexual isolation among geographically isolated populations of a species has been documented in a variety of vertebrates (e.g. fish: Ayvazian, 1993, Ziuganov, 1995; amphibians: Houck et al., 1988, Verrell and Arnold, 1989; mammals: Pillay et al., 1995, Pillay, 2000), intraspecific sexual isolation as a result of specific pheromone expression has not yet been observed in other vertebrate species. It is, however, a common phenomenon in insects and often results in the disruption of courting and mating between such isolated populations (Lanier et al., 1972; Löfstedt et al., 1986; Miller et al., 1997; Huang et al., 1998; Wu et al., 1999).

After mating, female red-sided gartner snakes become both unattractive and unreceptive (Gregory, 1974; Ross and Crews, 1977;1978; Whittier et al., 1985; Shine et al., 2000). The loss of attractiveness following mating depends upon male pheromones associated with mating, and which are released though the copulatory fluid secreted by the male at the onset of mating (Shine et al., 2000; Mendoça and Crews, 2001). Loss of the female's receptivity appears to be due to a physiological, neurally mediated response to the sensation of stimuli associated with the act of mating, by which circulating prostaglandin-F2α levels may play an important role (Mendoça and Crews, 2001).

Female gartner snakes and newly emerged males produce male-attractive components, which are quantitatively and qualitatively identical (LeMaster et al., 2008). This explains the courting of these young males by adult males as if they are females During the breeding season, besides females, certain adult male gartner snakes (termed she-males) are also courted by other males. As newly emerged males, she-males probably also produce a similar pheromone blend as females, since in choise-tests, males appear equally interested in she-male trails as in those from females (LeMaster and Mason, 2001a). Gonadal oestrogen production and levels of aromatase activity in the skin could be responsible for the release of the sex pheromone that attract male gartner snakes (Mason, 1993).

Male brown tree snakes, *Boiga irregularis*, display stereotyped courtship behaviours that, like in red-gartner snakes, are triggered by a sex pheromone located in female skin lipids (Greene and Mason, 1998). Besides, during the breeding season, males of this species display ritualised combat behaviour towards other reproductively active males to gain access to females (Andrén, 1986; Schuett and Gillingham, 1989), which is stimulated by a pheromone located in male skin lipids (Greene and Mason, 2000). The nature of these male and female sex pheromones, however, still has to be elucidated. In contrast to gartner snakes, the identified methylketones sequestered in skin lipids of brown tree snakes do not function as sex pheromones.

After mating, males of different snake species deposit a gelatinous plug in the cloaca of the courted female, which makes the female temporarily unattractive and unreceptive, and other males sexually quiescent (Ross and Grews, 1978; O'Donnell et al., 2004). This

phenomenon is due to a pheromone associated with the formation of the copulatory plug. It is, however, unclear whether the plug, the female's cloaca, the male's ejaculate or some combination thereof is the source of this inhibitory pheromone. Field tests showed that, in gartner snakes, squalene could be a major pheromonal component (Shine et al., 2005), but this compound has still to be isolated from one or more potential sources.

Crocodiles

The paracloacal gland is an integumentary organ embedded in the cloacal walls of all modern crocodylians, and a putative source of mating and/or nest-marking pheromones (Weldon and Ferguson, 1993). This gland secretes various esters, hydrocarbons, alcohols, ketones, diketones and other compounds, including many terpenes (Mattern et al., 1997; Schulz et al., 2003; Krückert et al., 2006). Some of the detected ketones, like 11,12-dihydrocembren-10-one in the Chinese alligator (*Alligator sinensis*) and 3,7-diethyl-9-phenylnonan-2-one (dianeackerone) in the African dwarf crocodile (*Osteolaemus tetraspis*) are unique for a crocodile species. In paracloacal gland secretions of the common caiman (*Caiman cocodilus*), the broad-snouted caiman (*C. latirostris*), the yacare caiman (*C. yacare*), the dwarf caiman (*Paleosuchus palpebrosus*), and the smooth-fronted caiman (*P. trigonatus*) a new family of 43 aliphatic carbonyl compounds has been demonstrated (Krückert et al., 2006). This family includes aldehydes, ketones, and β-diketones with an ethyl branch adjacent to the carbonyl group. Some of the detected compounds appeared present in samples of only one sex, such as 2-ethyloctanal in female *C. crocodilus* and *C. latirostris* and 7-ethyldodec-4-en-6-one in males of these species, which may point to possible sex differences in secretion composition. It still has to be proved, however, whether such compounds have a pheromonal function.

Sex pheromones in birds

For a long period, birds were thought to be anosmic and, for sexual activity, to depend on their tetrachromic vision to detect the colourful plumages at sexual maturity (Stoddard, 1980; Keverne, 1999; Webb et al., 2004). Morphological, neuroanatomical and electrophysiological data and numerous data obtained from laboratory experiments have, however, shown that most birds still have a sense of smell (Roper, 1999; Balthazart and Taziaux, 2009; Caro and Balthazart, 2010). Information on the production of sex pheromones is, however, scarce.

Studies with Japanese quail (*Coturnix japonica*) indicate that male brain activation (measured via immunocytochemical detection of c-fos) induced by sexual interactions with a female is significantly affected by olfactory deprivation (Ball and Balthazart, 2001). Changes observed concerned two brain areas that play a key role in the control of male sexual behavior, the hypothalamic medial preoptic nucleus and the bed nucleus of the stria terminalis, therefore suggesting a potential role of olfaction in the control of reproduction.

Few species of birds have been found to produce olfactory signals: (i) the crested auklet, *Aethia cristatella*, which produces a tangerine-scented social odour (Hagelin et al., 2003), (ii) the Australian musk duck, *Biziura lobata*, of which the male produces a musky odour during the breeding season (Gamble, 1966), and (iii) the mallard duck, *Anas platyrhynchos*, of which females contain a pheromone in their single sebaceous gland, located at the base of the tail and called the uropygial (or preen) gland (Bohnet et al., 1991). From this bilobated gland two efferent ducts run to the dorsal body surface, one on each side of the pygostyle (Webster and Webster, 1974). Uropygial gland-extirpated domestic chicken females are less attractive to males (Hirao et al., 2009). The exact role of male and female duck pheromones is unknown, but they probably also have a function in mate attraction, while those produced by the males moreover may play a role in male-male competition. During the mating season, a dramatic change in the composition of the uropygial gland secretion has been found. Under the probable influence of circulating higher oestradiol levels (Bohnet et al., 1991), the usual short-chain monoester wax was completely replaced by long-chain diesters of 3-hydroxy C_8-, C_{10}-, and C_{12}-fatty acids (Kolattukudy and Rogers, 1987; Bohnet et al., 1991), that have been reported to be duck pheromones (*Table 7;* Jacob et al., 1979; Balthazart and Schoffeniels, 1979). Sexual differences in secretion components of uropygial glands were also found in dark-eyed Juncos (*Junco hyemalis*; Soini et al., 2007), Bengalese finches (*Lonchura striata*; Zhang et al., 2009) and budgerigars (*Melopsittacus undulates*; Zhang et al., 2010). The uropygial gland of the male budgerigars was found to poduce a volatile alkanol blend, consisting of octadecanol, nonadecanol and eicosanol, which attracted female conspecifics (Zhang et al., 2010).

A synthetic analogue of a mother-hen odour termed MHUSA (mother-hen uropygial secretion analogue) has an attractive effect *on* and reduces stress-related behaviour *in* chickens (*Gallus gallus*) (Madec et al., 2008a), which probably enhances their welfare (lower corticosterone serum levels) and growth (higher body and filet weights) (Madec et al., 2008b). Under the influence of MHUSA, broiler chickens tend to better assimilate food, leading to a faster growth, because they cope better with stress in their surrounding (Madec et al., 2009). Uropygial gland secretion and MHUSA show a pattern of fatty acids, comparable to the calming pheromones discovered in mammals (dogs, cats, pigs, horses and ruminants; see the concerned paragraphs below). In addition to the female attractant odour, released by the male uropygial gland, chemical signals from the female's uropygeal gland stimulate mating behaviours (the frequency of mounts and copulations) in male domestic chickens (Hirao et al., 2009).

Among birds, petrels have a well-developed olfactory system. Antarctic prions (*Pachyptila desolata*) are able to recognise and follow the odour of a partner (Bonadonna and

Nevitt, 2004). Later data, however, did not support the ability of Antarctic prions to distinguish the sex of a conspecific through its odour (Bonadonna et al., 2009). Chemical analysis of uropygial secretions from two closely related petrel species, the Antarctic prion and the blue petrel (*Halobaena caerulea*) revealed 20 species-specific analytes (including fatty esterified acids, alcohols and a formate) and 19 sex-specific chemosignals (fatty esterified esters; Mardon et al., 2010). If some or all of these compounds can really be considered as pheromones still has to be investigated.

Female Seychelles warblers (*Acrocephalus sechellensis*) appear more likely to obtain extra-pair paternity when their social mate had low MHC diversity, and the MHC diversity of the extra-pair male was significantly higher than that of the cuckolded male (Richardson et al., 2005). This finding points to a possible release of odorous MHC proteins by the males of this bird species. As the female's choice for a mating partner will result in offspring of higher MHC diversity, MHC-dependent extra-pair paternity may provide indirect benefits in the Seychelles warbler, if survival is positively linked to MHC diversity. Ekblom et al. (2005) found no evidence for a role of more or rare male MHC genes in the female's preference for males in the lekking bird species, the great snipe (*Gallinago media*). They did, however, find that some MHC allelic lineages were more often found in males with mating success than in males without mating success. Females thus seem to prefer males with certain allele types. Whether MHC peptides are released as odourants in birds has, however, still to be proven.

Sex pheromones in mammals

Mammalian pheromones can induce alterations in hormone production and are used a.o. for territory marking, alarming conspecifics, maternal recognition, puberty timing, dominance signaling, and induction or modulation of aggression and reproductive events, like sexual attraction and behaviour, oestrous and ovulation, and pregnancy success (for reviews, see Marchlewski-Koj, 1984; Vandenbergh, 1994; Døving and Trottier, 1998; Keverne, 1999; Novoty et al., 1999b; Sharrow et al., 2002). Rodent species are the most studied species in regard pheromone production and the mechanisms of their actions. Generally spoken the identity of mammalian pheromones is poorly understood. From the studies so far carried out, it appears that both proteins and small, low-molecular weight molecules from urine, sweat, and fluid secreted by anogenital glands or specialised exocrine glands are able to function as mammalian pheromones, their production being hormonally dependent.

The major low-molecular weight urinary constituents that have been identified in rodents are alcohols, ketones, aldehydes, hydrocarbons, pyrazines, and nitrils (for references, see *Table 8* and the paragraph on rodents). In other mammalian species certain fatty acids (cows, monkeys) and steroids (pigs, humans) from the urine or secretions of various glands have been found to act (pigs) or are thought to act (humans) as pheromones (for detailed information and references, see the paragraphs on ungulates and primates). In addition to these low-molecular molecules, also high-molecular proteinaceaous compounds like MHC molecules and certain family members of the lipocalin family may function in pheromone or odourant signaling (Beynon et al., 2002; Hedge 2003; Brennan 2004; Beynon and Hurst, 2004; Boehm and Zufall, 2006; Kelliher, 2007; Havlicek and Roberts, 2009).

Introductory information on MHC peptides, lipocalins, MUPs and vomeronasal binding proteins

MHC molecules bind peptide antigens and present them to T-lymphocytes. These cells organise an immune response only if they recognise a foreign (non-self) peptide in conjunction with (self) MHC. There are two main classes of MHC, which comprise class-I and class-II molecules, respectively, of which the latter molecules are expressed on antigen-presenting cells of the immune system (Björkmann and Parham, 1990). By contrast, MHC class-I molecules are expressed on the surface of nearly all nucleated cells, including the neurons in the basal zone of the vomeronasal organ (VNO) (Ishii et al., 2003; Dulac and Torello, 2003; see also the paragraph on rodents and the next chapter), where they may be involved in pheromone detection. Besides, MHC class-1 molecules are thought to serve as odour signals that carry information about individuality (Penn and Pots, 1998a; Reusch et al., 2001; Jacob et al., 2002a; Beauchamp and Yamazaki, 2003; Spehr et al., 2006). This may offer vertebrates the possibility to choose a genetically dissimilar reproductive mate to prevent inbreeding, or to raise or to be raised by a genetically similar conspecific in case of nesting and maternal bonding.

Results of studies with mammals and other vertebrate classes have indicated that MHC may obviously affect fitness, either by influencing reproductive success or progeny survival to pathogens infections (reviewed by Bernatchez and Landry, 2003). Evidence of odour-based MHC mate preferences have been found not only in mammals (for rodents, see Yamazaki et al., 1979; 1999; Beauchamp et al., 1985; Halpin, 1986; Brown et al., 1987; Potts et al., 1991; Boehm and Zufall, 2006; for humans, see Ober et al., 1997; Eggert et al., 1998; Jacob et al., 2002a; Martins et al., 2005; Pause et al., 2006), but also in fish (Landrey et al., 2001; Reusch et al., 2001; Milinski et al., 2004), birds (Freeman-Gallant et al., 2003; Ekblom et al., 2004) and reptiles (Olsson et al., 2003; 2004). MHC-based individual recognition may

occur through the VNO or the main olfactory sytem (MOS) (Yamazaki et al., 1979; Penn and Potts, 1998b; Leinders and Zufall, 2004).

Like in mammals, MHC genes have been well-characterised in fish (Godwinn et al., 2000; Sambrook et al., 2005), amphibians (Bos and DeWoody, 2005; Ohta et al., 2006), reptiles (Radtkey et al., 1996; Miller et al., 2005) and birds (Moon et al., 2005; Aguilar et al., 2006), and MHC peptides influence behaviour decisions in fish (Landry et al., 2001; Reuch et al., 2001; Milinski et al., 2005), reptiles (Olsson et al., 2003; 2004) and birds (Freeman-Gallant et al., 2003; Ekblom et al., 2004). The molecular mechanism of MHC-based mate selection strategies in these vertebrates is, however, unknown. For more information on MHC molecules of nonmammalian vertebrates, see Kaufman et al. (1990) and Bernatchez and Landrey (2003).

Lipocalins (15-30 kDa) form part of a protein superfamily (the calycins), that includes the fatty acid binding proteins, avidins, a group of methalloproteinase inhibitors, and triabin. They are structurally heterogeneous proteins in animals, plants and bacteria (Flower et al., 2000; Grzyb et al., 2006). Lipocalins comprise >100 relatively small proteins secreted in various biological fluids (Parvaiz and Brew, 1987) and share the fundamental tertiary structure of eight β-sheets that form a β-barrel open at one end with α-helices at both the N and C termini (Ganfornina et al., 2000). Inside the β-barrel lies the ligand binding site. The structure of this barrel allows the non-covalent binding of small apolar molecules such as lipids, steroids and odourants, and therefore are particularly suited for pheromonal communication (Grzyb et al., 2006). Lipocalins can be formed by the liver and from there are transported by the circulary system to the kidneys where they are filtered and then appear in the excreted urine (Cavaggioni and Mucignat-Caratta, 2000). These urinary lipocalins are termed major urinary proteins (MUPs) in mice and urinary α_{2u}-globulins in rats, and their synthesis is androgen-dependent.

Mouse MUPs are the product of a multigene family, consisting of 21 genes and 21 pseudogenes (Logan et al., 2008), clustered in a single locus on chromosome 4 (Bishop et al., 1982; Logan et al., 2008). Rat urinary α_{2u}-globulins are encoded by a multigene family, consisting of 9 gens and 13 pseudogenes (Logan et al., 2008), clustered on chromosome 5 (Kurtz DT, 1981; Logan et al., 2008). MUP genes and/or pseudogenes are furthermore found in the horse (*Equus caballus*; 3 genes), the lemur (*Microcebus murinus*; 2 genes and 1 pseudogene), the Orangutan (*Pongo pygmeus*; 1 gene), the chimp (*Pan troglodytes*; 1 gene) the dog (*Canis familiaris*; 1 gene), the pig (*Sus scrofa*; 1 gene), the bush baby (*Otolemur garnetti*; 1 gene), the macaque (*Macaca mulatta*; 1 gene) and the human (*Homo sapiens*; 1 pseudogene) (Logan et al., 2008).

Urinary lipocalins play a role in the capture of volatile small molecules and their slow release from dried urine (or other secreted fluids) over time (Beynon et al., 1999; Hurst et al., 2001; Novotny, 2003; Armstrong et al., 2005), gain entry to the VNO (Wysocki et al., 1980; Halpern and Martinez-Marcos, 2003; Morè, 2006) and may promote the detection of released lipophilic molecules herein by enhancing their solubility in the mucus flow that occurs as a consequence of the VNO pumping mechanism (Brennan, 2004; Beyon and Hurst, 2004; see also next chapter). On the other hand, MUPs may have a direct role in chemosignaling, even when deprived of natural ligands (Mucignat-Caretta et al., 1995; Hurst et al., 1998; Kreiger et al., 1999; Roberts et al., 2010). In wild-stock house mice, a single atypical male-specific MUP of mass 18.9 kDa, termed darcin, stimulates female memory and sexual attraction (Roberts et al., 2010). MUPs themselves or their amino-terminal peptides have furthermore been found to accelerate puberty (Mucignat-Caretta et al., 1995) and trigger ovulation by stimulating the VNO (Morè, 2006). Like urinary MHC molecules, the highly polymorphic MUPs may also function as cues for species, gender, strain and individual recognition (Hurst et al., 1998; 2001; Krieger et al., 1999; Cavaggioni et al., 2003; Brennan, 2004; Beynon and

Hurst, 2004). MUPs further promote neurogenesis and survival of differentiating vomeronasal neurons as they undergo turnover and development from their stem cell population (Xia et al., 2006). The relationships between MUPs and MHC peptides are, however, unclear. Counter-marking behaviour of male mice, in response to marks from competitors, is influenced by individual-specific patterns of MUPs rather than MHC molecules (Hurst et al., 2001), and also rather than volatiles emanating from the scent (Nevison et al., 2003). Both signs of individuality thus may be used in different behavioural contexts. A mixture of MUP-ligand complexes and MHC-related odours may enable animals to establish the age of a scent mark, the gender, and the reproductive, social and health status of the donor, as well as the identity and possible relationship of the donor.

The presence of MUPs in the nasal system of the mouse suggests that some MUP forms have a role similar to that reported for nasal odourant binding proteins (OBPs) and vomeronasal binding proteins (VNBPs) (Pelosi, 1998; Pes et al., 1998). Besides their presence in urine, lipocalins are formed in and secreted by various exocrine glands (e.g., parotid, sublingual, submaxillary, lacrymal, preputial and mammary glands). Consequently, these proteins can be found in mouse (*Mus musculus*) and porcine (*Sus scrofa*) saliva, human (*Homo sapiens*) sweat, human and hamster tears, Norway (= brown) rat (*Rattus norvegicus*) preputial gland secretion (Shaw et al., 1983; Shahan et al., 1987; Archunan et al., 2004; Srikantan and De, 2008), and tammar wallaby (*Macropus eugenii)*, common brush-tail possum (*Trichosurus vulpecula)* and bovine (*Bos taurus)* milk (Collet and Joseph, 1993; Brownlow et al., 1997; Piotte et al., 1998). In golden (= Syrian) hamster (*Mesocricetus auratus*) vaginal fluid, the 17kDa lipocalin has been termed aphrodisin (Singer et al., 1986). Aphrodisin consists of 151 amino acids with two disulphide bonds and a blocked N-terminus (Singer et al., 1986; Henzel et al., 1988). This protein and all other lipocalins may also have a role in chemical communication (see paragraph on hamster pheromones for further information). Most lipocalins share three characteristic conserved amino acid sequence motifs, the kernal lipocalins, to which a.o. the MUPs and α_{2u}-globulins belong (for more detailed information about their structure, see Beynon and Hurst, 2004), while others, the outlier lipocalins, are more divergent family members of which a.o. aphrodisin, OBPs and VNBPs are representatives, and which share only one or two of these amino acid sequence motifs (Flower et al., 2000; Grzyb et al., 2006). Apolipoprotein-D is another lipocalin that binds the odourant heptanoic acid in human axillary sweat (Spielman et al., 1995; Zeng et al., 1996a).

Odourants are almost all chemicals of a molecular weight lower than 300 to 400 kDa, that are volatile enough to reach the nose, irrespective of their structure or chemical proportions (Tegoni et al., 2000). OBPs, are low molecular weight (around 20 kDa), monomeric (e.g., in pigs) or dimeric (e.g., in cows) soluble proteins with an affinity for odourants in the micromolar range (Pevsner et al., 1990; Garibotti et al., 1997; Vincent et al., 2004; Ikematsu et al., 2005). Dimeric OBP is more reactive than monomeric OBPs (Ikematsu et al., 2005). Among vertebrates, OBPs are only found in mammals, and among invertebrates only in insects (Eisthen, 2002). OBPs are synthesised by lateral and septal glands of the nasal epithelium and excreted in the MOS in the hydrophylic extracellular fluid surrounding the olfactory receptors (ORs) (Avanzini et al., 1987; Ohno et al., 1996). As firsts, Pevsner et al. (1985) and Bignetti et al. (1985) have identified OBP from bovine nasal mucosa. Because of its strong affinity to the bell pepper odourant 3-isobutyl-3-methoxy pyrazine (known as the odourant with the lowest detection threshold in humans; Pelosi et al., 1982), the protein has initially been termed pyrazine binding protein. It is located in the MOS in tubulo-acinar cells of the respiratory epithelium of nasal mucosa, including olfactory neurons, and in nasal secretions. OBPs bind inhaled hydrophobic odourant molecules with high specificity, and may transport them to membrane-bound receptors to evoke an olfactory response and/or

terminate olfactory signals by removing the odourants from the sensory epithelium once the receptor has been stimulated (Bignetti et al., 1987; Pevsner and Snyder 1990; Snyder et al., 1988; Bignetti et al., 1988; Steinbrecht, 1998). OBPs are furthermore proposed to act as protectors of the nasal epithelium, which is exposed to airflow and oxidative injuries (Pevsner et al., 1990; Vincent et al., 2000; Grolli et al., 2006). Nevertheless, clear evidence for a role of OBPs in olfaction and odourant perception has not yet been produced (Vincent et al., 2004).

Multiple forms of OBP have been isolated and identified in vertebrates: two in humans (Lacazette et al., 2000), three in pigs; Dal Monte et al., 1991; Scaloni et al., 2001), rabbits (Garibotti et al., 1997), black rats (*Rattus rattus;* Löbel et al., 2001) and bank voles (*Myodes glareolus; Stopková* et al., 2010)), six in mice (Utsumi et al., 1999), and eight in porcupine (*Hystrix crystata*; Felicioli et al., 1993). Furthermore OBP has been demonstrated in elephant (*Elephas maximus*; Lazar et al., 2002), cow (Bianchet et al., 1996; Tegoni et al., 2000; Vincent et al., 2004), sheep *(Ovis aries;* Baldaccini et al., 1986), dog (*Canis familiaris;* D'Auria 2006), northern leopard frog (*Rana pipiens*; Lee et al., 1987), and insects (Prestwich et al., 1989; Vogt et al., 1991; Dickens et al., 1998). Despite their common function of odourant-binding, insect OBPs are evolutionary and structurally unrelated to mammalian OBPs (Pelosi, 1994; 1998; Lazar et al., 2002). As has been shown for the (black) rat (Löbel et al., 1998; 2001; Nespoulous et al., 2004) and the pig (Scaloni et al., 2001), the multiple OBPs that coexist in the nasal mucus may display characteristic binding specificity. The length and the size, but not molecular weight, appear the major selective criteria for recognition among the structural features of odourants involved in OBP binding (Pevsner et al., 1990). In pre-pubertal pigs, OBP is not only expressed in the nasal mucosa but also in the VNO of these farm animals, and is likely to be associated with the coding of pheromonal appeasing signals (Guiraudie et al., 2003).

Thus far, VNBPs have not been found in the MOS. There is a sequence similarity of some OBPs to the two (mouse) pheromone carriers VNBP I (~19 kDA) and VNBP II (~20 kDA), secreted in the VNO mucus by the vomeronasal posterior glands of the nasal septum (Miyawaki et al., 1994; Garibotti et al., 1997). VNBPs and OBPs may interact directly with membrane lipids and membrane-localised protein receptors (Grzyb et al., 2006). Tear and Von Ebner's gland protein (VEG) are also expressed in the mucosa of the MOS and the VNO, and the salivary lipocalin (SAL) from the submaxillary gland also in the VNO (Guiraudie et al., 2003) where they, once released in the mucus of the olfactory organs, may function as an OBP or VNBP. In mouth salivery secretions, VEG probably has a comparable function (binding and transport of chemicals to receptors in sensory epithelium; in this case taste receptors) as the binding proteins have in the mucus of the MOS and VNO (Schmale et al., 1990). Indeed, the high similarity between OBPs from the nasal area and lipocalins from secretory glands suggest a common role in binding the same pheromonal ligands, the former delivering chemical messages to specific receptors, the latter carrying them into the environment (Scaloni et al., 2001).

Based on thus far obtained information, it is proposed that MHC, lipocalin and (vomero) nasal binding proteins may serve as (i) solubilisers and carriers of apolar odourants, which detach from the bound small molecules after drying of the excreted product, (ii) peripheral filters in odourant discrimination by selectively binding certain classes of odourants, (iii) transporter molecules in the mucus of the MOS or VNO, (iv) cleaners of the perireceptor space to remove unwanted and toxic compounds, (v) facilitators of signal transduction by presenting the stimulus molecule in a particular way to the receptor proteins, or (vi) scavenger molecules, which remove or deactivate the bound small molecules after attaching to their receptors (Boudjelal et al., 1996; Steinbrecht, 1998; Lazar et al., 2002). Despite opinions, arguments and indications delivered by various authors, it is still a matter

of debate whether the nonvolatile MHC peptides, lipocalins and (vomero) nasal binding proteins themselves, the protein-small molecule complexes or the small molecules are the active pheromones at the receptor level (Leinders-Zufall et al., 2004; Hurst et al., 2005; Touhara, 2007).

The following paragraphs deal with the currently known data on pheromones in marsupials, rodents, carnivores, ungulates, elephants, and primates, respectively.

Marsupials

Relatively little is known about marsupial semiochemicals and their functionality. From the data available, most has been obtained from the gray short-tailed opossum (*Monodelphis domestica*), a South American nocturnal marsupial, which is supposed to live solitary and nomadic, and changes its home area according to climatic conditions and availability of food (Streilein, 1982). Adult females of this species require pheromonal stimulation for the expression of oestrous (Fadem, 1987). They normally remain in anoestrous when housed with only females, but will enter oestrous within 5-10 days after exposure to a male (Fadem, 1985; Fadem and Rayve, 1985) or to odours remaining in a male's cage after his removal (Fadem, 1987; Fadem, 1989). The pheromone is likely deposited by the male's scent marking. The VNO appears an essential component for transduction of male pheromones required for oestrous induction in these marsupials, since the removal of this organ in female opossums blocks the pheromonal induction of oestrous (Jackson and Harder, 1996).

Pheromones of male grey short-tailed opossums have also been demonstrated to stimulate the onset of puberty in female conspecifics as measured by the occurrence of first oestrous and uterine weight increase (Stonerook and Harder, 1992), the increased rate of body growth and the increased mean diameter of antral follicles in ovaries (Harder and Jackson, 2003). Mature opossums use secretions of their whole underside head (ventral marking), their flank, their chin, their neck and their chest, where the suprasternal gland is located, and anal/cloacal excretions for scent marking (Fadem, 1985; Poran et al., 1993a;b). Females, however, do not possess a suprasternal gland (Fadem and Schwartz, 1986). The identity of male and female pheromones is unknown, but the oestrous-inducing pheromone produced by the male's suprasternal gland is non-volatile (Harder et al., 2008).

Male grey short-tailed opossums nuzzle and scent mark the odours of unfamiliar conspecifics significantly longer than familiar male odours (Poran et al., 1993b). Such nuzzling enables them to dissolve dry conspecific odour deposits in naso-oral secretions and to incorporate them in the VNO, thus recognizing familiar and individual animals (Poran et al., 1993a; Shapiro et al., 1996; Zuri and Halpern, 2005). Based on their findings with conspecific odour investigation, Zuri et al. (2003) concluded that the use of glandular secretions is more common and more effective than urine for intraspecific communication between grey short-tailed opossums, since in the inhabited semiarid conditions glandular secretions are less volatile and are effective for longer periods than urine, and thus would be of greater value for these nomadic-living opossums which meet one another infrequently.

Pairing of isolated female woolly opossums (*Caluromys philander*) with a male or exposure of an isolated female to male urine resulted in oestrous induction in all females (Perret and M'Barek, 1991). These findings point to the involvement of a male urinary pheromone. The latency of occurrence of oestrous in the stimulated females depends upon their sexual state before male stimulation, the inter-oestrous interval being shortened when females were in the luteal phase, and lengthened when they were in the follicular phase of the oestrous cycle. In this way the pheromonal interactions can play a role in synchronizing oestrous cycles in wild females during the dry season, as they regroup to feed on spatially localised food resources.

A characterisation of the fatty acid fraction of the secretions of the two pairs of paracloacal glands and the sternal gland sebum of the common brushtail possum revealed a highly complex distribution of lipids, which were virtually identical in adult males and females (Woolhouse et al., 1994). A unique suite of low-molecular-weight branched-chain carboxylic acids (i.e., C_7-C_9, C_{14}, C_{16} and C_{18} fatty acids) has been shown to be produced by chemical degradation of the holocrine gland secretion. Unlike the holocrine secretion, the apocrine lipids contain larger amounts of regular triaglycerides typical of animal tissue fats. Among the demonstrated fatty acids, $C_{16:0}$ and $C_{18:1\omega9}$ predominate. This possum odour signature is suggested to function as a unique scent marker of the habitat, that might act as an pheromonal attractant to all members of the species.

When in olfactory contact with grouped females, isolated female Stuart's antechinus (*Antechinus stuartii*; a rat-sized, nocturnal, forest dwelling marsupial, also called brown antechinus or MacLeay's marsupial mouse), ovulate synchronously (Scott, 1986). Like all antechinuses, male bown antechinuses die after their first breeding season as a result of stress and exhaustion (Menkhorst, 2001).

Rodents (mice, rats, voles, lemmings, hamsters, and beavers) and rabbits

Most studies on pheromones in rodents have been done with house mice. Urine of grouped female mice delays their oestrous cycle (termed Lee-Boot effect; Van der Lee and Boot, 1955; Drickamer, 1982), while male urine can induce and synchronise the oestrous cycle of non-cyclic females (termed Whitten effect; Whitten, 1956; Bronson and Dezell, 1968), or accelerate puberty onset in females (termed Vandenbergh effect; Vandenbergh, 1967; Lombardi and Whitsett, 1980). Exposure of a recently mated female mouse to another male prevents implantation of fertilised ova (termed the Bruce effect; Bruce, 1959; 1960; Bronson et al., 1969). As in house mice (Lombardi and Vandenbergh, 1977), prairie deermice (*Peromyscus maniculatus;* Teague and Bradley, 1978) and white-footed mice (*P. leucopus;* Rogers and Beauchamp, 1976), oestrous is induced by the presence of a male in a number of arvicoline rodents (voles and lemmings), i.e., pine (*Microtus pinetorum*; Schadler and Butterstein, 1979; Taylor et al., 1992; Solomon et al., 1996), prairie (*M. ochrogaster*; Richmond and Conaway, 1969; Richmond and Stehn, 1976; Hasler and Nalbandov, 1974; Taylor et al., 1992), montane (*M. montanus*), and meadow (*M. pennsylvanicus*; Taylor et al., 1992) voles and brown lemming (*Lemmus trimucronatus;* Coopersmith and Banks, 1983), and in rats (Drewett and Spiteri, 1979; Mora and Cabrera, 1997).

As in mice, male vole chemosignals generally are stimulatory on the female's reproduction cycle, while those from conspecific females are inhibitory (Getz et al., 1983) or not effective (Lepri and Vandenbergh, 1986), at least in prairie voles. In rats sharing a common air supply, the pheromone released during the ovulatory phase lengthened cycles in recipient female rats, while the preovulatory (i.e., follicular phase) pheromone shortened their cycles (McClintock, 1984). Modulation of the rat oestrous cycle was furthermore brought about by pheromones from pregnant and lactating specimens (McClintock, 1983), the cycle being shortened by odours from pregnant rats and lengthened by odours from lactating rats and their pups. In ageing female rats, extended cyclicity and normal gonadotropin secretion is maintained by caging them with fertile males (Nass et al., 1982). Male Wistar rats (an outbred strain of albino rats belonging to the species *Rattus norvegicus*) and from Wistar rats developed Long-Evans rats prefer oestrous to dioestrous urine odour, and dioestrous urine odour to distilled water odour (Pfaff and Pfaffman, 1969; Lydell and Doty, 1972; Lucas et al., 1982; Bressler and Baum, 1996). Rat oestrus odours (i.e., pheromonal stimuli emitted from sexually receptive females) are not only attractive to males, but also produce sexual arousal (Sachs, 1997), and increase LH and testosterone levels in their blood (Graham and

Desjardins, 1980). Pheromonal stimuli of male and female rats influence sexual maturation of unisexually reared male rats by stimulating their hypothalamic 5α-reductase and aromatase activity and increasing their plasma testosterone and oestradiol levels (Dessi-Fulgheri and Lupo, 1982).

The presence of a male has furthermore been shown to hasten puberty not only in house mice, but also in other rodents like prairy deermice (Lombardi and Whitsett, 1980), prairie voles (Hasler and Nalbandov, 1974), meadow voles (Baddalo and Clulow, 1981), collard lemmings (*Dicrostonyx groenlandicus*; Hasler and Banks, 1975), and rats (Vandenbergh, 1976). This male pheromonal effect is possibly due to hastening of the final maturation of the positive feed back system controlling ovarian function by inducing LH release, which in turn results in enhanced ovarian oestrogen secretion (Bronson and Desjardins, 1974). Presence of a male partner during the gestation period facilitates pregnancy maintenance in montana voles (Taylor, 1990) and prairie voles (Dewsbury, 1995). In pine voles, postimplantation abortion is induced by nonfamiliar males and pheromones of them (Schadler, 1981). The effects are thought to be dependent on olfactory, visual and auditory cues, but not on prolonged vaginal stimulation of the female or any other mechanism requiring full contact between sexual partners.

The male effect on the female oestrous cycle in rodents is due to the production of an urinary pheromone which, although there is some confusion about the source of the male chemosignals, is likely produced by the preputial glands (Chipman and Albrecht, 1974; Marchlewska-Koj et al., 1990; Ma et al., 1999a). In mice, preputial glands and their homologous clitoral glands in females are also found to be sources of a sex attractant (Bronson and Caroom, 1971; Pandey and Pandey, 1985) and an aggression-promoting signal (Mugford and Nowell, 1971), respectively. In contrast to urine of female mice, homogenates of clitoral glands do not suppress oestrous in regularly cycling females, indicating that the responsible urinary chemosignals originate from other sources than the clitoral glands (Pandey and Pandey, 1986). Likewise, Bronson and Whitten (1968) conclude that the preputial gland is *not* the source of the pheromone, since bladder urine was found as potent as voided urine in its oestrus-inducing effect. In rats, pheromones in urine excreted from males and females induce various changes in gonadal functions such as reflex ovulation in the absence of coitus and mounting (Johns et al., 1978), a reduction in the oestrous cycle of female rats from 5 to 4 days (Chateau et al., 1976) and oestrous synchrony among female rats living together (McClintock, 1978). Both rat male preputial and female clitoral glands produce sex attractant odours (Noble and Collip, 1941; Stanley and Powell, 1941; Orsulak et al., 1972; Gawienowki et al., 1975; Thody and Dijkstra, 1978; Donohoe et al., 1981). Merkx et al. (1988), however, deducted from their data that pheromones from clitoral glands play only a minor role as sex attractants for female (Wistar) rats, and are of opinion that urinary, vaginal or total body odours may be more important in determining the attractiveness of an oestrous female. Apart from preputial or clitoral glands, rat cheek glands are able to produce pheromonal attractants which have a reproductive or social function (Kannan and Archunan, 2001b).

The pheromonal low-molecular weight molecules that thus far have been identified in urine or in preputial glands of rodents are listed in *Table 8*. Novotny and co-workers have to be particularly mentioned as pioneers in the field of rodent pheromone identification and functioning. They have demonstrated that 2-*sec*-butyl-dihydrothiazole and 2,3-dehydro-*exo*-brevicomin from male mouse urine potentiate inter-male aggression (Novotny et al., 1984; 1985; 1990a), attract females (Jemiolo et al., 1985) and induce oestrus (Jemiolo et al., 1986;1991). Additionally, they have shown that the sequiterpenes *E,E,*-α-farnesene and *E*-β-farnesene from male mouse urine may exert the same effects (Jemiolo et al., 1986; Novotny et al., 1990b; 1999b). Furthermore, *n*-pentyl acetate, and *cis*-2-penten-1-yl acetate, 2-

heptanone, *trans*-4-hepten-2-one, *trans*-5-hepten-2-one, 2,5-dimethyl pyrazine, present in the urine of adult females, has been found to delay puberty in juvenile females (Novotny et al., 1986), while 6-hydroxy-6-methyl-3-heptanone from male mouse urine accelerates it (Novotny et al., 1999a). Gas-chromatography linked mass-spectrometry (GC-MS) analysis of urine of mature Swiss male mice demonstrated ten different compounds of which five are specific to males, namely 3-cyclohexene-1-methanol (I), 3-amino-*s*-triazole (II), 4-ethyl phenol (III), 3-ethyl-2,7-dimethyl octane (IV) and 1-iodoundecane (V) (Achiraman and Archunan, 2002). The compounds (II) and (IV) are similar to 2-*sec*-butyl-dihydrothiazole and 2,3-dehydro-*exo*-brevicomin, which have been reported in several strains of male mice (Novotny et al., 1985; Cavaggioni and Mucignat-Caretta 2000). A mixture of these latter two pheromones synchronises oestrous cyclicity in adult female mice (Jemiolo et al., 1986), but appears unable to block pregnancy, indicating that, in different behavioural contexts, different urinary components are involved in signaling maleness (Brennan et al., 1999). The two male urinary compounds and 4-ethyl phenol act as sex attractants for female Swiss mouse and induce aggression toward males (Achiraman and Archunan, 2002).

Isobutyl amine and isoamyl amine, that were also demonstrated in the urine of male mice, accelerate puberty in female mice (Nishimura et al., 1989). Puberty delay is also caused by 2,5-dimethyl pyrazine, 2-heptanone, *trans*-5-hepten-2-one, *trans*-4-hepten-2-one, *n*-pentyl acetate, and *cis*-2-penten-1-yl acetate which are present in the urine of female mice (Novotny et al., 1986). In the urine of female house mice, isocroctylhydrazine, 4-methyl-2-heptanone and auzulene are specific for the pro-oestrous stage, while 1-H-cyclopop-e.auzulene, caryophyllene and copanene are specific for the oestrous stage (Achiraman and Archunan (2006). However, 1-iodo-2-methyl undecane, present in both pro-estrous and estrous urine, has been demonstrated to be involved in the attraction of male mice and is thus considered to act as a sex pheromone ((Achiraman and Archunan, 2006; Achiraman et al., 2010).

Compared to the volatile, urinary chemical compounds present in the urine of house mice, those of mound-building mice (*Mus spicilegus*) quantitatively and qualitatively differ (Soini et al., 2009). Paricularly, a series of volatile and odouriferous lactones, the presence of coumarin, and the absence of 2-sec-butyl-4,5-dihydrothiazole and other sulphur-containing compounds are characteristic for mound-building mice. The role of the characteristic compounds is under investigation. Male, but not female, mouse urine has furthermore been demonstrated to contain (methylthio)methanethiol, which induces a neural response in a subset of mitral cells of the MOB, and serves as an attractant for females (Lin et al., 2005).

In contrast to male urine, female mouse urine contains at least 13 sulphated steroids, of which corticosterone-21-sulphate, 4-pregnene-11β,20,21-triol-3-one-21-sulphate and 4-pegnene-11β,21-diol-3,20-dione-21-sulphate (Nodari et al., 2008; Hsu et al., 2008) have been identified. Sulphated steroids are detected in nanomolar concentrations by de vomeronasal organ of both males and females. Urine concentrations of these sulphated steroids increases approximately threefold in stressed animals. Thus, in regard the mouse, the urinary presence of sulphated steroids signals a female, while the urine concentration of particular sulphated steroids reflects the physiological condition of females. Oestradiol and testosterone have been found in urine and faeces of both mouse sexes (Muir et al., 2001; Vella and deCatanzaro, 2001; deCatanzaro et al., 2003; 2004; Beaton and deCatanzaro, 2005). Intranasal administration of androgens and oestrogens, 17β-oestradiol in particular (given in three doses, each of 140 ng on days 2-4 of gestation), disrupts intrauterine implantation (deCatanzaro et al., 1991; 2001; 2006), while urinary oestradiol and testosterone levels from novel mice approach values (up to 20 ng/ml and 160 ng/ml, respectively) sufficient to disrupt early pregnancy in nearby inseminated females, and thus may explain the Bruce effect (deCantanzaro et al., 2006).

The hormonally dependent low-molecular weight (volatile) compounds found in the urine of pine vole (Boyer et al., 1989), California mice (*Peromyscus californicus;* Jemiolo et al., 1994) and prairie deermice (Ma et al., 1999b) structurally contrast with the identified pheromonal urinary compounds in the house mouse. Furthermore, the numbers of volatile constituents in these three species are relatively low (30-40 *vs* about 100 in house mice), and they do not show qualitative gender differences. A number of urinary low-molecular weight molecules, however, show quantitative differences with sex, age and the endocrine state, which might indicate their pheromonal role. Urine thus contains a mixture of urinary volatile compounds. Different compounds may evoke the same response and the same compound may elicit different effects in males and females. The use of pheromonal blends may increase the specificity of recognition, or allow the transmission of more complex messages (Dulac and Torello, 2003). In spite of that, distinct behavioural and hormonal responses in mammals can be caused by a single chemical substance or a relative simple synthetic mixture (Novotny, 2003). Different concentrations of pheromones elicit distinct behavioral responses and may even result in diametric effects (Beauchamp et al., 1982; Humphries et al., 1999; Nevison et al., 2003; Hurst and Beynon, 2004). They can also evoke distinct endocrine changes (Drickamer, 1982), and may influence the onset of puberty (Drickamer and Assmann, 1981; Drickamer, 1986a;b).

Lipid extracts of the preputial glands of male mice contain about 5% of fairly volatile *n*-alkyl-(I) acetates, of which the major constituents are hexadecyl, hexadecenyl and octadecyl acetates, while those of females contain less than 1% long-chain alkyl acetates (Spener et al., 1969) with relatively less hexadecyl acetate and more hexadecenyl acetate than in male glands. Although experimental proofs have not been delivered, the acetates are believed to act in chemical signaling. As mentioned before, two terpenic male urinary constituents, *E*,*E*,-α-farnesene and *E*-β-farnesene have been found to induce oestrus (Jemiolo et al., 1986; Novotny et al., 1990b; 1999b). These terpenes appear to be elevated in dominant male urine when compared to subordinate or control males. These two urinary compounds were absent in the bladder urine of males, whereas they were the most prominent constituents of the perputial gland's aliquots. A mixture of these two farnesenes was as effective as the homogenate of the intact preputial gland in inducing oestrous cycles in grouped female mice (Ma et al., 1999a).

In rat male and female scent glands (i.e., preputial, clitoral and cheek glands), pheromones exist as a mixture of alcohols, aldehydes, acids of unsaturated or saturated aliphatic or aromatic compounds (Dominic, 1991; Kannan et al., 1998; Kannan and Archunan, 1999; 2001a;b). GC-MS analysis of clitoral gland homogenates of mature oestrous female rats reveal the presence of three compounds in higher concentration, i.e., the aromatic ketone 6,11-dihydro-dibenz-b,e-oxepin-11-one, the aliphatic unsaturated alcohol 2,6,10-dodecatrien-1-ol-3,7,11-trimethyl(*Z*), and 1,2-benzene-dicarboxylic acid butyl (2-ethyl-propyl) ester (Kannan and Archunan, 2001a) of which only the first compound was not found in male rat preputial glands (Kannan et al., 1998; *Table 8*). Odour preference tests demonstrated that the first compound attracts male conspecifics, while the other two attract both sexes.

Male preputial glands contain eleven different compounds among which three compounds constitute major fractions of which two (e.g., 2,6,10-dodecatrien-1-ol-3,7,11-trimethyl(*Z*) and di-*n*-octyl phalate) serve as sex attractants for female rats (Kannan et al., 1998). Dodecyl proprionate is a small pheromonal molecule, which is formed in the preputial glands of male pups, and induces maternal licking of the anogenital region (Brouette-Lahlou et al., 1999). Psychosocial stress factors (housing and rank status) have significant effects on the volatile content of preputial glands, certain compounds being quantitively enhanced in glands of single-housed (26 from 55 compounds) and dominant (5 from 55 compounds) rats

(Pohorecky et al., 2008). From preputial glands and voided urine of the brown rat (*Rattus norvegicus*), in total 36 compounds were characterised, of which 2 were male-specific (4-heptanone and phenol) and 3 other compounds (squalene, 2-heptanone and 4-ethyl phenol) were more abundantly present in males, whereas 2 (*E*,*E*-β-farnesene and *E*-α-farnesene) were more abundant in females (Zhang et al., 2008a). Based on these sex differences, the 7 compounds are considered to be putative pheromones, the male ones playing a role in sex attractiveness. In castration and testosterone-supplementation experiments with brown rats, the volatile preputial gland compounds farnesol, lanosterol, oxirane and geranyl lialool isomer, as well as a 18 kDa protein came forward as testosterone-dependent, suggesting that the latter substance could be a carrier for the four volatile components which might act as sex pheromones (Ponmanickam et al., 2010).

GC-MS analysis of cheek gland secretions from sexually mature and reproductive active male and female Wistar rats identified alkanes, aliphatic acid esters and alcohols (Kannan and Archunan, 2001b). In male rats, cheek gland secretions contained predominantly three compounds, i.e., di-*n*-octyl phthalate (I), 1,2-benzene diacarboxylic acid butyl (2-ethyl hexyl) ester (II), and 1,2 benzene dicarboxylic acid (2-methylpropyl) ester (III), whereas in female cheek glands two compounds, 1,2-benzene dicarboxylic acid (2-methylpropyl) ester, and 2,6,10 dodecatrien-1-ol, 3,7,11-trimethyl-(*Z*, *E*) were the major products. Compound I from males only attracted females, whereas compounds II and III of males and the two female compounds attracted both sexes (*Table 8*).

Golden hamster vaginal secretions at oestrus abundantly release dimethyldisulphide (a male sex attractant according to O'Connell et al. (1978), but not confirmed by Petrulis and Johnston (1995)), methylthiobutyrate (an airborne molecule signaling female oestrus to males, which serves as a precursor of dimethyldisulphide; Singer et al. (1983)), and the odourant 2-isobutyl-3-methoxy-pyrazine, which are bound in this fluid to the lipocalin aphrodisin (Briand et al., 2000). The protein aphrodisin is formed in cervical glands and the glands of the lower parts of the uterus (Kruhøffer et al., 1997), and also in the parotid glands of female hamsters (Mägert et al., 1999). Briand et al (2004b) identified five other compounds specially bound onto natural aphrodisin, i.e. hexadecanol, 1-octadecanol, *Z*-9-octadecen-1-ol, *E*-9-octadecen-1-ol and 1-hexadecanol, which are also described as part of insect pheromone blends (Arn et al., 1992). A similar phenomenon has been observed in regard to the farnesenes secreted by male mouse preputial glands (see Ma et al., 1999a). Aphrodisin is highly homologous with rat OBP-1 and OBP-1F, which are able to transport volatile odourants towards olfactory receptors through the nasal mucus (Briand et al., 2000). It is thought to stimulate male copulatory behaviour through the vomeronasal organ (Clancy et al., 1984; Kroner et al., 1996). Like these OBPs, aphrodisin may interact directly with membrane lipids and membrane-localised protein receptors (Grzyb et al., 2006). However, as for the olfactory lipocalins, it is still unclear if aphrodisin itself has pheromonal activity or needs the combination with small molecular ligands to be active (Briand et al., 2004a).

Beavers (*Castor sp.)* produce scent marks which may play a role in territory advertisement, sex recognition, sex attraction, colony size advertisement and food marking (Butler and Butler, 1979; Müller-Schwarze and Heckman, 1980). The scent mark is produced by externalised castor sac fluid (castoreum) and anal gland secretion (Walro and Svendsen, 1982). The nonglandular castor sacs (or oil sacs; Müller-Schwarze and Heckman, 1980) and the holocrine anal glands are paired structures, located in the wall of the rectum just inside from the anus. The castoreum (a yellow liquid) of castor sacs the Eurasian beaver (*Castor fiber*) consists of numerous compounds of which over 40, including C_{14}-C_{19} alcohols, ketones, C_5-C_{22} carboxylic acids, phenols, aldehydes and amines, have been identified (Lederer, 1949; Gronneberg, 1978-1979). In contrast, the straw to light brown anal gland secretion contains over 50 different wax esters (Gronneberg (1978-1979). In the USA,

Table 8: Source and effect(s) of identified rodent and rabbit low-molecular weight pheromonal compounds.

Pheromonal compound	Source	Effect	Author
2-*sec*-butyl-4,5-ihydrothiazole 2,3-dehydro-*exo*-brevicomin	♂ mouse urine	♀-attraction; oestrous induction; intermale aggression	a-f
α-and β-farnesenes	♂ mouse urine	♀-attraction; oestrous induction; intermale aggression	g,h
4-ethyl phenol	♂ mouse urine	♀-attraction; intermale aggression	f
isobutyl amine; isoamyl amine	♂ mouse urine	♀-puberty acceleration	i
6-hydroxy-6-methyl-3-heptanone	♂ mouse urine	♀-puberty acceleration	j
(methylthio) methanethiol	♂ mouse urine	♀-attraction	k
oestradiol; testosterone	novel ♂ mouse urine	pregnancy loss	l
n-pentyl acetate; *cis*-2-penten-1-yl-acetate 2-heptenone; *trans*-4-hepten-2-one; *trans*-5-hepten-2-one; 2,5-dimethylpyrazine	♀ mouse urine	♀-puberty acceleration	m
corticosterone-21-sulphate; 4-pregnene-11β,20,21-triol-3-one-21-sulphate; 4-pegnene-11β,21-diol-3,20-dione-21-sulphate	♀ mouse urine	signals physiological status ♀	n,o
1-iodo-2-methyl undecane	♀ mouse urine	♂-attraction/premating behaviour	p,q
dodecyl proprionate	rat pup preputial gland	maternal anogenital licking	r
4-heptanone; phenol; squalene; 2-heptanone, 4-ethyl phenol	rat preputial gland/ urine	♀-attraction	s
di-*n*-octyl phalate	♂ rat preputial and cheek gland	♀-attraction	t,u
6,11-dihydro-dibenz-b,e- oxepin-11-one	♀ rat clitoral and cheek gland	♂-attraction	u,v
2,6,10-dodecatrien-1-ol-3,7,11-trimethyl-(*Z*); 1,2-benzene-dicarboxylic acid butyl (2-ethyl-propyl) ester	rat clitoral and preputial gland	♀- and ♂-attraction	u
1,2-benzene-diacarboxylic acid butyl (2-ethyl hexyl) ester; 1,2 benzene-dicarboxylic acid (2-methylpropyl) ester	♂ rat cheek gland	♀- and ♂-attraction	v
1,2-benzene-dicarboxylic acid (2-methylpropyl) ester; 2,6,10 dodecatrien-1-ol, 3,7,11-trimethyl-(*Z,E*)	♀ rat cheek gland	♀- and ♂-attraction	v
dimethyl sulphide	hamster vaginal secretion	♂-attraction	w
methyl thiobutyrate	hamster vaginal secretion	signals oestrus	x
2-methylbut-2-enal	rabbit milk	nipple search response pups	y

Legend belonging to Table 8: a, Novotny et al., 1984;b, Novotny et al., 1985; c, Novotny et al., 1999b; d, Jemiolo et al., 1985; e, Jemiolo et al., 1986; f, Achiraman and Archunan, 2002; g, Novotny et al., 1990b; h, Ma et al., 1999b; i, Nishimura et al., 1989; j, Novotny et al., 1999a; k, Lin et al., 2005; l, deCatanzano et al., 2006; m, Novotny et al., 1986; n, Nodari et al., 2008; o, Hsu et al., 2008; p, Achiraman and Archunan, 2006; q, Achiraman et al., 2010); r, Brouette-Lahlou et al., 1999; s, Zhang et al., 2008a; t, Kannan et al., 1998; u, Kannan and Archunan, 2001a; v, Kannan and Archunan, 2001b; w, O'Connoll et al., 1978; x, Singer et al., 1983; y, Schaal et al., 2003.
Note: Possible pheromonal effects of MUPs, MHC-peptides and ESPs, mentioned in the text, are omitted in this table.

expansion of beaver populations (*Castor canadensis*) causes dramatic damage to developed land by flooding and destruction of valuable trees (Larson and Gunson, 1983; Peterson and Payne, 1986). The removal of excessive beavers by live-trapping and transplanting of beavers becomes more and more expensive and available sites for new indroductions are restricted. Therefore, application of repellent pheromones on beaver sites could be a good option to prevent colonisation of these sites. When unoccupied beaver sites in New York State were for two years experimentally scented with a mixture of beaver castoreum and anal gland secretion, these sites were colonised less often than unscented control sites (Welsh and Müller-Schwarze, 1989). Thus, territorial pheromones may be useful as repellents for beavers. Unfortunately, no further experiments on this topic have been published.

Pubs of the European rabbit (*Oryctolagus coniculus*) prefer the abdominal odour of lactating females compared to the odour of either nonlactating, nonpregnant or pregnant females (Coureaud and Schaal, 2000). The mammary pheromone triggers orocephalic responses involved in the quick localisation of nipples and sucking, and promotes rapid appetitive learning of novel odourants, acting as a potent organiser of neonatal cognition (Couread et al., 2010). The abdominal pheromone does not depend on the vomeronasal organ to release nipple-search behaviour and nipple attachment (Hudson and Distal, 1986). In rabbit milk, 2-methylbut-2-enal has been identified as a pheromone that in concentrations between 10^{-8} and 10^{-2} g/ml triggers pups to exhibit stereotypical searching behaviour and nipple attachment (Schaal et al., 2003). Its effect generalises across strains and breeds, but is ineffective in closely related species (Luo et al, 2004). In the chin gland of this species, 34 volatile components were identified that consist primarily of aliphatic and aromatic hydrocarbons (with a series of alkyl-substituted benzene derivatives as main constituents), which vary in composition among different populations (Hayes et al., 2002). The rabbit uses the chin gland secretion to maintain dominance hierarchies in the wild. When a rabbit becomes dominant, 2-phenoxyethanol appears in his chin gland secretion, which probably functions as a fixative for released chin gland scent compounds, so that his scent will persist in the environment and not fade rapidly (Hayes et al., 2003).

Apart from small, volatile compounds, the urine of rodents contains high levels of MUPs. The MUP concentration in mouse urine is as much as 10^6 times greater than soluble MHC fragments (Beynon and Hurst, 2003), while the profile of expressed MUP isoforms may vary substantially, depending on strain, gender and hormonal levels (Clissold and Bishop, 1982; Johnsen et al., 1995; Robertson et al., 1996; Armstrong et al., 2005; Stopková et al., 2007). Secretion of plasma protein into urine, proteinuria, is not a normal physiological process in mammals, because of the high molecular mass of the plasma proteins which prevents their glomerular filtration in the kidney. Proteinuria in rodents is an exception and is possible because of the relative low molecular weight of the filtered proteins (Finlayson et al., 1959). As mentioned in the introduction of the paragraph on mammalian pheromones, MUPs play a role in the capture of volatile small molecules and their slow release from dried urine

(or other secreted fluids) over time, gain entry to the VNO to promote the detection of released lipophilic molecules and, like urinary MHC molecules, may function themselves as signs for species, gender, strain and individual recognition. Individual mice do not express the entire repertoire of MUPs, i.e. 21 genes and 21 pseudogenes (Logan et al., 2008), but only 4-12 isoforms of these proteins (Robertson et al., 1997; Beynon and Hurst, 2003; Armstrong et al., 2005; Cheetham et al., 2007). This variable expression pattern could function as a protein 'barcode' defining individuality.

Five pheromonal components are identified as MUP ligands, i.e. 2-*sec*-butyl-4,5-dihydrothiazole, 2,3-dehydro-*exo*-brevicomin, α- and β- farnesenes and 6-hydroxy-6-methyl-3-heptanone (Bocskei et al., 1992; Novotny et al., 1999a; Sharrow et al., 2002). MUP isoforms 1,2,8, and 9 show very similar affinities for 2-*sec*-butyl-4,5-dihydrothiazole, 6-hydroxy-6-methyl-3-heptanone, and 2,3-dehydro-exo-brevicomin (Sharrow et al., 2002). MUP-7, however, has approximately twofold higher affinity for 2-*sec*-butyl-4,5-dihydrothiazole but approximately twofold lower affinity for the other pheromones, whereas MUP-4 has approximately 23-fold higher affinity for 2-*sec*-butyl-4,5-dihydrothiazole and approximately fourfold lower affinity for the other pheromones. Perez-Miller and allies (2010) confirmed the high specificity of MUP-4 for 2-*sec*-butyl-4,5-dihydrothiazole and remarked that it is the only MUP isoform known to be expressed in the vomeronasal mucosa. MUP-1, abundantly secreted into the circulation by the liver, functions as a regulator for systemic glucose and lipid metabolism, probably through autocrine/ paracrine regulation of hepatocyte metabolic activity (Zhou et al., 2009; Hui et al., 2009).

Together with their bound urinary ligands, urinary proteins may elicit various effects in rodents, like attraction of females, repelling of males, aggression in males, oestrous synchronisation, acceleration or delay of puberty in females, and ovulation induction (Vandenbergh et al., 1975; Mucignat-Caretta et al., 1995; 1998; 2004; Jemiolo et al., 1989; Novotny et al., 1999a;b; More, 2006; Chamero et al., 2007). The proteins probably enter the VNO of a conspecific after sniffing, when its nose touches the anogenital region. In that case, it has to be noted that protein-bound small molecules cannot be regarded as volatile. The role of the VNO in detecting urinary chemical signals has been demonstrated in experiments with vomeronasalectomised female rats (Mora et al., 1985) and pine voles (Solomon et al., 1996), which failed to undergo reproductive activation when housed with males, and showed a prolonged cycle length, respectively. In female mice, interruption of vomeronasal afferents eliminates the acceleration of puberty in juveniles, the suppression of oestrous cyclicity in grouped females and the blockage of pregnancy by exposure of unfamiliar males (Reynolds and Keverne, 1979; Kaneko et al., 1980; Bellringer et al., 1980). When confronted to female odours, both agonistic and copulatory behaviours, and reflexive release of LH are blocked in male mice lacking a functional VNO (Wysocki et al., 1982; Clancy et al., 1984; Coquelin et al., 1984). Small molecules, like the male mouse pheromones 2-*sec*-butyl-4,5-dihydrothiazole and 2,3-dehydro-*exo*-brevicomin, can elicit in-vitro responses from vomeronasal neurons in the absence of MUPs (Moss et al., 1998; Leinders-Zufall et al., 2000).

In adult rats, α_{2U}-globulins have been demonstrated as glycosylated rat MUPs (Cavaggioni and Mucignat-Caretta, 2000) with pheromonal significance (Krieger et al., 1999). Lipocalins have also been found in preputial and clitoral glands, as were higher molecular weight proteins (35, 50, 60, 70 and 90 70 kDa in preputial glands; 90 kDa in clitoris glands) (Archunan et al., 2004; Kamalakkannan et al., 2006). The authors prematurally concluded from their data that the proteins from the preputial glands are important for the maintenance of reproductive and dominance behaviours, and that the glandular 20 kDa proteins may have a role in pheromonal communication through their potency to bind ligands. Hard evidence for that proposition has, however, not delivered. Recently, Rajkumar et al. (2010) detected an 18.5 kDa α_{2U}-globulin in the preputial gland of

the Indian commensal rat, *Rattus rattus* and the presence of farnesol 1 and 2 bound to this globulin. It is, however, unknown if the demonstrated volatile compounds are involved in intraspecific chemocommunication. Additionally, vomeromodulin, a 70 kDa glycoprotein with N-linked glycans (Mechref et al, 1999) which is highly concentrated in the mucus of the VNO but absent in mucus of the MOS, is considered as a putative pheromone transporter in lateral nasal, posterior septal and vomeronasal gland secretions to promote access of pheromones to the VNO receptors (Khew-Goodall et al., 1991; Krishna et al., 1994). In the rat, vomeromodulin (and thus not the lower molecular weight VNBP) and OBPs have been localised in different and complementary sets of nasal glands (Khew-Goodell et al., 1991; Krishna et al., 1994; Steinbrecht, 1998). Coexistence of multiple OBPs in the nasal mucus may indicate that each of the proteins display a characteristic binding specificity. Indeed, binding studies have shown that rat OBP-1 interacts only with aromatic heterocyclic odourants such as pyrazine derivatives (Löbel et al., 1998), whereas OBP-2 does so with long-chain aliphatic aldehydes and carboxylic acids (Nespoulous et al., 2004), and OBP-3 interacts strongly with odourants composed of saturated and unsaturated ring structure (Löbel et al., 2001).

In mice, and probably most other mammals, secreted MHC molecules may function in pheromone or odourant signaling by offering them the possibility to discriminate between genetically similar or dissimilar conspecifics and thus, to prevent inbreeding (Potts et al., 1994). This may unmask deleterious recessive alleles in the population and reduces reproductive success in competitive natural environments (Maegher et al., 2000). Nesting with MHC-similar individuals and maternal bonding are other mouse behaviours that rely on the ability to discriminate MHC-based individuality (Manning et al., 1992; Yamazaki et al., 2000; Brennan and Peele, 2003; Potts et al., 1991). Mouse MHC class-I peptides form a pheromonal recognition memory in females, and alters social preference of males (Leinders-Zufall et al., 2004). When added to familiar male's urine, which otherwise had no effect, a MHC peptide from an unfamiliar male caused pregnancy block. It is, however, not yet clear whether MHC peptides on theirselves are sufficient to cause this effect, because the experiments were done in presence of urine, and so do not exclude a possible role of MHC peptides only in combination with bound volatile scents.

Another peptide with pheromonal significance has been found to be secreted in tears from the extraorbital lacrimal gland of male mice. This 7-kDa male-specific peptide is termed exocrine gland-secreting peptide I (ESP1) and elicits action potentials in female VNO neurons through its binding to a V2R-type vomeronasal receptor (Kimoto et al., 2005; for V2R-type receptors, see the chapter on olfactory receptor sites), V2Rp5 in particular (which is expressed in both male and female mice and thus does not show a sexually dimorphic expression pattern; Haga et al., 2007). ESP1-V2Rp5 interaction results in sex-specific signal transmission to the amygdaloid and hypothalamic nuclei via the accessory olfactory bulb (Haga et al., 20010). ESP1 is a member of the ESP family, which (like MUPs) shows a sex- and strain-specific expression pattern (Kimoto et al., 2007). The ESP family consists of 38 members in mice and 10 members in rat, but is absent from the human genome. Fifteen from the 38 mouse ESPs are expressed in the extraorbital lacrimal gland, the Harderian gland, and/or the submaxillary gland, and thus are expected to be secreted in tear fluid and saliva (Touhara, 2007). ESP peptides consist of 60 to 160 amino acids. In addition to the male-specific ESP1, a female-specific ESP (ESP36) has been found in the extraorbital lacrimal gland of adult BALB/c mice (Kimoto et al., 2007). The authors conclude from their findings that sexual dimorphism and strain differences of ESPs and their reception in the VNO is indicative for the ESP family conveying information about sex and individual identity via the vomeronasal system. Thus, the chemosensation of this nonvolatile peptide family by direct contact is one of the possibilities for sociosexual communication in rodent species. The

involvement of the male pheromone ESP1 in female sexual behaviour has been demonstrated by Kikusui and allies (referred by Touhara et al., 2008) and Haga et al. (2010). The number of ESP family members has quickly decreased within rodent species, successively followed by their disappearance somewhere prior to the appearance of primates (Kimoto et al., 2006) and the loss of VNO function (Meredith, 2001; Rodrigues et al., 2000; Rodrigues and Mombaerts, 2002).

Like MUPs, 2-heptanone, 2,5 dimethylpyrazine, α- and β-farasenes and sulphated steroids, ESP1 has been found to be present at micromolar concentrations in mouse urine (Novotny et al., 2007; Nodari et al., 2008). The urinary pheromones can reach the VNO at a concentration of ~ 1% of that in urine (He et al., 2010). At this level, urinary pheromones elicit responses from a subset of VNO neurons that are tuned to sex-specific cues and provide unambiguous identification of the sex and strain of animals. Low cencentrations of urine do not activate these cells but another population of neurons, which are masked by high-concentration pheromones. VNO neurons respond to ESP1 at (pheromonal) concentrations of 10^{-13} to 10^{-5} M, and to the female pheromone 2,5 dimethylpyrazine (Novotny et al., 1986) at concentrations of 10^{-11} to 10^{-5} M (He et al., 2010). It is supposed that the differential activation of VNO neurons trigger neural circuits that lead to distinct behavioural outputs. Dominant and/or better fed male rodents produce more pheromone and are more attractive to females (Ferkin et al., 1994; Hurst, 2009).

Carnivores

Felines

Wild carnivores, like tigers (*Panthera tigris*), lions (*Panthera leo*), cheetahs (*Acinonyx jubatus*), and leopards (*Panthera pardus)* frequently discharge a lipid-rich fluid through the urinary channel to mark their territory and attract the opposite sex (Poddar-Sarkar and Brahmachary, 2004). It is considered to be a source of pheromones (Poddar-Sarkar and Brahmachary, 1997). In lions and cheetahs, the fluid being sprayed is predominantly a male activity, while in tigers both sexes demonstrate a high marking frequency (Brahmachary et al., 2006). Although several authors believed that the marking fluid used by lions (Schaller, 1972; Bertram, 1978) and tigers (Schaller, 1967; Smith et al., 1989) is a mixture of urine and anal gland secretion, it is nowadays accepted that the urinary system and not the anal glands excretes the fluid (Anderson and Vulpius, 1999).

The marking fluid of tigers contains numerous volatile odourant molecules and a considerable amount of lipids (Brahmachary and Dutta, 1979; Brahmachary et al., 1992; Poddar-Sarkar, 1996; Brahmachary, 1996; Poddar-Sarkar and Brahmachary, 1999). The lipid fraction in the tiger's marking fluid comprise cholesterol ester, wax esters, triglicerides, diglicerides, monoglycerides, free sterols, phospholipids, free fatty acids (Poddar-Sarkar, 1996), aldehydes and ketones (Brahmachary et al., 1992). Although the previously reported tiger urine constituents butane-1,4-diamine (Brahmachary and Dutta, 1979) and 2-acetyl-1-pyrroline (Brahmachary, 1996) were not detected by Burger and coworkers (2008), these latter authors identified 98 other volatile compounds and elemental sulphur in the urinary marking fluid of Bengal tigers, of which the majority are alkanols, alkanals, 2-alkanones, branched and unbranched alkanoic acids, dimethyl esters of dicarbolic acids, γ- and δ-lactones and compounds containing nitrogen or sulphur. Among these compounds, ketones, fatty acids and lactones are dominant, which could point to a possible pheromonal role. Besides, the authors identified proteins (16-69 kDa), among which the carboxylesterase cauxin, previously identified in the urine of cats (see below, the paragraph on felines).

Table 9 shows detected compounds in excretions of the tiger and other wild felines. Among the eleven free fatty acids quantitatively estimated, relatively high proportions of

palmitoleic (biosynthesised from palmitic acid by the action of the enzyme δ-9-desaturase) and myristic acids and highly unsaturated fatty acids, among which isohexanoic and heptanoic acids, were demonstrated (Poddar-Sarkar, 1996; Poddar-Sarkar and Brahmachary, 1999). Especially, the palmitic acid and triglycerid content is relatively high. Free fatty acids may function as pheromones in a number of mammals, including the tiger (Brahmachary et al., 1992; Poddar-Sarkar et al., 1991). The lipids serve as fixatives for sprayed volatile pheromonal compounds to attach them for a longer period on leaves of trees and shrubs, stones, etc. in the tiger's territory. The lipid fraction of sprayed cheetah fluid also contains diglycerides, triglycerids and free sterols (Poddar-Sarkar and Brahmachary, 1997), but no aldehydes and ketones, which are prominent in tiger and leopard marking fluid (Brahmachary et al., 1992; Poddar-Sarkar and Brahmachary, 2004). The cheetah marking fluid contains acetic, (iso)propionic, (iso)butyric, (iso)valeric, hexanoic, and (iso)octanoic acids (Poddar-Sarkar and Brahmachary, 1997).

The fatty acid pictures of the leopard's marking fluid do not dramatically deviate from those of the cheetah and tiger (Brahmachary and Dutta, 1981; Poddar-Sarkar and Brahmachary, 2004). Like tigers (Brahmachary et al., 1992) and dissimilar with cheetahs (Poddar-Sarkar and Brahmachary, 1997), leopards contain the free fatty acids isohexanoic acid and heptanoic acid in their marking fluid (Poddar-Sarkar and Brahmachary, 2004). Although the total lipid extracted in the cheetah is much higher (3.87 mg/ml) than in the tiger (1.88 mg/ml; Poddar-Sarkar, 1996) and leopard (1.15 mg/ml; Poddar-Sarkar and Brahmachary, 2004), the fixative property of cheetah lipid is considerably less, which means that smelly volatiles escape from the cheetah marking fluid far more rapidly than in that of tigers and leopards. The lipid profile of the Asiatic lion marking fluid differs at certain points from the other big cats, such as the relative absence of sterol, monoglycerids and diglycerids, and the higher proportions of wax esters and sterol esters (Brahmachary and Singh, 2000).

In addition to fatty acids and lipid, the marking fluid of wild carnivores contain various amines (*Table 9*). 2-Phenylethylamine has been put forward as a biochemical marker of the pheromonal mixture of amines present in the marking fluid of (Bengal) tigers (Brahmachary and Dutta, 1979). It has also been demonstrated in leopard marking fluid (Poddar-Sarkar and Brahmachary, 2004). This amphetamine is known as a "love drug" for humans, women especially (Doughty, 2002), since it is a naturally occurring compound in the brain, where it releases the opioid peptide β-endorphin in the mesolimbic pleasure-centres (Millward, 2001). Likewise, phenylethylamine gives people a sense of well-being and contentment, while it peaks during orgasm. This mood elevator is a component of chocolate (DiTomaso et al., 1996). Therefore, it is thought be the reason why chocolate is believed to be an aphrodisiac (Doughty, 2002). In contrast to the studies of Brahamachary and Dutta (1979), Banks et al. (1992) were unable to detect 2-phenylethylamine in the marking fluid and the anal sac secretion of a Bengal and a Sumatran tiger. These latter authors, however, showed the presence of seven structurally comparable compounds in the marking fluid, i.e., ammonia, methylamine, dimethylamine, trimethylamine, triethylamine, propylamine, and butane-1,4-diamine (putrescine). Besides phenylethylamine, the basic fraction of the leopard's marking fluid contains dimethyl amine, triethylamine, ethylenediamine, putrescine, cadaverine (Poddar-Sarkar and Brahmachary, 2004). Whether amines play an important role in chemical communication of tigers is still unclear. Resident bacteria may play a role in the production of more specific tiger pheromones, as they do in the anal glands of various other carnivores (Donovan, 1969; Gorman et al., 1974; Albone et al., 1977), and in human skin and vagina (Michael et al., 1974).

2-Acetyl-1-pyrroline, is seen as an elusive volatile aromatic compound in the marking fluid of tigers and leopards, but not in that of African lions and cheetahs (Brahmachary, 1996; Poddar-Sarkar and Brahmachary, 2004). More recent GC-MS studies on the territorial

marking fluid of male tigers were, however, unable to confirm the presence of this compound in tiger urine (Burger et al., 2008). 2-acetyl-1-pyrroline was first reported as the principal component of the pleasant aroma of basmati and other fragrant varieties of rice (Buttery et al., 1982), in which they could be useful in fighting bacterial, viral and fungal attacks (Brahmachary, 1996). 2-acetyl-1-pyrroline has also been demonstrated in mung bean of Bengal (Brahmachary and Ghosh, 2002).

Apart from free fatty acids, amines and the aroma molecule 2-acetyl-1-pyrroline, acetone and acetaldehyde are components of the leopard's marking fluid that is sprayed through the urinary channel (Poddar-Sarkar and Brahmachary, 2004). In the cheetah, 27 and 37 constituents have been identified in the headspace vapor of the urine of male and female cheetah, respectively (Burger et al., 2006). These constituents are hydrocarbons, short-chain ethers, aldehydes, saturated and unsaturated cyclic and acyclic ketones, 2-acetylfuran, dimethyl disulphide, dimethyl sulphone, phenol, myristic acid (tetradecanoic acid), urea, and elemental sulphur, and are all present in very small quantities. In the lion, 55 volatile compounds were detected in urine samples (Andersen and Vulpius, 1999) of which seven were considered potentially species-specific (i.e., acetone, 2-butanone, 1-pentene, 2-pentylfuran, heptanal, 1,2-cyclooctadiene and diethylbenzene). Six other constituents are specific to male lions and eleven specific for females (*Table 9*). Furthermore, males had a significantly higher absolute content of 2-butanone in their urine than females, whereas females had a significantly higher relative content of acetone than males. The authors conclude that in combination qualitative and quantitative aspects of the scent marks are likely to be able to carry a message of sex identity.

Civet cats rub their bottom on trunks and on stones of his territory to signal its presence to females and to rivals. In these carnivores, anal glands most likely are involved in the production of a territorial musky odour. The secretion of the African civet cat, *Civetticus (= Viverra) civetta,* contains waxes, short-chain fatty acids, skatol and civetone (Kingston, 1984). Short-chain carboxylic acids have also been demonstrated in the anal gland secretion of the binturong (or beermarter; *Arctictis binturong)* (Weldon et al., 2000). Unfortunately, although such compounds, other fatty acids, specific amines, 2-acetyl-1-pyrroline, acetone, acetaldehyde or other demonstrated chemicals are characteristic components of the marking fluid of wild carnivore species and are considered as putative pheromones, there is as yet no conclusive proof for such a supposition.

Adult domestic cats (*Felis catus*), males in particular, spray their urine in backward direction against all kinds of objects such as walls, posts and shrubs. As for the big feline species living in the wild, spraying of tomcat odour is meant to mark its territory (Hart, 1975). Besides, the smell of a male can evoke typical oestrous behaviour in cats (Michael and Keverne, 1968). Although it is conceivable that both the urine and the anal glands contain tomcat odour, its production by the anal glands has not yet been proven (Bland, 1979). The urine odour of tomcat is caused by a lipid component (Fox, 1975), which is produced by the first segment of the proximal convoluted tubules of the kidneys (Gairns and Morrison, 1949). The quantity of the renal lipid varies with the sex, reproduction state and age of he animal (Lobban, 1955; Bland, 1979). Triglyceride is the major ingredient of the renal tubular lipid, which furthermore contains cholesterol and cholesterol ester (Helmy and Longly, 1966). In female domestic cats, spraying is predominantly a feature of the oestrous period. The urine smell of oestrous females, positively influences the frequency of flehmen in tomcats (Verberne, 1976) and thus probably functions to inform the male about the condition of the female (McDougal, 1977). In cats, flehmen is a characteristic male behaviour which consists of the raising of the upper lip with the mounth half-open and rapid tongue movements (Pageat and Gaultier, 2003). Blocking of the entrance of the VNO negatively influences the

Table 9: Detected compounds, among which putative pheromones, in excretions of wild carnivores.

Animal	Source	Detected compounds
Tiger	urine	cholesterol ester, wax esters, monoglycerides, diglicerides, triglicerides, sterols, phospholipids (a), aldehydes, ketones (b,c), palmitoleic acid, myristic acid, isohexanoic acid, heptanoic acid (a-d), ammonia, methylamine, dimethylamine, trimethylamine, triethylamine, propylamine, butane-1,4-diamine (e), 2-phenylethylamine (f), 2-acetyl-1-pyrroline (g) and lactones (c)
Cheetah	urine	diglycerides, triglycerids, sterols (h), (iso)propionic acid, (iso)butyric acid, (iso)valeric acid, hexanoic acid, and (iso)octanoic acid (h)
Leopard	urine	isohexanoic acid, heptanoic acid, 2-phenylethylamine, dimethyl amine, triethylamine, ethylenediamine, putrescine, cadaverine, 2-acetyl-1-pyrroline, acetone, and acetaldehyde (i)
Lion	urine	wax esters, sterol esters, (relative absence of) sterols, monoglycerids, and diglycerids (j), 55 volatile compounds, among which the potentially species-specific acetone, 2-butanone, 1-pentene, 2-pentylfuran, heptanal, 1,2-cyclo-octadiene and diethylbenzene, the male specific 3-methyl butanal, 3-methyl-1-butylamine (and possibly also 1,4-dihydro-1,4-ethenonaphthylene, 3-pentanone, and methyl-ketone), and the female specific pentane, ethanol, 2-methylbutanol, heptane, S-methylthioethanoate + coelute, 2-heptanone, alkane, 2,2,- dimethyl-3-hexanone, dimethyl phtalate and diethylphtalate (k)
African civet cat	anal gland secretions	waxes, short-chain fatty acids, skatol, and civetone (l)
Binturong (beermarter)	anal gland secretions	short-chain fatty acids (m)
Bobcat	urine	mercapto-3-methyl-1-butanol, 3-methyl-3-methylthio-1-butanol, and 3-methyl-3-(2-methyldisulfanyl)-1-butanol (n)
Ocelot	urine	2-amino-7-hydroxy-5,5-dimethyl-4-thiaheptanoic acid (o)

Legend belonging to Table 9: a: Poddar-Sarkar, 1996; b: Brahmachary et al., 1992; c: Burger et al., 2008; d: Poddar-Sarkar and Brahmachary, 1999; e: Banks et al. 1992; f: Brahmachary and Dutta, 1979; g: Brahmachary, 1996; h: Poddar-Sarkar and Brahmachary, 1997; i: Poddar-Sarkar and Brahmachary, 2004; j: Brahmachary and Singh, 2000; k: Andersen and Vulpius, 1999; l: Kingston, 1984; m: Weldon et al., 2000; n: Mattina et al., 1991; o: Datta and Harris, 1951.

flehmen frequency in tomcats, showing the involvement of this organ in the perception of urinary pheromones (Verberne, 1976).

Table 10 shows the chemical compounds with a putative pheromonal function in domestic carnivores. The amino acid felinine, 2-amino-7-hydroxy-5,5-dimethyl-4-thiaheptanoic acid, is abundant in domestic cat urine and is excreted at a rate of around 95 mg/day in male cats and around 19 mg/day in female cats (Westall, 1953; Hendriks et al., 1995). Chemically synthesised felinine and native felinine purified from urine develop an odour during storage that is characteristic of cat urine (Hendriks, 1995). Therefore, it has been postulated that feline acts as a teritorial marker for intraspecies communication (Hendriks et al., 1995) and serves as a putative precursor of a pheromone that plays a role in attracting females (Tarttelin et al., 1998). Felinine is also present in the urine of ocelots (*Leopardus pardalis* or *Felis pardalis*), but not in that of the lion, tiger and puma (*Puma concolor*) (Datta and Harris, 1951). However, the biological significance of felinine to cats is still a matter of speculation. The urine of male cats contains a high concentration of proteins (~0.5-1.0 mg/ml) of which over 90% consists of a 70 kDa component named cauxin (Miyazaki et al., 2003). This major urinary protein is a carboxylesterase that is expressed only in the kidney and secreted from the proximal straight tubular cells into the urine, where it regulates felinine production by hydrolysis of the felinine precursor 3-methylbutanol-cysteinylglycine to felinine and glycine (Miyazaki et al., 2006). Glycine is then reabsorbed in the proximal straight tubular cells, whereas felinine is excreted and derivatised in the urine into sulphur containing volatile compounds. 3-mercapto-3-methyl-1-butanol, 3-mercapto-3-methylbutyl formate, 3-methyl-3-methylthio-1-butanol, and 3-methyl-3-(2-methyl-disulphanyl)-1-butanol are identified as candidates for felinine derivatives, the levels of these compounds being both sex and age dependent. It is not unlikely that these volatile compounds are used as (sex) pheromones in cats for conspecific recognition and reproductive purposes. Indeed, preliminary behavioural studies of Miyazaki et al. (2006) have demonstrated that male and female cats show interest in 3-mercapto-3-methyl-1-butanol, but not in felinine. These observations suggest that one or more of the felinine derivatives rather than felinine itself may function as a pheromone. Except for 3-mercapto-3-methylbutyl formate, the demonstrated butanols were also detected in bobcat (*Lynx rufus*) urine that contains felinine (Mattina et al., 1991). It is notable, that the role of the urinary protein cauxin as an enzyme in the synthesis of a putative cat pheromone is different from the pheromone binding function that rodent MUPs have (see the paragraph on rodents). The odour of cat urine is unpleasant for many people and therefore a problem. Development of cauxin-specific inhibitors could be an excellent tool to solve the odour problem, since felinine production will then be blocked. In urine of great cats (*Panthera*), felinine is absent, while cauxin is present but only in extremely low levels (Gang et al., 2010). These latter authors have recently sequenced the gene encoding cauxin, *CES7*, in 22 species within the cat family and have shown that this gene has undergone rapid evolutionary change, which points to rapid changes in the regulation of urinary pheromones among the different cat species, which in turn may influence social behaviour, such as territorial marking and recognition of conspecifics.

Swabs of vaginal secretions from oestrous cats contain a detectable amount of valeric acid, which points to a high concentration of this compound in the vaginal secretions (Bland, 1979). Both isomeric forms of valeric acid occur in high concentration in the valerian (*Valeriana officinalis* Linnaeus) root, which is known for its attractiveness to cats (Bland, 1979). The odour of valeric acid induces marked changes in the behaviour of cats (Endröczi et al., 1956). Males search about and become restless, while females exhibit sexual behaviour patterns. Females become restless, lick themselves, and show lordotic posture and the series of motions characteristic of copulation. Furthermore, valeric acid odour evokes electrical

activity in the rostral hypothalamus of female anoestrous cats similar to that observed in untreated oestrous cats (Lissák, 1962). The latter author has also demonstrated that application of vaginal contents from oestrous cats onto the nose of an anoestrous cat evokes the same behavioural changes and responses to vaginal stimulation as does the odour of valeric acid (Lissák, 1962). The findings indicate that valeric acid in the vaginal secretion of oestrous female cats may function as a female cat pheromone by inducing or facilitating oestrus in other conspecific females.

In contrast to male receivers who pay more attention to sprayed urine, female cats are more interested in skin gland secretions. Cats have scent glands on multiple places on their body, including their feet, tail, and face (Moore, 1995). In the face, the glands are located around the eyes, below the ears, and on the cheeks, the lips, and the chin. By rubbing their face on various objects, they are leaving their scent thus marking their territory. When a cat rubs a human, he is marking the person with his scent, thus claiming him or her as its possession. Besides urine, cheek gland secretions of females, appear to contain pheromones that inform tomcats about the female's hormonal status (Verberne and de Boer, 1976). Thus far, five different facial scent marking pheromones have been isolated from the cheek's sebaceous gland secretions of which the function of only three is known (MacDonald, 1985). The pheromones are mixtures of fatty acids. One pheromonal mixture is a sexual marker produced by male cats, which seems to improve the efficiency of the sexual display (Pageat and Gaultier, 2003). It is deposited during sexual behaviour, when the male rubs his face on several points at the site where he is with the female cat, and consists of oleic acid, palmitic acid, propionic acid, and *p*-hydroxyphenylacetic acid. Another facial pheromone mixture, consisting of 5β-cholestan acid 3β-ol, oleic acid, pimelic acid and *n*-butyric acid, decreases the probability of aggressive behaviour between a cat and another individual (for example another cat, a human, or a dog with whom the cat lives together). A human is marked by the cat with these fatty acids and a glycoprotein termed Fel-d-1. This skin glycoprotein is mainly produced by the sebaceous glands, those from the cheeks particularly (Mata et al., 1992; Carayol et al., 2000), and comprises two 17-kDa subunits, which have a similar structure as pheromone binding proteins and has a high affinity for hydrophobic small molecules like the fatty acids that are components of the secreted pheromonal mixture (Zielonka et al., 1994; Carayol et al., 2000). It is thought that the glycoprotein is secreted to protect the secreted pheromonal fatty acids in order to enhance the probability that the pheromone mixture is detected. In skin collected from various sites of the body, in all 10 isoforms of Fel-d-1 were detected, ranging from 7 to 40 kDa (Bienboire-Frosini et al., 2010). A third facial pheromonal mixture consists of oleic acid, azelaic acid, pimelic acid and palmitic acid, and may appease cats and may help them by making the environment feel familiar and safe. Synthetic analogues of such pheromonal fatty acids are used in behavioural medicine, because of their therapeutical features (Pageat, 1995; Pageat and Gaultier, 2003).

Exposure to a synthetic analogue of feline facial pheromone (Feliway; US Patent number 5709863) significantly lowers the mean level of urine spraying in cats having a problem with it in households (Mills and Mills, 2001; Ogata and Takeuchi, 2001), increases grooming and interest in food in clinically ill cats (Griffith et al., 2000), and calms cats in unfamiliar surroundings but does not reduce struggling in cats before venous catheterisation (Kronen et al., 2006). Feliway, is a composition containing an emulsion comprising a mixture of fatty acids or derivatives thereof (oleic acid, azelaic acid, pimelic acid and palmitic acid) and a compound of vegetal origin, i.e. an extract of *Valeriana officinalis*, that has an attractive effect on cats (Pageat, 1995), and which, as has been mentioned before in this chapter, is present in vaginal secretions of oestrous cats (Bland, 1979). Pageat and Gaultier (2003) note that the range of action of such pheromones could cover the wild field of reduction of stress, and that therefore the use of pheromones should not be reduced to

Table 10: Detected compounds, among which putative pheromones, in excretions of domestic carnivores.

	Source	Detected compounds	Functions
Cats	♂♀ urine	2-amino-7-hydroxy-5,5-imethyl-4-thiaheptanoic acid (felinine) (a,b)	territorial marker (Hendriks et al., 1995) and putative precursor of a pheromone that plays a role in attracting queens (c)
		3-mercapto-3-methyl-1-butanol, 3-mercapto-3-methylbutyl formate, 3-methyl–3-methylthio -1-butanol, and 3-methyl-3- (2-methyldisulfanyl)-1-butanol (d)	tranquillise kittens and adult conspecifics in stress situations
	sebaceous glands around nipples of nursing queens	oleic acid, palmitic acid, linoleic acid, mysteric acid, lauric acid, and stearic acid (e,f,g)	tranquillise kittens and adult conspecifics in stress situations
	♂♀ sebaceous glands lining anal sacs	short-chain fatty acids (h)	signal reproductive status and induce sexual behaviour
	vaginal secretion of oestrous females	valeric acid (i)	attracts cats (i), makes males restless, stimulates female sexual behaviour (j), and induces or facilitates oestrus in other female conspecifics (k)
	cheek glands	oleic acid, palmitic acid, propionic acid, and *p*-hydroxyphenylacetic acid (f)	improve the efficiency of the sexual display
		5β-cholestan acid 3β-ol, oleic acid, pimelic acid, and *n*-butyric acid (f)	decrease the probability of aggressive behaviour between a cat and another individual
Dogs	sebaceous glands around nipples of nursing bitches	oleic acid, palmitic acid, linoleic acid, mysteric acid, lauric acid, pentadecanoic acid, and stearic acid (f,g,l)	tranquillise puppies and adult conspecifics in stress situations
	♂♀ anal sac secretion	short-chain fatty acids and trimethylamine (h)	scent-mark territory
	vaginal fluid of oestrous females	methyl *p*-hydroxybenzoate (m)	stimulates ♂ sexual arousal and sexual behaviour

Legend belonging to Table 10: a, Westall, 1953; b, Hendriks et al., 1995; c, Tarttelin et al., 1998; d, Miyazaki et al., 2006; e, Pageat, 1995; f, Pageat and Gaultier, 2003; g, Pageat, 2000; h, Preti et al., 1976; i, Bland, 1979; j, Endröczi et al., 1956; k, Lissák, 1962; l, Green, 2003; m Goodwin et al., 1979. For effects of synthetic feline and canine appeasing pheromones, see text.

treatment of behavioural disorders in pets, but should be included in a strategy of improving their welfare in veterinary structures (during examination and hospitalisation) and in breeding networks (separation from the mother and transport). To evaluate the use of pheromones for treatment of undesirable behaviour in cats, Frank et al. (2010) systematically reviewed the existing scientific literature over the period January 1998 through December 2008 (i.e. Frank et al., 1999; Hunthausen, 2000; Griffith et al., 2000; Mills and Mills, 2001; Ogata and Takeuchi, 2001; Gunn-Moore and Cameron, 2004; Kronen et al., 2006) to identify, assess the quality of, and to determine outcomes of studies conducted. They came to the shocking conclusion that all studies provided insufficient evidence for the effectiveness of feline facial pheromone for management of idiopathic cystitis or calming cats during catheterisation and lack of support for reducing stress in hospitalised cats.

Besides facial glands, pedal (sweat) glands, like supracaudal glands and interdigitous glands, preputial glands and anal glands are involved in the cat's territory marking (Pageat and Gaultier, 2003). Furthermore, the glands may produce alarm pheromones. Little is known about the chemical structure of possible pheromonal compounds. The secretion of the sebaceous glands lining the anal sacs comprises short-chain (C_2-C_6) fatty acids (Berüter, referred by Preti et al., 1976), is rich in lipids (MacDonald, 1985) and contains large amounts of the Fel-d-1 protein that may bind produced pheromones (Dornelas de Andrade et al., 1996). In the cat, the functions of sebaceous glands of the prepuce or the vulva and the mucous glands of the urethra or the genitals are not well studied yet (Pageat and Gaultier, 2003).

Canines

GC-MS analysis of vaginal secretions and urine, which were collected from female beagles (*Canis familiaris)* during their oestrous cycles, demonstrated methyl *p*-hydroxybenzoate in the vaginal secretions of dogs that were in oestrus (Goodwin et al., 1979) (*Table 10*). Although this compound causes a relatively feeble response in the electrical activity of the dog's olfactory receptor cells (Tonosaki and Tucker, 1985), male dogs become sexually aroused (i.e., they exhibit intense anogenital investigation and licking of female conspecifics, the sexual bowing posture, and frequent urination) and attempt to mount anoestrous or spayed females, when small amounts of methyl *p*-hydroxybenzoate are applied to their vulvas and males are confronted to these bitches (Goodwin et al., 1979).

The secretion of the sebaceous glands around the nipples of a nursing bitch from 3-4 days post partum onward to 2-5 days after the weaning of the puppies (i.e., 4 months of age) has an appeasing effect on puppies and adult dogs in stress situations (Pageat, 2000; Pageat and Gaultier, 2003; Green, 2003). The chemical structure of the appeasing pheromones of the bitch corresponds to that of queens, mares, cows, ewes and does in having oleic acid, palmitic acid and linoleic acid as the three fatty acids that could be considered as the 'mammalian appeasing message' (Pageat and Gaultier, 2003). The other components in the pheromonal message create its species-specificity, and always include mysteric acid in a varying ratio. In the bitch, species-specificity of the appeasing pheromone is caused by mysteric acid, lauric acid, pentadecanoic acid, and stearic acid (Pageat, 2000; Pageat and Gaultier, 2003). In the queen's appeasing pheromone, pentadecanoic acid is lacking, and so the ratios of each component are different from those in the bitch. There is a balance between acids and methyl-esters in the mammary sebaceous gland secretions. Both have the same efficiency according to the pheromonal message but the methyl-esters are more volatile (Pageat, 2000; Pageat and Gaultier, 2003).

In combination with behaviour therapy, treatment with a collar impregnated with a synthetic equivalent to dog appeasing pheromone (DAP; Ceva Santé Animale; trade mark name "Comfort Zone™"; US Patent number 6077867) for 6 weeks is effective in dogs,

having problems when travelling in the car (Gandia Estellés and Mills, 2006). The DAP-treated dogs showed more improvement in somatic signs (salivation, vomiting, urination) than in behavioural signs (barking, activity). DAP- treatment through a plug-in diffuser also appears significantly effective for dogs that show signs of fear in response to fireworks (Sheppard and Mills, 2003; Mills et al., 2003). Unfortunately, no placebo control group has been investigated in the referred papers, i.e., a group receiving a dummy plug-in diffuser that did not dispense DAP. A placebo control also lacks in the studies of Gaultier et al. (2005), who have shown that DAP has a better effect on dogs showing distress (destructiveness, excessive vocalisation and house soiling) when separated from their owners, than clomipramine which is regularly used to treat this type of problem. Police dogs wearing a DAP-impregnated collar show, however, significantly less stress symptoms during training than dogs wearing a placebo collar in which the components of DAP were destroyed (Schroll et al., 2004). Thus, DAP really seems to cause a dog to feel more relaxed and more safe. However, after systematically reviewing the scientific literature from January 1998 through December 2008 to evaluate the use of pheromones for treatment of undesirable behaviour in dogs, Frank et al. (2010) came to an astonishing conclusion. Only one study (Deneberg and Landsberg, 2008) yielded sufficient evidence that DAP reduces fear or anxiety in dogs during training, whereas six studies yielded insufficient evidence of the effectiveness of DAP for treatment of noise phobia (Sheppard and Mills, 2003; Levine et al., 2007), travel-related problems, fear or anxiety in the veterinary clinic, and stress- and fear-related behaviour in shelter dogs as well as vocalizing and house soiling in recently adopted puppies (Todd et al., 2005; Gandia Estelles and Mills, 2006; Mills et al., 2006; Taylor and Mills, 2007). After 2008, thus beyond the period studied by Frank and collegues (2010), placebo-controlled experiments of Gaultier et al. (2009) and Kim et al. (2010) once again described that DAP treatment results in lowered signs of distress and fear, and improves socialisation in newly adopted puppies and hospitalised dogs, respectively. In a clinical setting, DAP furthermore has been demonstrated to affect behavioural and neuroendocrine perioperative stress responses by modification of lactotropic axis activity, and in this way may improve the recovery and welfare of dogs undergoing surgery (Siracusa et al., 2010). Hopefully, these latter studies were sufficiently verified.

Remarkably, chicken uropygial gland secretions of domestic chickens show a pattern of fatty acids comparable to the mammalian calming pheromones which, like in mammals, reduce stress-related behaviour in these birds (Madec et al., 2008a,b; see the paragraph ‘Sex pheromones in birds’).

Except the possible pheromonal cheek and perioral glands that are spread throughout the chin, lips, and cheeks of cats, dogs additionally possess an ear gland. The facial complex seems to be involved, especially in social relationships (Pageat and Gaultier, 2003). Information about the chemical composition of these gland secretions in dogs is, however, scarce.

Chromatographic analysis of the volatile compounds from the anal sac secretions of male and female beagles and coyotes (*Canis latrans*), has shown short-chain (C_2-C_6) acids and trimethylamine as major constituents, which may scent-mark their territories. These compounds could have been arisen via bacterial action on proteins, carbohydrates and lipids (Preti et al., 1976) (*Table 10*). Differences in the pattern of volatiles that could be indicative of oestrous state or gender have not been found by the latter authors. In the aardwolf (*Proteles cristatus*), the chromatographically identified volatile constituents of anal gland secretion and scent marks are eight short-chain to medium-chain fatty acids, a complex series of twenty-three medium-chain and long-chain esters, indole, and hexanol (Apps et al., 1989). In the red fox (*Vulpes vulpes*), anal sac secretions contain C_2-C_5 aliphatic acids and 4-methylvaleric acid as well as phenylacetic, 3-phenylpropionic, *p*-hydroxyphenylacetic, *p*-

hydroxy phenylpropionic acids and trimethylamine (Albone and Fox, 1971; Albone and Eglinton, 1974). The latter component was not found in the anal sac secretions of three other species, i.e., cat (Preti et al., 1976), lion (Albone and Eglinton, 1974) and Indian mongoose (*Herpestes auropunctatus*) (Gorman et al., 1974). Short-chain aliphatic acids are also present in cat anal sacs, guinea pig perineal glands, and in vaginal secretions of beagles, coyotes, rhesus monkeys and humans (reviewed by Preti et al., 1976). Variations of the bacterial flora are common in anal sacs, and may modify the composition of the chemical signals (Donovan, 1969; Gorman et al., 1974; Albone et al., 1977). This could be a reason for aggression or other behavioural disorders in groups of dogs displayed towards a dog with an anal sac infection (Pageat and Gaultier, 2003).

Raymer et al. (1984;1986) have analyzed the pattern of volatile constituents in the urine of intact wolves (*Canis lupus*), as well as the influence of testosterone, oestradiol and progesterone on 77 volatile urinary compounds of gonadectomised males and females to find out which substances most likely are important in chemical communication. They conclude that many of those compounds could be used to communicate gender as well as reproductive status. Among them, acetophenon, 3-ethylcyclopentanone, 1-octen-3-ol, and 2-octen-1-ol were put forward to be characteristic for female urine, and methyl-propyl-sulphide and methyl-isopentyl sulphide for male urine. Methyl-isopentyl sulphide, is also present in the urine of red fox (Whitten et al., 1980), and has been found to undergo a seasonal variation in concentration in this urine (Bailey et al., 1980) and to induce scent marking by foxes in the wild (Sukeno et al., 1971).

Previously, sexually dimorphic profiles have been identified in urines of red foxes during the winter season when mating occurs, the aromatic nitrogen compound quinaldine (2-methyl quinoline; an anti-malarial drug) being found only in male fox urine (Jorgensen et al., 1978). In contrast, Bailey et al. (1980) have demonstrated this latter compound also in the urine of female foxes. A solution, made from synthetic copies of eight of the compounds identified by Jorgensen et al. (1978), provokes significantly more counter-marking by wild foxes than does the control solution (Whitten et al., 1980), which indicates a pheromonal role of volatile urinary constituents in these animals.

Mustelids

Ferrets (*Mustela furo*) and stoats (*M. erminea*) recognise individual conspecifics and their sex by anal gland secretions (Erlinge et al., 1982; Clapperton et al., 1989; Woodley and Baum, 2003; 2004). Behavioural tests indicate that the major compounds originating from ferret anal gland indeed could act as chemosignals for sex discrimination (Crump, 1980b, Crump and Moors, 1985; Clapperton, 1989; Cloe et al., 2004; Woodley et al., 2004).

From seven *Mustela* species, chemical profiles of anal gland secretions have been reported, i.e. from the American mink (*M. vison*) (Brinck et al., 1978; Sokolov et al., 1980), the stoat and the domestic ferret (Crump, 1980a;b; Crump and Moors, 1985), the mountain weasel (*M. nivalis*) and the European polecat (*M. putorius*) (Brinck et al., 1983), the steppe polecat (*M. eversmanni admirata*), and the Siberian weasel (*M. siberica fortanieri*) (Zhang et al., 2002; 2003). Initially, a total of 18 volatiles have been identified in the anal gland secretions of these mustelids, of which 16 were sulphur-containing compounds (nine thietanes and five dithiolanes) that are unique to the *Mustela* genus. The two other volatiles are nitrogen- containing compounds that have been found in both urine and anal gland secretions (the sulphur-containing quinoline, 2-methylquinoline, and 4-methylquinazoline) may have a role in sex discrimination, since they show significant differences between males and females in their urinary concentrations (*Table 11*). Zhang et al. (2005), furthermore, demonstrated the nonsulpherous *o*-aminoacetophenone, especially in male ferret anal gland secretions. This compound has also been found in anal gland secretions of the male stoat

Table 11: A selection of chemical constituents of urinary and anal gland secretions in Mustela species that are suggested to act as sex signaling pheromones, because of their presence or relative abundance in one of the sexes (large symbol).

	Compound	Source	Authors
Ferret			
	quinoline	♂/♀ anal gland and ♂/♀ urine	a
	2-methylquinoline	♂/♀ anal gland and ♂ urine	a
	4-methylquinazoline	♂/♀ anal gland and ♂/♀ urine	a
	2-heptanone	♂/♀ urine	a
	4-heptanone	♂/♀ urine	a
	2,5-dimethylpyrazine	♂/♀ urine	a
	dimethoxyacetophenone	♂/♀ urine	a
	o-aminoacetophenone	♂/♀ urine and ♂ anal gland	a
	E-2,3-dimethylthietane	♂/♀ anal gland	a
	3-ethyl-1,2-dimethyl-1,2-dithiolane	♂/♀ anal gland	a
	E- or *Z*-2,4-dimethyl-1,2-dithiolane	♂/♀ anal gland	a
	2-propylthietane	♂/♀ anal gland	a
	3,3-dimethyl-1,2-dithiolane	♂/♀ anal gland	a
	3-propyl-1,2-dithiolane	♂/♀ anal gland	a
	indole	♂/♀ anal gland	b (not in a)
		♂/♀ anal gland	
Stoat			
	3-ethyl-1,2-dithiolane	♀ anal gland	c,d
	2-ethylthietane	♀ anal gland	d
	o-aminoacetophenone	♂ anal gland	c,e
Weasel			
	Z-2,3-dimethylthietane	♂/♀ anal gland	e
	Z- or *E*-2,4-dimethylthietane	♂/♀ anal gland	e
	2-ethylthietane	♂/♀ anal gland	e,f
	Z-2-ethyl-3-methylthietane	♂/♀ anal gland	f
	3-ethyl-1,2-dithiacyclopentane	♂/♀ anal gland	f
	3,3-dimethyl-1,2-dithiacyclopentane	♂/♀ anal gland	e,f
	4- or 3-propyl-1,2-dithiacyclopentane	♂/♀ anal gland	f
	indole	♂/♀ anal gland	f
	o-aminoacetophenone	♂/♀ anal gland	f
		♂/♀ anal gland	
Polecat			
	2,2-dimethylthietane	♂/♀ anal gland	f
	3-ethyl-1,2-dithiacyclopentane	♂/♀ anal gland	f
	o-aminoacetophenone	♂/♀ anal gland	f
	Z-3,4-dimethyl-1,2-ithiacyclopentane	♂/♀ anal gland	e,f
	3,3-dimethyl-1,2-dithiacyclopentane	♂/♀ anal gland	e (not in f)
	2-pentylthietane	♂/♀ anal gland	f
	Z- or *E*-2,4-dimethylthietane	♂/♀ anal gland	f
	E-2,3-dimethylthietane	♂/♀ anal gland	f
	Z- and *E*-2-ethyl-3-methylthietane	♂/♀ anal gland	e
		♂/♀ anal gland	

Legend belonging to Table 11: a, Zhang et al., 2005; b, Clapperton et al., 1988; c, Brinck et al., 1983; d, Crump, 1980a; e, Zhang et al., 2002; f, Zhang et al., 2003.

(Brinck et al., 1983; Zhang et al., 2002) and both sexes of the Siberian weasel and steppe polecat (Zhang et al., 2003) (*Table 11*). Like in ferrets, its concentration in male Siberian weasels is higher than in females, but higher in female than in male polecats. Findings of Clapperton et al. (1988), that show higher indole concentrations in male ferret anal glands than in those of females, have not been confirmed by (Zhang et al., 2005).
Apart from the male specific *o*-aminoaceto-phenone, 2-ethylthietane and 3-ethyl-1,2-dithiolane are specific female constituents of the anal gland secretions of stoats, (Brinck et al., 1983; Crump, 1980a). Among the sulphur-containing compounds, 2,2-dimethylthietane is predominant in the anal gland secretions of male and female Siberian weasel, and 2,4-dimethylthietane in the steppe polecat, while 2-ethyl-3-methylthietanes and 3,4-dimethyl-1,2-dithiacyclopentane are present in those of the polecat, but not in those of the weasel (Zhang et al., 2002). These differences can possibly be used for species recognition, since they are consistent between the two species, regardless of sex and age. In the weasel, 2-ethylthietane is only (Zhang et al., 2002) or predominantly (Zhang et al., 2003) produced by females. Additionally, as in polecats, the relative abundance of several compounds varies with age, and is significantly different between male and female weasels (*Table 11*). In this way, the volatile anal gland substituents could also be used to communicate information about sex and age. In addition to ferrets (Zhang et al., 2005), 2-methylquilonine has also been detected in the urine of red fox (Jorgensen et al., 1978; Raymer, 1984) and coyote (Preti et al., 1976), and the anal glands of skunks (*Conepatus mesoleucus;* Wood et al., 1993). In total 13 other compounds have been identified in the volatile fraction of the anal sac secretion of skunks. For a survey of the qualitative and quantitative differences of these volatile anal sac constituents between four different species of North-American skunks, see Burger (2005).

Anal sac secretions of *Mustela* species show great similarities in their chemical composition, whereas pine marter (*Martes martes*), otter (*Lutra lutra*) and badger (*Meles meles*) each show a different pattern (Brinck et al., 1983). For example, sulphur-containing compounds are characteristic for *Mustela* species, while benzaldehyde is the predominant compound in the secretion of marters. The relative amounts of the identified compounds vary between the species, and some of the sulphuric compounds are species-specific (Setzer, 2008). In the secretions of the unique scent-marking skin gland, the subcaudal gland, of badgers, Buesching et al. (2002a;b) have demonstrated 110 different compounds, of which 21 (most of them being fatty acids) are present in every profile. No single compound appears typical for the season, body condition, age, sex, or reproductive status, but the chemical composition is highly individual-specific. The chemical composition of the subcaudal gland secretion furthermore varies over seasons and between sexes and is influenced by body condition, age, and reproductive status, while group members have more similar profiles than do badgers from different groups.

In ferrets, volatile anal scent odours activate the main olfactory epithelium-main olfactory bulb system to identify opposite-sex mating partners (Kelliher and Baum, 2002; Woodley et al., 2004), sex hormones and gender being of influence on their attraction thresholds (Woodley and Baum, 2003). VNO removal shows that this olfactory organ seems not required for olfactory sex discrimination or mate recognition in this species, but may play a role in promoting continued contact with nonvolatile body odours that have been previously deposited by opposite-sex conspecifics during terrtorial scent marking (Woodley et al., 2004). Although the studies on Mustelids provide strong indications for the presence of (sex) pheromones in anal gland secretions and urine, there is no real solid experimental evidence available that proofs the pheromonal role of a specific component or a specific mixture of body secretion and excretion products in these species. Sulphur-containing compounds, for example, may (also) have a role in the interspecific defence mechanism of *Mustela* species.

For, the sulphur-containing compounds derived from high- protein diets are thought to be responsible for the malodorous carnivore secretions (Brinck et al., 1983; Wood et al., 1993).

Bears

Reproduction-related glandular, urinary or faecal volatile substances of these bears may trigger the reproductive behaviour. Giant pandas (*Ailuropoda melanoleuca*), brown bears (*Ursus arctos*), and spectacled bears (*Tremarctos ornatus*) have volatile medium-chain fatty acids octanoic (C_8), decanoic (C_{10}) and dodecanoic (C_{12}) acids in their urine that increased in concentration simultaneously with their mating period (Dehnhard et al., 2006). Male giant pandas exhibit olfactory preference for urine expelled from females during oestrus (Swaisgood et al., 2000), which may indicate a possible function of urinary volatiles in the communication of the reproductive status of female bears. From their GC-MS data on anogenital gland secretions of giant pandas, Zhang and coworkers (2008b) conclude that 5-methylhydantoin, indole, and erucic acid could be putative female pheromones, whereas squalene and hydroquinone are putative male pheromones in this species. However, further bioassays have to be carried out to prove this supposition.

When excited, the red panda (*Ailurus fulgens*) emits a musky odour from its paired anal glands (Nowak and Paradiso, 1991), while secretions of these glands, in addition to urine and faeces, are used to mark its territory (Roberts and Gittleman, 1984). The volatile components of the red panda's anal sac secretions are several long-chain saturated and unsaturated fatty acids, 2-piperidinone, squalene, and cholesterol (Wood et al., 2003). As the anal sacs of the red panda, those of the northern (common) racoon (*Procyon lotor*) also contain long-chain saturated and unsaturated fatty acids and cholesterol, but short-chain carboxylic acids, 3-phenylpropanoic acid, 4-hydroxyphenylpropanoic acid and mandelic acid are additionally present (Schildknecht and Ubl, cited by Wood et al., 2003). Whether the detected compounds in these latter two Musteloidea have a pheromonal significance remains to be proven. Studies on the behavioural relevance of demonstrated urinary fatty acids are required to find out if they function as pheromones. A better knowledge of the function of identified urinary and anal sac fluid compounds may be of help in stimulating the sexual motivation of endangered species like the world's bears.

Ungulates

The order Ungulates comprises even-toed (Cetardiodactyla) animals (e.g., pigs, camels, giraffes, cows, buffaloes sheep, goats, deers, antelopes, lama's, and rhinoceroses) and odd-toed (Perissodactyla) animals (e.g., horses, donkeys, zebra's, and tapirs). From these ungulates, relevant information on pheromones is especially available for pigs, deers, and ruminants.

Pigs

Upon introduction of a boar, an oestrous sow will resist moving when pushed and, while perking her ears, act if she is in trance. 16-Androstenes, like 3α -androstenol (5α-androst-16-en-3α-ol), 3β-androstenol (5α-androst-16-en-3β-ol) and their precursor steroid 5α-androstenone (5α-androst-16-en-3-one), have particularly been demonstrated to function as mature boar pheromonal cues to sows that are in heat, and to evoke the immobilisation reflex (lordosis) that characterises their readiness to mate (Brooks and Cole, 1970; Melrose et al., 1971; Gower, 1972) (*Table 12*). 5α-androstenone additionally stimulates oxytocine release in oestrous sows (Mattioli et al., 1986).

The pheromonal steroids are synthesised in the porcine testes (Gower, 1972; Gower et al., 1972; Sinclair et al., 2005), subsequently transported by the blood, stored in the adipose

tissue and salivary glands (submaxillary glands especially), and then secreted via saliva (Claus et al., 1971; Claus, 1975; Booth, 1975; Perry et al., 1980). They are also found in sweat glands (Stinson and Patterson, 1972). Chemical communication in pigs is, however, notably mediated by saliva (Kirkwood et al., 1981; Gower and Booth, 1986). In the circular system, 3β- and 3α-androstenol are predominantly present as sulphates (Sinclair and Squires, 2005), whereas boar urine has high levels of 16-androstene glucuronides and no observable sulphates (Gower and Patterson, 1970). Conjugation with glucuronides and sulphates makes steroids more water-soluble in blood and urine. It cannot be excluded that, as in fish (Van den Hurk and Resink, 1992; Stacey and Sorensen, 2002), steroid glucuronides and steroid sulphates may act as sex pheromones also in pigs.

Excessive accumulation of 5α-androstenone in adipose tissue together with 3-methyl-indole (skatole) leads to the development of the boar taint (Doran et al., 2004), which quickly elicits lordosis in sows that are in oestrus (Dorries et al., 1997), and results in an unpleasant odour to humans when boar meat is heated during cooking (Sinclair et al., 2005). The steroid is sold as 'Boarmate' to pig farmers to assist in artificial insemination (http://www.antecint.co.uk/main/rm/boarmate.ram).

In mature female pigs, the steroidal stimulus is an olfactory one, since surgical removal of the olfactory bulbs delays puberty (Hillyer, 1976; Aworwi and Anderson, 1985) and induces anoestrus (Signoret and Mauleon, 1962; Booth and Baldwin, 1983), high-affinity binding receptors for 16-androstenes have been demonstrated in the olfactory but not the respiratory epithelium of sows (Gennings et al., 1977), and neuronal signaling in the sow's olfactory bulb is influenced by nasal presentation of 5α-androstenone (MacLeod et al., 1979). Experiments with domestic pigs, in which the vomeronasal organs were blocked, have shown that these organs are not necessary for androstenone detection or androstenone-mediated sexual behaviour in oestrous females (Dorries et al., 1997).

5α-andostenone and its alcohol derivative (it has not been described whether the 3α- or 3β-variant of androstenol has been tested) are bound with high affinity by porcine OBP-3 and salivary lipocalins (Scaloni et al., 2001). In contrast, porcine OBP-1 binds several classes of odourants different from these boar sex pheromones (Paolini et al., 1998; 1999), while the physiological function of porcine OBP-2 is still unclear (Scaloni et al., 2001). In addition to the neural pathway for signaling pheromones, a local humoral pathway has been demonstrated in gilts, whereby such pheromones may be resorbed from the nasal cavity into the bloodstream and then pass locally from the perihypophysial vascular complex into the arterial blood of the carotid rete, supplying the brain and hypophysis to selectively accumulate in the hypophysis and certain brain structures (Krzymowska et al., 1999; Stefanczyk-Krzymowska et al., 2000b). The ovarian steroid hormones oestradiol and progesterone modulate the vascular tension of the nasal and facial veins in prepubertal gilts and thus may influence the transfer of boar pheromones from the nasal mucosa to the brain via local humoral pathway during sexual maturation (Grzegorzewski et al., 2010a;b).

Besides their role in the sow's mating behaviour, boar pheromones have been shown to accelerate puberty in gilts by about 30 days, to synchronise pubertal oestrus, and to reduce the postpartum period in lactating sows (Brooks and Cole, 1970). The accelerating effect of pheromones on puberty appears to be dependent on the boar's age, young boars (6.5 months-old) being unable to advance puberty (Kirkwood et al., 1981). This inability of young boars could be due to the presence of underdeveloped submaxillary salivery glands (Izard, 1983), and thus a decreased ability to produce the pheromonal 16-androstenes 5α-androstenone and 3α-androstenol as has been demonstrated by Booth (1975). Gilts, that reached early puberty through the presence of a boar, have higher ovulation rates, more oestrous cycles and therefore a higher reproductive potential than controls (Izard, 1983). Furthermore, around the moment of insemination, boar stimuli affect reproductive performance by influencing sperm

transport and ovulation processes in sows (Soede, 1993). Boar pheromones thus can be used as efficient tools to improve reproduction in swine.

Because sows do not take care of their litter, it is more important for piglets than for other mammals to rapidly find the nipple, essential for the survival of neonates (Orgeur *et al.*, 2002). Maternal pheromones are involved in the regulation of nursing pig behaviour (Morrow-Tesch and McGlone, 1990a). Olfactory cues are located near the nipple, which facilitates nipple attachment (Morrow-Tesch and McGlone, 1990b) and the intake of colostrum and milk. Odours, that were isolated from the nipple areas of milking sows, reduce agonistic behaviours in piglets (Pageat, 2001; Pageat and Teyssier, 1998). The maternal pheromone is composed of six fatty acids, which are present in different proportions: hexadecanoic acid (palmitic acid, 35%), *Z*-octadec-9-enoic acid (oleic acid, 25%), (*Z,Z*)-9,12-octadecadienoic acid (linoleic acid, 22%), dodecanoic acid (lauric acid, 8%), tetradecanoic acid (mysteric acid, 7%) and decanoic acid (capric acid, 2%) (Pageat, 2001) (*Table 12*). A synthetic analogue, termed porcine appeasement pheromone (Suilence®, US Patent no. 6,169,113; Pageat, 2001) and applied once at weaning, similarly reduces agonistic behaviours in piglets and stimulates their feeding behaviour, resulting in an increase in daily weight gain (McGlone and Anderson, 2002). The paternal pheromone 5α-androstenone additionally reduces agonistic behaviour and improves feeding behaviour of growing pigs (McGlone et al., 1986).

Camels and giraffes

The mating behaviour of the camel (*Camelus dromedarius*) largely corresponds to that of the pig (Claus et al., 1999). Like boar testes, those of male camels are able to synthesise the 16-androstenes 3α-androstenol, 3β-androstenol and 5α-androstenone. In reverse with boar testes, concentrations of 3β-androstenol are the lowest in those of camels, while concentrations of 3α-androstenol are the highest. From the three 16-steroids, 5α-androstenone and 3β-androstenol are released primarily by the occipital gland, the palatal flap, and the submandibular and parotid salivary glands. In the camel, the quantitative contribution of salivery glands is lesser than that of the occipital gland and a reduction of the ketosteroid into androstenol seems not to occur. Although the findings are suggestive for a function of these steroids as pheromones in the camel, such a role has still to be proven.

Two alkaloids, i.e., indole and 3-methylindole (= skatol), are primarily responsible for the strong scent that reticulated giraffes (*Giraffa camelopardalis reticulata*) emit. Other odouriferous compounds identified in extracts of hair and associated epidermal materials are an alkane (octane), four aldehydes (benzaldehyde, heptanal, octanal, and nonanal), a phenol (*p*-cresol), two carboxylic acids (tetradecanoic and hexadecanoic acid, and a steroid (3,5-androstandien-17-one) (Wood and Weldon, 2002). Sebaceous glands, apocrine glands and the epidermis are considered as likely sources for these compounds. Most of the demonstrated compounds possess bacteriostatic or fungistatic properties against microorganisms like skin pathogens. Whether these odorous skin compounds have any pheromonal role is unclear.

Deers and antelopes

Apart from urine, various ungulate species emit volatile compounds through tarsal, metatarsal, interdigital, forehead and/or tail gland secretion (Müller-Schwarze, 1971; Jameson, 1988). In black-tailed deer (*Odocoileus hemionus columbianus*), the glandular consistuents may act as alarm substances or as (sex) pheromones (Müller-Schwarze, 1971). In this species, urine and metatarsal odours convey messages over moderately large distances, while the tarsal scent serves to identify sex, age, or an individual at close distance. The deer's home range is marked by the forehead scent, and escaping specimens leave their interdigital scent on the ground. In this way chemical communication among conspecific deers may serve

Table 12: Putative (sex) pheromones in farm animals.

	Detected compound	Source	Effects
Pig	5α-androst-16-en-3-one	testis*	stimulates lordosis oestrous sows (a,b,c,d)** stimulates oxytocine release oestrous sows (e) reduces agonistic behaviour piglets (f) induces feeding behaviour piglets (f)
	5α-androst-16-en-3α-ol, 5α-androst-16-en-3β-ol	testis*	stimulate lordosis oestrous sows (a,b,c,d)** reduce agonistic behaviour piglets (g,h)
	palmitic acid, oleic acid, linoleic acid, lauric acid, mysteric acid, capric acid	sebaceous glands around milking sow nipples	induce feeding behaviour piglets (h)
Cow	1-iodoundecane and di-*n*-propyl phthalate	urine oestrous cow	signal oestrus to attract bulls (i)
	6-methyl-1-heptanol, 2-methyl-7-hydroxy-3-4-heptene, 7-hyroxy-3-4-heptene, and other 1-heptanols or methyl hydroxy-heptens	vaginal secretion	signal oestrus to attract bulls (j)
Horse	palmitic acid and mysteric acid	faeces oestrous mares	signal oestrus to attract stallions (k)
Sheep	1,2-hexadecanediol, 1,2-octadecanediol, and (unknown) acid compound(s)	ram fleece and ante-orbital gland secretions	stimulate LH secretion and urine emission ewes (l,m)***
Goat	4-ethyl octanoic acid derivative(s)	buck fleece	stimulate LH secretion female conspecifics (n,o)***

Legend belonging to Table 12: * compound is synthesised in testes, then stored in adipose tissue, salivary glands and sweat glands, and then secreted (Claus et al., 1971; Claus, 1975; Booth, 1975) and sweat (Stinson and Patterson, 1972), respectively. ** compound possibly also accelerates puberty, synchronises pubertal oestrus, and reduces post-partum period in lactating sows (Brooks and Cole, 1970). *** unknown sheep (Underwood et al., 1944) and buck (Shelton, 1960) pheromones have also been found to accelerate puberty. a, Brooks and Cole, 1970; b, Melrose et al., 1971; c, Gower, 1972; d, Sinclair et al., 2005; e, Mattioli et al., 1986; f, McGlone et al., 1986; g, Pageat, 2001; h, McGlone and Anderson, 2002; i, Kumar et al., 2000; j, Preti, 1984; k, Kimura, 2001; l, Cohen-Tanoudji et al., 1994; m, Gelez and Fabre-Nys, 2004; n, Sugiyama et al., 1981; o, Iwata et al., 2003.

to identify territorial boundaries and individuals and to induce sexual encounters by advertising sexual condition (Müller-Schwarze et al., 1979; Lawson et al., 2001).

Metatarsal gland secretion of the female sika deer (*Cervus nippon*) possesses 35 major volatile compounds that include 13-straight-chain carboxylic acids, a single branched-chain carboxylic acid, 9 straight-chain aldehydes, 3 monounsaturated aldehydes, 5 long-chain alcohols, a ketone, and cholesterol (Wood, 2003). Among them, heptanal, nonanal, octanoic acid and 6-methyl-2-heptanone appear most abundantly present. In metatarsal gland secretions of the impala (*Aepyceros melampus*) two major volatiles, 2-nonanone and 2-methylbutanoic acid, have been identified. (Wood, 1997a). The lactone *(Z)*-6-dodecen-4-olide (Brownlee et al., 1969) and several other unsaturated lactones (Müller-Schwarze, 1969) are the main components of the tarsal scent of black-tailed deer, which release various aspects of social behaviour like sniffing and licking. Later studies have shown that the former lactone is not a component of the tarsal gland, but of the deer's urine (Müller-Schwarze et al., 1977; 1978).

The major volatile constituent in the interdigital gland of the bontebok (*Damaliscus dorcas dorcas*) is (*Z*)-5-undecen-2-one, while 4 methyl ketones (2-haptanone, 2-nonanone, 2-undecanone, and 2,5-undecanedione) are minor components (Burger et al., 1976; 1977). In a reinvestigation of the bontebok's interdigital secretion, 85 compounds, belonging to widely different compound classes, have been characterised (Burger et al., 1999), and listed in a table (Burger, 2005). No qualitative differences have been observed when the secretions of the bontebok are compared with those of the blesbok (*Damaliscus damaliscus phillipsi*), or when the secretions of the two sexes of both subspecies are compared.

The interdigital secretion of the red hartebeest (*Alcelaphus buselaphus caama*) contains fewer compound classes, and is characterised by its high aldehyde content (Reiter et al., 2003). From 100 detectable constituents, 25 are saturated and unsaturated aliphatic aldehydes. Besides, it contains a few alkanes, and short-schain, branched alsohols, fatty acids, an epoxide and 3 cyclic ethers. However, no significant qualitative or quantitative differences between secretions of male and female animals have been observed. Four methyl ketones (Andersson et al., 1979), different from those initially described for the bontebok (Burger et al., 1976;1977), and eight short-chain carboxylic acids (Brundin et al., 1978) are found in the interdigital secretion of the reindeer (*Rangifer tarandus*).

The volatile compounds secreted from the interdigital glands of the gemsbok (*Oryx gazella gazella*) and white-tailed deer (*Odocoileus virginianus dacotensis*) are short-chain carboxylic acids (Wood, 1997b; 1999), while in interdigital gland extracts of the black-tailed deer three ketones, e.g., 2-tridecanone, (*E*)-4-tridecen-2-one and (*E*)-3-tridecen-2-one, have been detected (Wood et al., 1995) of which the latter has a bacteriostatic and fungistatic effect. In studies from Gassett et al. (1996) with interdigital secretions of white-tailed deer, 46 volatile compounds have been identified, including seven alkanes, twelve arenes, six aldehydes, five ketones, one alcohol, three aliphatic acids, eight esters, two pyrroles, two furans, and one sulphur compound. When significance is accepted at $P<0.1$, eleven compounds occur in higher concentrations in dominant (3.5-year-old) than in subordinate (1.5-year-old) animals. At $P<0.05$, however, only five compounds (butanone, pyrrole, acetic acid, ethyl 2-methylbutanoate, and methyl salicylate) are higher in dominant deer. Dominant males typically have higher serum testosterone levels, and fatty acids and esters fluctuate with sebum production, which is under hormonal control. The authors conclude that these compounds may reflect testosterone levels and act as chemical signals indicating the presence of a dominant male. They may, however, also reflect differences in age, since the studied dominant animals are two years older than subordinate deers.

Other glandular sources in deers of volatile compounds with possible pheromonal properties are the various straight and branched-chain fatty acids secreting preorbital glands

(Wood, 2004) and the sebaceous and apocrine glands of the forehead region (Gassett et al., 1997). In the preorbital gland secretion from a female sika deer, 11 major volatile compounds have been found, i.e., 6 straight-chain and five branched-chain fatty acids (Wood, 2004). The sika deer preorbital gland differs in this from the composition reported for most other species. Gassett and co-workers (1997) have identified 57 compounds from the forehead and back secretions of white-tailed deers, including 12 alkanes, 5 arenes, 7 aldehydes, 5 ketones, and 6 alcohols. From these compounds only one (bomeol), found on the forehead hair, is present in higher concentrations in dominant deer, while the concentrations of 8 compounds are higher in subordinate deer.

Although analysis of the odours from periorbital glands of red deer (*Cervus elaphus*), sika deer, Chinese muntjac (*Muntiacus reevesi*), and Chinese water deer (*Hydropotes inermis*), from interdigital glands of roe deer (*Capreolus capreolus*), and from metataral glands of red, sika, fallow and roe deer reveals differences between odour profiles characteristic of age, sex or population, it does not imply that the signal is deliberatively coding for such information, or that the deer use the information available (Lawson et al., 2001). The components of preorbital gland secretion have also been identified for the reindeer, the arctic muskox (*Ovibos moschatus)* and many species of African antelope. Reindeer preorbital glands contain free and esterified cholesterol, lanosterol, fatty acids, triglycerides, and the ketones, 4-heptanone and 2-methyl-4-heptanone (Andersson, 1979). Saturated lactones are among the major components in the secretion of arctic muskox (Flood et al., 1989). The preorbital gland secretions of African antelopes contain many components with several different types of chemical groups. Formate esters, for example, appear major compounds in the glandular secretions of suni (*Neotragus moschatus*), Cape grysbok (*Raphicerus melanotis*), and orbi (*Ourebia ourebia)*, while ketones are characteristic for those of bontebok, blesbok, klipspringer (*Oreotragas oreotragas*), and blue duiker (*Cephalophus monticola*), and thiazoles for those of grey duiker (*Sylvicapra grimmia*) and red duiker (*Cephalophus natalensis*). For more detailed information on the chemical composition of antelope skin gland secretions, see Wood (2004) and Burger (2005).

Studies on urinary volatiles from white-tailed deer have shown that the presence and concentration of urinary compounds depend on season, reproductive status, and social rank (Jemiolo et al., 1995). In total 63 compounds have been identified in the urine of females and 55 in the urine of males, of which 27 compounds occur in both sexes, 36 exclusively in females, and 28 only in males. Thiol esters, benzene, ketals, disulphides, and nitrils have been found exclusively in male urine, while phenols were characteristic for female urine. Alcohols, aldehydes, alkanes, alkenes, amines, ethers, furans, and ketones are demonstrated in urine of both sexes, and also in female vaginal fluid in which 44 volatiles have been found. In urine of male white-tailed deers, ketones are most numerous, followed by alcohols and alkanes (Miller et al., 1998). Three compounds (3-methyl-3-buten-1-ol, phenylacetonitril, and 3,4,5,6-tetrahydropyridine) are present in higher concentrations in dominants, and six are higher in subordinates. The concentration of compounds detected in the nonbreeding season differ from those being found in the breeding season. During the breeding season, 9 compounds are exclusively present in the urine of dominants, and 19 compounds exclusively in subordinates. Although there is no evidence available whether the demonstrated urinary and glandular compounds in this deer species and other Artiodactyls are used for chemical communication, they may be important in delineating territory and establishing social status, signaling sexual readiness, attraction of mates, or identifying individuals.

Cows

In dairy practice, detection of oestrus is often considered as a problem. Exposure of bulls to cows, either continuously or twice a day, has no effect on behavioural expression of oestrus

(Shipka and Ellis, 1998). Likewise, fenceline bull exposure does not affect oestrous expression, when an assigned number of points is attributed to displayed behavioural actions as flehmen, restlessness, sniffing the vulva of another cow, being mounted, mounting other cows, resting with the chin on the back of another cow, and standing heat (Roelofs et al., 2008).

Although there are some controversial data, many reports have shown, however, that bull pheromones do hasten the onset of puberty in heifers, stimulate the occurrence of oestrus in groups of cows, shorten the postpartum interval from calving to the resumption of ovarian cycling activity, and stimulate the pregnancy rate to artificial insemination (for reviews, see Izard, 1983; Rekwot et al., 2001; Tauck, 2005). Factors that influence the obtained results are the timing and duration of bull exposure to the cows, the season experiments are carried, the quality and quantity of the applied diet and, in case of pregnancy rate stimulation, the use of progestin in the applied oestrus-synchronisation protocol. For example, continuous bull exposure reduces the postpartum anoestrus interval of first-calf suckled beef cows (Custer et al., 1990; Fernandez et al., 1996), while exposure of such cows to bulls for 2 h every third day for 18 days does not (Fernandez et al., 1996). In this regard, body configuration of bulls does not seem to be a sensory cue, since androgen treated cows elicit the same effect as bulls (Burns and Spitzer, 1992). When cows are exposed to bulls from 4 to 5 days after calving for 3-4 h daily and then inseminated within 30 days after calving, more cows exhibit oestrus than when cows are not exposed to bulls (Sipilov, 1966).

Tauck and co-workers (Tauck, 2005; Tauck et al., 2006) have shown that continuous exposure of primiparous, suckled beef cows to mature bull urine, in comparison with continuous exposure to steer urine, does neither affect the interval from urine exposure to resumption of luteal activity nor proportions of cows that resumed luteal activity during the urine-exposure period of luteal activity. It is speculated that pheromonal stimulation requires cows to be in close proximity to bulls or their excretory products periodically and repeatedly throughout the day to evoke periodic stimulation of neuronal activity at olfactory sites (Tauck, 2005), and that cows in this experiment were overstimulated (Tauck et al., 2006). Thus, the mode of pheromonal stimulation could be an important factor in the effect of bull urine on resumption of luteal activity in postpartum, suckled beef cows and do not preclude the possibility that bull urine contains pheromones. The possibility that bull urine contains pheromonal compounds is feeded by the finding of a significantly enhanced pregnancy rate (and thus an improved breeding performance) following artificial insemination, when first-calf suckled beef cows were continuously exposed to bull urine until an oestrous synchronisation protocol was applied that included progestin, PGF2a and GnRH (Tauck, 2005; Tauck and Berardinelli, 2007). There is other evidence, that urine (Baruah and Kachev, 1993; Tauck, 2005) and/or other excreted body fluids (Berardinelli and Joshi, 2005) are sources of bull pheromones. Spraying once per week for 7 weeks in the nose and mouth with bull urine hastens puberty in heifers (Izard and Vandenbergh, 1982). The effects of bull urine may have been brought about by the priming of the pituitary by released bull pheromones. For, bull urine sprayed into the nasal passages of diary cows 7 days after calving increased serum LH and FSH levels within 70 minutes of exposure (Baruah and Kanchev, 1993). When rubbed individually onto the genital regions of non-oestrous cows, urine and cervicovaginal fluid attract bulls and stimulate their sexual behaviour (Hart et al, 1946; Paleologou, 1977). The observed stimulating effect of vaginal secretions of heifers at oestrus on sexual activity and mounting behaviour of herdmates (Nishimira et al., 1991) is in line with the former data. Likewise, the frequency of the bull's flehmen behaviour is enhanced by samples of vaginal mucus, saliva, faeces and milk of cows in oestrus, the response to oestrous vaginal fluid being significantly higher than the other body fluids (Sankar and Archunan, 2004). Flehmen is a characteristic behaviour for many male ungulates (but not boars) whereby the head is raised,

the mouth is opened and the upper lips are curled (Hafez and Bouissou, 1975). Faeces of oestrous cows also contain compounds that are attractive to bulls (Donovan, 1967), while cervical mucus synchronises oestrus in cows (Izard, 1983).

During the reproductive cycle of cows, volatile fatty acids are present in urine and vaginal secretions (Hradecky, 1986). The concentrations of these fatty acids in vaginal secretions increase shortly before oestrus and then rapidly decrease. In total seven volatile compounds have been identified in the cow's urine during the oestrous cycle (Kumar et al., 2000), among which two (1-iodoundecane and di-*n*-propyl phtalate) are characteristic for the ovulatory period, one (undecane) only occurs during the postovulatory period, and one (1-iododecane) is only found in the preovulatory period. The other constituents are ethylbenzene, 2,2,-dimethylbutane and oxiranemethanol, the latter compound being absent in the preovulatory period. Bulls can discriminate oestrous from non-oestrous urine, and the oestrous urine has been shown to elicit sexual behaviour in cattle (Sambraus and Waring, 1975). Urinary 1-iodoundecane and di-*n*-propyl phtalate may function as sexual attractants that allow bulls to detect cows in heat.

1-iodoundicane is not only a urinary component in the bovine, but also one of three specific substances detected in oestrous faeces (Sankar and Archunan, 2008). The other two compounds are acetic acid and propionic acid. When a synthetic mixture of these three oestrus-specific compounds (in unpublished concentrations and ratios) is rubbed onto the genital region of nonoestous cows, and bulls are allowed to sniff the genital region, they exhibit repeated flehmen and mounting behaviours. When individual compounds are applied, 1-iodoundicane primarily attracts bulls, whereas acetic acid and propionic acid primarily stimulate their mounting behaviour. The synthetic mixture, however, evoked the highest incidence of precopulatory behaviour of bulls. Thus, like *urinary* 1-iodoundecane and di-*n*-propyl phthalate, *faecal* 1-iodoundicane, acetic acid and propionic acid can be used as indicators of oestrus in cows.

Nine compounds (an alcohol, a diol, an ether, four ketones and two amines) have been identified in cervico-vaginal mucus extracts that evoke the male sexual behaviour, which is shown naturally when bulls are exposed to females in oestrus, i.e., olfactory inspection and licking of sample, flehmen, penile contraction, preputial secretion (Klemm et al., 1987). One or more of these compounds may be considered as putative sex pheromones. After monitoring cow's vaginal secretions over time, an increase in the amount of at least one indicator compound contained in the secretions can be detected, concentrations above about 0.1 micrograms per gram of collected secretion being indicative of oestrus (Preti, 1984). In particular, these compounds are methyl-1-heptanols, such as 6-methyl-1-heptanol, or are methyl hydroxy heptenes, such as 2-methyl-7-hydroxy-3-4-heptene or 7-hyroxy-3-4-heptene. A cow may be detected to be in oestrus simply by determining that the concentration of 6-methyl-1-heptanol is at least 0.1 microgram per gram of collected vaginal secretion.

Behavioural studies, in which trained dogs are used, have shown that bovine milk from the follicular, oestrus and luteal stage of the oestrous cycle, respectively, have different odours (Hawk et al., 1984; Kiddy et al., 1984). The major compounds among the 80 volatile substances that have been identified in bovine milk belong to six structurally distinct classes: ester, aldehyde, ketone, alcohol, fatty acid and lactone (Weidong et al., 1997). Although no unique compounds are found to be specific for the respective stages of the oestrous cycle, 36 of them exhibit significant differences in concentration among the reproductive periods. These quantitative differences may account for the variation in milk odours during the cow's oestrous cycle. In milk produced by New Zealand cows, the volatile compound γ-12:2 lactone appears the most active odourant among the 66 aroma compounds identified (Bendall, 2001). Although the current data suggest that some of the volatile constituents in milk may function as pheromones for olfactory communication, no conclusive evidence has

been delivered thus far. Interspecific regognition of bovine oestrus has also been demonstrated by using mice as oestrous detectors. Male mice kept in a Y-maze apparatus appear able to detect oestrous odour in bovine urine and to discriminate it from non-oestrous urine, while a higher level of grooming behaviour was observed when mice were exposed to bovine oestrous urine (Rameshkumar et al., 2008).

The absence of OBPs in significant amounts in bovine olfactory cilia and its presence in large amounts in respiratory membranes, suggests that these proteins make no direct contact with odourant receptors. The presence of OBP receptors in membranes from nasal mucosa and in various tissues unrelated to olfaction suggests that OBPs have a minor role in olfaction, but rather play a role in the general defence mechanism of the body by removing potentially toxic substances that could find entry via nasal, respiratory and intestinal pathways, and thence into the bloodstream. Nevertheless, bovine OBPs are able to bind many different odourant molecules, including a range of pyrazine and thiazole derivatives and a number of terpenes (Pevsner et al., 1986; 1990; Pelosi and Tirindelli, 1989; Cavaggiani et al., 1990). The insect attractant 1-octen-3-ol, a typical volatile component of bovine breath and in general of odorous body emanations of many mammals including humans, has been identified as ligand of bovine OBP (Ramoni et al., 2001).

Buffaloes

The occurrence of silent ovulations without any behavioural signs of oestrus is a main problem in buffalo reproduction (Dobson and Kamonpatana, 1986). It makes the detection of heat in buffaloes even more difficult than in cattle (Danell et al., 1984). The detection of pheromones that mark oestrus could be an important tool to overcome this problem. As in bulls, male buffaloes (*Bubalus bubalis*) exhibit flehmen behaviour upon exposure to heifers, especially during oestrous periods (Rajanarayanan and Archunan, 2004). The source(s) and identity of pheromones responsible for this behaviour of buffalo bulls are, however, still unknown.

Sheep and goats

In seasonal breeds of goats and sheep, the introduction of a male into a group of anoestrous females results in the activation of sexual activity by activation of the LH secretion and synchronisation of ovulation (Shelton, 1960; Knight et al., 1978; Chemineau, 1983; Martin et al., 1986, Ungerfeld et al., 2004). This phenomenon is called the ‘male effect’ or ‘teasing’, and is widely used in husbandry of these species (Thimonier et al., 2000). In the middle of the anoestrous season, the response of female goats to the ‘male effect’ is weak or absent, but can be induced by the introduction of teaser bucks that had previously been exposed to artificial long days (Delgadillo et al., 2006; Rivas-Muñoz et al., 2007). Recently, some major physiological and physical factors that affects the ‘male effect’ in sheep and goats have been challenged (Delgadillo et al., 2009). It brought the authors to their conclusion that male ‘novelity’ is more important than isolation per se, and that the neuroendocrine component of the ‘male effet’ is not restricted to anovulatory females.

Odour of the male and its sexual behaviour play a primary role in inducing ovulation, while vocalisations appear to facilitate the display of the does’ oestrus (Delgadillo et al., 2006; Rivas-Muñoz et al., 2007). In *sheep*, the ‘male effect’ is largely mimicked by exposure to male fleece only (Knight and Lynch, 1980). The response of ewes to rams or their odours is dependent on previous sexual experience, the LH response probably being the result from an associative learning process (Gelez and Fabre-Nys, 2006a). The ram’s chemosignal activating the female LH secretion is a mixture of compounds that have been partially identified. It appears that both neutral and acid fractions of fleece or ante-orbital secretion are required for this process, whereas urine is ineffective (Cohen-Tanoudji et al., 1994). The

pheromonal activity of the neutral fraction is due to the presence of male specific 1,2-hexadecanediol and 1,2-octadecanediol (*Table 12*). The necessary acid compounds are still unknown. Branched-chain fatty acids and oxygenated fatty acid derivatives have been put forward as possible candidates, since they are absent in female wool extracts. The ram or the odour of its fleece do not induce drastic behavioural changes (like strong interest or attraction) in anoestrous ewes, but induce urine emission (Gelez and Fabre-Nys, 2004).

Sebaceous glands have been indicated as sources of (testosterone-dependent) primer pheromone production in *goats* (Sugiyama et al., 1981; Sasada et al., 1983; Iwata et al., 2000). Among them, the cornual glands are the major sources, while the mental and smaller skin glands located in the head and neck regions have a lesser contribution in odour production (Van Lancker et al., 2005). The subcaudal glands and preputial glands appear not involved in this process. Priming pheromones from ram and buck have furthermore been found to accelerate puberty in sheep (Underwood et al., 1944) and goats (Shelton, 1960). In the buck, 4-ethyl octanoic acid is the major fleece component that is responsible for male goat odour (Sugiyama et al., 1981). Although this branched-chain fatty acid does not evoke a LH response in female conspecifics itself (Claus et al., 1990), some of its derivatives (among which octanoic acid, the methyl ester of 4-ethyl octanoic, and 2,6-di-t-buthyl-4-methylphenol) probably do this since, when stored at room temperature, 4-ethyl octanoic acid solution appears to be converted in these products, and then becomes positive in its primer pheromone activity (Iwata et al., 2003) (*Table 12*). Although the identity of these pheromones still was not elucidated, recent analyses of male goat hair extracts revealed that it is a volatile substance with relatively small molecular weight (Murata et al., 2009). Notably, male goat hair stimulatates pulsatile LH secretion in the ewe (Over et al., 1990) while, the other way around, ram wool stimulates pulsatile GnRH/LH release in the female goat (Ichimura et al., 2008). These data suggest that the male effect in sheep and goats is caused by very similar or identical pheromonal compounds. Electrophysiological multiple-unit activity recordings point to a subset of kisspeptin neurones in the arcuate nucleus as the intrinsic source of the GnRH pulse generator (Okamura et al., 2010).

VNO lesion experiments with ewes and immunohistochemical studies of ewe brains using c-fos show that the MOS is essential in detecting ram primary pheromones, while that of the VNO is limited (Gelez and Fabre-Nys, 2004; 2006b). Rams are also able to discriminate oestrous and non-oestrous ewe urine odours in the absence of an active VNO (Blissitt et al., 1990), but they do not discriminate between odours of urine samples from different ewes in oestrus (Blissitt et al., 1994). A role of the VNO in the detection of oestrus has also been put forward for bucks (Hart and Jones, 1975). The perception of pheromones by the VNO stimulates the sexual performance of rams, which is reflected by a faster response to the stimulus of oestrous ewes, an increase in mountings and ejaculations, and a different mate choice (Ungerfeld et al., 2006). Pheromones secreted through the ewe's wool and wax (Tilbrook and Cameron, 1989) and vaginal secretions (Ungerfeld and Silva, 2004) sexually attract rams. Experiments, whereby the naso-incisive duct was cauterised, showed that the VNO in ewes is also used for neonatal offspring recognition (Booth and Katz, 2000).

In ungulates, like ewes (Bouissou, 1968), goats (Hersher et al., 1963) and cows (Griffith and Williams, 1996), an exclusive and enduring bond between the postparturient mother and her offspring is rapidly established within the first hours after delivery, which results in the acceptance of only her own young at the udder. This maternal selectivity depends on the individual odour of the offspring, since it appears not developed in mothers made anosmic before paturition (Porter et al., 1994; Hernandez et al., 2002). In cows, olfaction and vision are equally effective in permitting calf identification (Griffith and Williams, 1996). Elimination of both senses prevents calf identification and the negative effects of suckling on LH secretion. As in cows, stimulation of oxytocin secretion during

suckling is modulated by olfacory cues emitted by the young (Hernandez et al., 2002). In contrast to cows, however, maternal olfaction does not affect prolactin release during suckling in goats.

Horses

Little information is available on equine pheromones. In the breeding season, the female horse (*Equus caballus)* show clear differences in excretion and scent-marking frequency when these are compared with values from the non-breeding season (Kimura, 2001). Concomitantly, the concentrations of fatty acids, alcohols, aldehydes, phenols, amines and alkanes in the faeces of this species differ according to the reproductive period, and also to maturity and sex. Faecal tetradecanoic (mysteric acid) and hexadecanoic acid (palmitic acid) signal oestrus in mares (*Table 12*), since their levels are higher in oestrous than in non-oestrous females. This difference, however, disappears when the faeces are scent-marked by stallions. During he breeding season, the urine of stallions contains high concentrations of cresols, which may indicate that a role of this scent-marking is masking the odour of the mares faeces. The urine of mares contains 54 (unidentified) volatile compounds, that were visualised by capillary gas chromatography, and of which one (with a retention time of 6.86 min) was present in urine collected at oestrus and absent in urine from the luteal phase of the oestrous cycle (Ma and Klemm, 1997). Furthermore, six unidentified compounds have increased concentrations and five lower concentrations at oestrus than in the period thereafter. The data are suggestive for a pheromonal role of certain mare urinary compounds, the more since oestrous urine has been shown to elicit in the stallion an increased rate of flehmen (Stahlbaum and Houpt, 1989).

Identification of the isolated mare urinary compounds may be of benefit in equine reproductive management. Inaccurate oestrous detection, for example, is a major problem in this regard, and has caused a low production rate of live foals (Bowen, 1989). As in pigs, a synthetic pheromone based on a natural appeasing pheromone secreted from specialised glands associated with the mammary glands is commercially available for horses. This equine appeasing pheromone (EAP) is a product (Pherocalm® in Europe; Modipher EQ® in the USA) from the company Pherosynthese, and calms anxious horses (Riley et al., 2002). The components of this putative maternal pheromone have been identified as fatty acids in proportions that are species-specific (Pageat, 2001) (*Table 12*).

Horse sweat and parotid glands contain two major proteins which, in analogy with urinary (MUPs) and salivary (SALs) lipocalins from other species, may function as semiochemical carriers (D'Innocenzo et al., 2006). One of these proteins, lipocalin allergen EquCl is most abundant in sweat, and shows good selectivity toward volatile straight-chain C_9-C_{11} compounds. The other protein, with an apparent mass of 28 kDa, has a sequence similar to that of parotid salivary proteins (Wheeler et al., 2003; Shaw and Schibler, 1986) and also some similarity with vomeromodulin (Khew-Goodall et al., 1991). The 28 kDa protein is most abundant in the parotid glands, and its presence was not dependent on sex. Ligands for this protein have not been identified yet.

Elephants

Female elephants form groups comprising a number of families consisting of a mother, and her offspring of different ages. Adult males separate from these family herds and spend most of their time in so-called bull areas. In such areas elephant bulls spend much of their leisure time building up strength and sorting out the bull hierarchy. When testosterone reaches high serum levels and ketonic changes are manifest in lipid metabolism, bulls attain in musth (Rasmussen and Perrin, 1999). Musth is a period among adult male elephants (over 15-20

years old) affecting many aspects of elephant society (www.elephant.se/musth.php). There is a three weeks pre-musth-condition, about one month high-musth, and one post-musth condition. A bull that is in musth, regardless of size, becomes very aggressive and automatically becomes dominant to any bull that is not in musth (Slotow and Van Dyk, 2006). Musth bulls leave bull areas and proceed to female herds, in search of a mating opportunity with a receptive female in oestrous. Bulls in musth typically stream secretions from their temporal glands and urine down their legs.

During that period, facial temporal gland secretions, urine and breath of male Asian elephants (*Elephas maximus*) discharge a variety of adult male-specific odorous compounds together with the bicyclic ketal, frontalin (1,5-dimethyl-6,8-dioxabicyclo [3.2.1] octane) (Rasmussen and Greenwood, 2003). Based on the mating-related behaviours (pre-flehmen and flehmen responses followed by checking of the male penis or temporal gland with the female's trunk) shown, it is postulated that frontalin functions as a male sex pheromone especially for females in the follicular phase of their cycle (*Table 13)*. Besides, frontalin also affects the behaviours of other conspecifics, the exhibited behaviour being dependent on the sex, developmental stage and physiological status of the responder. There are two chiral forms (enantiomers) of frontalin. These enantiomers are released by Asian elephants in a specific ratio that depends on the animal's age and stage of musth, and different responses are elicited in male and female conspecifics when the ratio alters (Greenwood et al., 2005). In African elephants (*Loxodonta africana*), frontalin has thus far not been demonstrated in male urine or glandular secretions. Studies with these elephants have shown that 2-butanone, acetone and 2-petanone, and 2-nonanone levels in field-collected urinary samples are considerably elevated in bulls during early musth, musth and late musth, respectively

Table 13: Putative sex pheromones in elephants.

	Source	**Detected compounds**	**Suggested function**
Asian elephant	facial temporal gland secretions, urine, and breath of bulls	1,5-dimethyl-6,8-dioxabicyclo [3.2.1]octane (frontalin) (a)	stimulate mating-related behaviour of follicular phase ♀
	♀ urine	(*Z*)-7-dodecen-1-yl acetate (b,c)	stimulate ♂ sexual behaviour
African elephant	♂ urine	butanone (elevated level during pre-musth), acetone and 2-petanone (elevated levels during musth), and 2-nonanone (elevated level during late-musth) (d)	signal reproductive status to ♀ conspecifics
	♀ urine	frontalin, *exo*-brevicomin, *endo*-brevicomin, α-farnesene and β-farnesene (e)	♂ signal reproductive status

Legend belonging to Table 13: a, Rasmussen and Greenwood, 2003; b, Rasmussen et al., 1997; c, Rasmussen et al., 1982; d, Rasmussen and Wittemyer, 2002; e, Goodwin et al. 2006.

(Rasmussen and Wittemyer, 2002). This suggests that the males communicate their condition via these ketones. Additionally, the similarity to compounds released during musth by Asian bulls that evoke bioresponses in conspecifics may indicate the existence of species-free musth signals.

Although it is not known whether frontalin is produced by male African elephants, it has recently been detected in this species in urine of *females*, as were *exo*-brevicomin, and *endo*-brevicomin, α-farnesene and β-farnesene (Goodwin et al. 2006), which have been shown to function as sex pheromones in insects (reviewed by Ma et al., 1999a; Dulac and Turello, 2003) and also strongly resemble or correspond with mice pheromones (*Table 8*). In contrast, urine of female Asian elephants contain high concentrations (~100 mM) of (*Z*)-7-dodecen-1-yl acetate (ZDA) (Rasmussen et al., 1997), which functions as a sex pheromone (Rasmussen et al., 1982) (*Table 13*). For, the latter authors have shown that, like the urine of those females, synthetic ZDA alone is able to elicit a series of behavioural responses in bulls ranging from sniffing and checking with the tip of the trunk to precopulatory behaviours, including flehmen, penile erections and mounting attempts. In the urine, a significant fraction of ZDA is bound to a 66-kDa protein, called elephant serum albumin, which is the probable initial carrier of frontalin also (Rasmussen et al., 2003). This albumin is thought to act as a pheromone transporter in urine, may extend the presence of pheromone in the environment without hampering detection, and/or may aid in the delivery of pheromone to chemosensory organs (Lazar et al., 2004).

The mucus of the trunk abundantly contains an 18.5-kDa OBP (Lazar et al., 2002). The trunk gives entry to an ethmoidal meatus complex around more than 32 highly scrolled olfactory turbinals and to an extensive bilobated VNO, which mirror the extraordinally well-development of the olfactory senses (Rasmussen et al., 2003). The elephant OBP only modestly increases the solubility of ZDA in the mucus, and is thought to serve as a scavenger of the pheromone and possibly other ligands, including odourants (Lazar et al., 2002). It is also presumed, that the OBP binds the urinary ZDA-albumin complex, where after there is a pulsatile release of ZDA from the albumin in the acidic trunk mucus (Rasmussen et al., 2003). Most ZDA, however, is supposed to remain bound to OBP on their way to the olfactory system, but some free ZDA may directly reach the olfactory MOS epithelium, or may reach the VNO where it is confronted with VNBPs. Unfortunately, data on receptor binding of pheromones in MOS and VNO neurons are lacking.

Summarizing, it can be concluded that the sexual and social status of elephants seems to be announced by chemical signals in at least the urine of males and females, and male temporal gland secretions. This may be of help to gain insight into societal interactions in elephants and to identify key breeding bull elephants within a population, and may be useful in implementing new conservation protocols. The role of binding proteins for elephant odourants and pheromones in secreted or excreted fluids is largely unknown, as is information about the olfactory receptors involved in the translation of pheromonal signs into a specific behaviour or physiological change.

Primates

Humans

Although humans and other primates are often believed to be worse smellers (microsmatic) and to depend more on their power of vision for their survival and reproduction, many recent studies have shown that olfaction (conscious and unconscious), either or not in combination with visual or tactile cues, does have an important role in human reproductive biology (for reviews, see Kohl et al., 2001; Wysocki and Preti, 2004; Grammer et al., 2005; Jacob, 2005; Evans, 2006). The existence of human pheromones is, however, controversial since humans

have a will of their own and can refuse the biological imperative (Jacob, 2005). Furthermore, the results in labs often differ from each other because of too many uncontrolled variables (for example, humans respond differently on a male or female researcher). Despite claims or suggestions reported in various scientific articles (Sobel et al., 1999; Grosser et al., 2000; Savic et al., 2001), no bioassay-guided study has thus far led to the isolation of true human pheromones (Wysocki and Preti, 2004).

Production of odourants and putative pheromones in humans is attributed to the apocrine glands of the skin (e.g., in the axillae and the genital area, on the chest and breasts, and around the navel, which become first functional during puberty when steroid hormone levels have increased (Cohn, 1994)), other glandular secretions and to skin flora present in moist body areas like the axillae, mouth, feet and genitals (Kohl et al., 2001; Penn et al., 2007; Soini et al., 2010). Freshly produced apocrine secretions are odourless, and become odorous after transformation by microorganisms (for a review, see Gower et al., 1986; Zeng et al., 1991; 1992; Dufort et al., 2001). Odours originating from the human skin, saliva, urine and genital secretions give rise to the characteristic natural human body odour. The characteristic axillary odour is brought about by a mixture of C_6-C_{11} straight-chain, branched, and unsaturated acids present in axillary sweat (Zeng et al., 1991; 1992; 1996a). In men sweat, the *E*-isomer of 3-methyl-2-hexenoic acid (liberated from non-odorous apocrine secretions by axillary *Corynebacteria*; Natsch et al., 2003) is the dominant component of the mixture (Zeng et al., 1991; 1992). This isomer is bound by two apocrine secretion proteins, the OBPs - apolipoproteins - ASOB1 and ASOB2 with a molecular weight of 45 kDa and 26 kDa, respectively (Spielman et al., 1995; Zeng et al., 1996b). In female sweat the straight-chain acids are relatively more abundantly present than in male sweat (Zeng et al., 1996a). These studies, however, deal with relatively few subjects and few or no repeat samples, which risk finding false GC-MS markers. Penn and allies (2007) have executed more extended and elaborated studies on axillary sweat, urine and saliva from 197 adult residents of an Austrian village, and collected five sweat samples per subject over 10 weeks using a novel skin sampling device, where after they analysed samples using stir bar sorptive extraction in connection with thermal desorption GC-MS. More volatile compounds have been found in axillairy sweat than in urine or saliva, and among them 373 peaks have been demonstrated in sweat that appear consistent over time. Of these GC-MS peaks, 166 have also been found in saliva and 78 in urine. Among the 373 candidate compounds, individually distinct and gender fingerprints have been demonstrated, while 44 individual (alcohols, ketones, phenols, aldehydes, esters and hydrocarbons) and 12 gender-specific volatile compounds have been identified. From the 12 gender-specific chemical compounds, six (a ketone, 6-phenylundecane, pentadecanoic acid, hexadecanoic acid, a methylhexadecanoic acid, and heptadecanoic acid) appear male-specific, while six others (a dialkyl ether, nonadecane, isopropyl hexadecanoate, 2-ethyl-hexyl-4-methoxy-cinnamate, docosane, and 1-octyl-4-methoxycinnamate) are female-specific.

Olfactory ability in women is generally better than that of men (Hirsch, 1992; Deems and Doty, 1987; Brand and Millot, 2001), and females may rely more on olfactory cues in mating behaviour than males (Herz and Inzlicht, 2002). When confronted to olfactory odours, male faces (presented briefly on a computer monitor) are significantly less attractive for women (using a 9-point visual rating scale) in presence of an unpleasant odour (rubber or synthetic body odour) than in presence of clean air or a pleasant odour (geranium or a male fragrance) (Demattè et al., 2007). In contrast, female ratings for male attractiveness in presence of a pleasant odour do not differ significantly from those in presence of clean air. Nevertheless, the findings match with the growing body of evidence related to the role of human scent in mate selection (e.g. Rikowski and Grammer, 1999). Though, women do rate the body odour of homosexual men as being comparatively more pleasant, sexier, and more

preferable than that of heterosexual men (Sergeant et al., 2007). Odours also effect human social preferences, like their daily interactions with other people. Social preferences (reflected by the likebility of neutral faeces) are influenced by subliminal smells (= odours that escape awareness) of differing hedonic value (pleasant, neutral or unpleasant), whereas the availability of conscious odour information may disrupt such effects (Li et al., 2007).

As in mice, (primer) pheromones are most likely also of influence on the timing of puberty in girls and the course of the human menstrual cycle. Pubertal maturation is more advanced in girls from stepfather-present homes than in those from single-mother homes (Ellis and Garber, 2000). Although findings are not unanimous, synchrony in menstrual cycles (either delayed or accelerated, dependent on the stage of the cycle of a so-called driver female whose cycle is thought to remain unaffected (Stern and McClintock, 1998)) has been reported in numerous studies on women who share a common environment (a.o. McClintock, 1971; Russell et al., 1980; Preti et al., 1986; Weller and Weller, 1993). A synchronizing effect on menstrual cycles has also been observed after application of *female* sweat extracts to the upper lips of women (Preti et al., 1986), while application of *male* axillary secretions to the upper lips of women results in a more regular menstrual cycle (Cutler et al., 1986). The findings on pheromonally influenced menstrual cycles, have received robust criticism for statistical and/or methodological errors (Wilson, 1987; 1992; Weller and Weller 1993; Schank, 2000). They, however, have been supported by findings of Shinohara et al. (2001), who showed that axillary pheromones from women either in the follicular or in the ovulatory phase of the menstrual cycle differentially modulate the LH pulse frequency in other women. Other scientists have also shown that natural compounds from the axillary region of humans can trigger in women neuroendocrine responses such as altered timing of the preovulatory LH surge (McClintock, 2000; Stern and McClintock, 1998) and altered pulse frequency (Preti et al., 2003; Wysocki and Preti, 2004). 3α-androstenol (which together with 5α-androstenone have been shown to act as releasers, that elicit the characteristic immobilisation response of oestrous sows) is proposed to be an axillary pheromonal component that is associated with the altering LH pulsing in women (Morofushi et al., 2000; Shinohara et al., 2000). The effective steroid dose (2.5 mM) tested by Shinohara and co-workers is, however, rather high for a putative pheromone. Pheromonal communication in vertebrates, in contrast to that of odourants, usually occurs without consciousness, and when pheromones are produced in high (suprathreshold) concentrations, they may evoke aversive effects, because conspecifics may become aware of them (Kohl et al., 2001). Apart from 3α-androstenol, 5α-androstenone, 5α-androstan-3α-ol-17-one (androsterone), 4,16-androstadien-3-one (androstadienone; ADIO), 1,3,5(10),16-oestratetraen –3-ol (oestratetraenol; EST), pregna-4,20-diene-3,6-dione, various fatty acids, and MHC peptides are considered as putative pheromones, which are listed in *Table 14* and which will be discussed in the following paragraphs.

16-Androstenes arise as metabolites of androgens secreted by apocrine skin glands, but only after the activity of microorganisms (Gower et al., 1986; Dufort et al., 2001). Among these 16-androstenes at least three of them, 3α-androstenol, 5α-androstenone and ADIO have pheromonal properties. 3α-Androstenol has a musk-like smell or floral odour, while 5α-androstenone has a urine-like scent or sandalwood odour (Amoore et al., 1977; Labows and Wysocki, 1982). However, perception of this and related steroids varies enormously between persons, from pleasant to unpleasant or odourless (Keller et al., 2007). A genetic variation in the OR gene *OR7D7* contributes to this variability in steroid perception. ADIO has been described as a low-odorous (Pause, 2004) to a strong urine-like (Olhoff et al., 1983), a musky (Jacob et al., 2002b) or an unpleasant (Lundström et al., 2003a) scent, or an odour whose quality changes during exposure-induced sensitisation from floral, vegetable, minty or fruity to predominantly putrid (Jacob et al., 2006). In contrast to ADIO, 3α-androstenol and 5α-androstenone do not activate the neuroepithelium of the human VNO, but significantly

activate that of the MOS (Jennings-White, 1995). In contrast to the latter authors, Knecht and co-workers (2003a;b) have found olfactory sensitivity of the human VNO towards 5α-andostenone. However, olfactory function toward 5α-androstenone sensitivity appears not affected after covering the VNO opening, which indicates that the VNO does not play a major role in the perception of androstenone. In *human* axillary sweat, volatile 16-androstenes are present in far lesser quantities than C_6-C_{11} acids (Zeng et al., 1996a). Due to sex differences in the colonisation of microorganisms (Coryneform bacteria in men *vs* Micrococcaceae in women) and androgen plasma levels, men contain a five-fold higher concentration of 5α-androstenone in their axillary sweat than women (Gower et al., 1985). The scent of 5α-androstenone increases skin conduction in humans (Van Toller et al., 1983), enhances intensive contacts of women with men (Cowley and Brooksbank, 1991), and positively influences human social attitudes as measured either by the rating of photos of women (more attractive, more sexy and friendlier) or men (warmer and friendlier) (Kirk-Smith et al., 1978), or by sniffing a bottle containing this steroid solved in silicone (Kline et al., 2007) (*Table 14*). 3α-Androstenol promotes the sexually attractiveness of men for women (possibly by increasing female sexual arousal (McCollough et al., 1981)), whereas 5α-androstenone, which is a more prominent odour than 3α-androstenol, induces negative emotions toward males (Filsinger et al., 1984; 1985; Maiworm and Langthaler, 1992). 3α-Androstenol is seen as the initial attractive signal that, within 20 minutes, becomes a repellent after its oxidation to 5α-androstenone (Labows et al., 1979), which is a long-term prevailing odour. Thus, less odorous males seem better off, which does appeal questions about the sense of this mechanism. Perception of 3α-androstenol and 5α-androstenone by females is, however, dependent on their hormonal status: the scent of 5α-androstenone being more pleasant for ovulatory women than for woman on other days of the menstrual cycle (Grammer, 1993). Thus, evaluation of the scent of 5α-androstenone by women changes when conception is most likely. This makes odorous males more attractive for ovulating females than for non-ovulating females.

In regard human reproduction, effects of olfactory cues are difficult to isolate from other sensory cues. Despite of that, humans are able to discriminate between males and females by olfactory cues alone, which could be ascribed to sex differences in the composition of axillary secretions. Various studies claim evidence for the effects of (not further described) synthetic pheromone-like substances (derived from underarm secretions and added to their usual perfume or aftershave lotion) on sexual attractiveness of young men (Cutler et al., 1978), young women (McCoy and Pitino, 2002), and postmenopausal women (Rako and Friebely, 2004), using petting/affection/kissing, formal dates, informal dates, sleeping next to a romantic partner, sexual intercourse, and self-stimulation to ejaculation (masturbation) as parameters of sociosexual behaviour. Although these findings are interesting, especially for the consumer product industry, they are disputable, because of a number of methodological imperfections (Grammer et al., 2005; Winman, 2004). Commercial pheromone products containing androstenol are: Scent of Eros, Perception, Alter Ego, Perfect 10, Attraction, Chikara, Passion Pheromone Attractant and Androstenone Phragrance Additive (http:/pherolibrary.com/androstenol.htm). Commercial pheromone products that contain 5α-androstenone (alone or in a mixture with androstenol) are: Primal Instinct, Rogue Male, Andro 4.2, Passion Pheromone Attractant, New Pheromone Additive, The Edge, Alter Ego, Perception, Perfect 10, Attraction, Pheromax, Chikara, and Androstenone Phragrance Additive. For a guide to available commercial pheromone products, see http:/pherolibrary.com/androstenone.htm. For additional information on pheromone-based cosmetic perfumes and human sexual behaviour, see Zaviacic et al. (2009).

Although androsterone, like 3α-androstenol, is not effective on the choice behaviour (rest room stalls) of either men or women (Gustavson et al., 1987), it is found to have a

significant impact on women's subjective ratings of the attractiveness and other attributes of photographed men (Maiworm and Langthaler, 1992) (*Table 14*). Therefore, it is used in some commercially available pheromone products, i.e. Scent of Eros, Perfect 10, Alter Ego and Perception (http://pherolibrary.com/human-pheromones/androsterone.htm). Androsterone has a musky odour and olfactory properties similar to those of 3α-androstenol (Kloek, 1961; Jennings-White, 1995). In the skin, androsterone is metabolised from dihydroepiandrosterone (Sharp et al., 1976; Kaufmann et al., 1990a; Belanger et al., 2003). Androsterone is found in lipids coating the axillary hair and is secreted by sebaceous glands (Toth and Faredin, 1983; Chen et al., 2002; Karlsson et al., 2003). It is absent in fresh apocrine secretions (Labows et al., 1979), but appears therein after the activity of micro-organisms. Like 3α-androstenol and 5α-androstenone (Kingsbury and Brooksbank, 1978; Smals and Weusten, 1991), androsterone is also present in human urine (Brown et al., 2004; Cawley et al., 2005; Saudan et al., 2006), and does not activate the neuroepithelium of the human VNO (Jennings-White, 1995). For the most part, the claimed active component in commercially available perfumes or perfume additives is an androstene without activity in the human VNO (for more detailed information, see Jennings-White, 1995). Data from experiments, in which the human VNO was either occluded or left open, confirmed, that the VNO is not involved in the perception of endogenous odours like ADIO (Frasnelli et al., 2010). Pheromonal effects in humans thus seem to be more likely mediated by intranasal sensory epithelia than the extranasal epithelium of the VNO. This assumption is strengthened by the finding that, among a group of many odours, androstenone and ADIO selectively activate a specific human odourant receptor (OR7D4) *in vitro* (Keller et al., 2007).

ADIO has been demonstrated in men's sweat (Brooksbank et al., 1972; Labows, 1988), semen (Kwan et al., 1992), axillary hair (Nixon et al., 1988) and skin cells (Kodis et al., 1998). This 16-androstene has little or no electrophysiological effect on the MOS (Monti-Bloch and Grosser, 1991; Berliner, 1994), but do have such an effect on the VNO (Berliner, 1993; 1994; Jennings-White, 1995; Monti-Bloch et al., 1998a; Grosser et al., 2000). The existence of a functional VNO in humans, is however, doubtful (for more information, see Trotier et al., 2000; Meredith, 2001, Frasnelli et al., 2010, and the next chapter), and is actually mainly accepted by researchers with commercial interests, like Monti-Bloch and co-workers and Berliner and co-workers. In spite of that, ADIO is currently considered to be the best steroidogenic candidate for a human pheromone (for a review, see Jacob, 2005; Jacob et al., 2006), particularly since it is the most prevalent 16-androstene in human (in particular male) secretions (Nixon et al., 1988), and, when administered in picomolar quantities directly to the vomeronasal organ, it has been shown to elicit hormonal changes and to stimulate positive mood state (i.e. significant reduction of nervousness, tension and other negative feeling states) in women (*Table 14*), where control subjects showed an increasing negative mood (Gower and Ruparelia, 1993; Grosser et al., 2000). Physiological and/or psychological effects (inclusive stimulating effects on sexual arousal) of ADIO have also been reported in studies with humans in which they were exposed to micromolar to nanomolar doses of this steroid, including quantities which are thought to be below conscious detection levels for the majority of the population (Jacob and McClintock, 2000; Jacob et al. , 2001; 2002 Bensafi et al., 2003; 2004a,b; Lundström et al., 2003a;b; Cornwell et al., 2004; Wyart et al., 2007; Saxton et al., 2008; Hummer and McClintock, 2009). The effects appear gender-specific, dose-dependent, and to depend on the exposure method (transient or continuous) (Bensafi et al., 2004a *vs* Jacob and McClintock, 2000), the context or meaning of the situation (Jacob and McClintock, 2000; McClintock, 2000), whether the experimenter was a man or a woman (Lundström and Olsson, 2005), and probably also on the applied statistical test (as has been demonstrated for obtained data on human's attractiveness (Winman 2004)) and sexual

orientation (as has been shown for human odours (Martins et al., 2005)). The mood effects are not influenced by the menstrual cycle phase (Lundström et al., 2003b).

The ADIO concentration (0.00625 M), that is necessary to affect autonomic function and mood following transient exposure, appears far greater than reported endogenous levels (98 and 36 ng/100 ml blood plasma in men and women, respectively; (Brooksbank et al., 1972), and 0-143 pmol/mg male hair (Nixon et al., 1988)). This may be in support of the thought that ADIO does not act through the VNO or MOS but through an alternative pathway. Alternative options that have been suggested in this regard are that ADIO follows a transdermal pathway of action, or that it acts after being absorbed into the circulation system (Bensafi et al., 2004b). Furthermore, ADIO and other putative steroidal pheromones have been shown to activate the non-olfactory nasal respiratory epithelium (Knecht et al, 2003a; Witt and Hummel, 2006), which may indicate that afferent nerves from the trigeminal nerve transport evoked electrical potentials to the brain. This is supported by the observed similar cortical responses to ADIO in intact humans and in humans, in which the VNO has been occluded (Gerber et al., 2005; Witt and Hummel, 2006). Savic et al. (2001a) have demonstrated that ADIO activates the hypothalamus in a gender-specific manner, i.e., in heterosexual women but not in heterosexual men. Several years later, in 2005, Savic et al. (2005) have shown a congruental effect on brain response to ADIO in homosexual men and heterosexual women, and conclude for a coupling between hypothalamic neuronal circuits and sexual preferences. Compared with other odorous substances, ADIO activates the anterior part of the inferior lateral prefrontal cortex and the superior temporal cortex in addition to olfactory areas, which are brain areas implicated in aspects of attention, visual perception and recognition and social cognition (Gulyas et al., 2004). Because of these actions, ADIO is considered to be a male modulator pheromone. The concerned androgen has been demonstrated to act through the MOS and not through the VNO, olfactory mucosa nor venous blood (Savic et al., 2009). This opinion corresponds with the observation that, ADIO and androstenone selectively activate a specific human odourant receptor OR7D4 *in vitro* (Keller et al., 2007). Commercial pheromone products that contain ADIO are Realm (women's version), Pheromax (men's version), and ADIO pheromone chemistry set bottle (http:/pherolibrary. com/androstadienone.htm).

Oestratetraenol (EST) is an odourless steroidal chemosignal (Ohloff et al., 1983) that modulates mood, memory and/or skin temperature (Jacob and McClintock, 2000; Jacob et al., 2001; Bensafi et al., 2004b), and is (like ADIO) a significant gender-specific and species-specific stimulator of the VNO in humans, ADIO acting on that of women and EST on that of men (Jennings-White, 1995). In contrast, like ADIO, its electrophysiological effect on the MOS is very small compared to that of 3α-androstenol, 5α-androstenone and several other olfactants of importance in perfumery tested, and not gender-specific. However, like ADIO, EST does activate the non-olfactory nasal respiratory epithelium (Hummel, 2000). Furthermore, EST activates the sexually dimorphic nuclei of the anterior hypothalamus (Savic et al., 2005) and other brain regions (the anterior medial thalamus and the right inferior frontal gyrus; Sobel et al.,1999) in heterosexual men (and lesbian women, Berglund et al., 2006) (*Table 14*), while effects are lesser in heterosexual women (Savic et al., 2005). Although related to substances extracted from the human skin (Sobel et al., 1999) this putative female pheromone is a synthetic compound never reported in axillae (Preti et al., 2003). This oestrogen-resembling steroid has, however, been detected in the urine from pregnant women (Thysen et al., 1968). The findings with ADIO and EST strongly suggest that the preferred pathway for transporting pheromone-like cues in humans is associated with the responder's sexual orientation rather than to the biological sex (Savic et al., 2005; Berglund et al., 2006). This opinion is confirmed by tests in which heterosexuals, lesbians, and gay men had to make two-alternative forced-choice preference judgments for the odours

Table 14: Putative sex pheromones in humans

Source	Compound	Effect
♂ axillary secretion (AS); urine (a-f)	3α-androstenol (high dose)	alters LH pulsing ♀ (g,h); promotes sexually attractiveness of ♂ for ♀ (possibly by increasing female sexual arousal) (i)
	5α-androstenone	skin conduction ♀♂ (j); enhances intensive contacts ♀♂ (k); positively influences human social attitudes towards ♀* and ♂ (l); induces negative emotions towards ♂ (m-o)
	5α-androstan-3α-ol-17-one (androsterone)	influences ♀ subjective ratings of the attractiveness and other attributes of photographed ♂ (o)
♂ AS (a,p); semen (q); axillary hair (r); skin cells (s)	4,16-androstadien-3-one (androstadienone; ADIO)	stimulates positive mood state ♀ (t,u); activates the hypothalamus in heterosexual ♀ and homosexual ♂ (v,w) activates brain areas implicated in attention, visual perception, recognition and social cognition (x); activates the ♀ VNO (y); activates the non-olfactory nasal respiratory epithelium (z) enhances cortisol salivary levels, maintains better mood, leads to higher sexual arousal and increases physiological arousal in ♀ (aa)
urine pregnant ♀ (bb)	1,3,5(10),16-oestratetraen-3-ol (oestratetraenol; EST)	modulates mood, memory and/or skin temperature (cc-ee); activates the ♂ VNO (z); activates the non-olfactory nasal respiratory epithelium (bb); activates the sexually dimorphic nuclei of the anterior hypothalamus (w), the anterior medial thalamus, and the right inferior frontal gyrus (ff) in heterosexual ♂ and lesbian (gg)
skin (hh)	pregna-4,20-diene-3,6-dione	reduces LH/FSH pulsatility and plasma levels, and testosterone levels (hh-ii), decreases respiratory frequency, increases cardiac frequencies, and changes electrodermal activity and EEG pattern ♂ (hh)
Vaginal secretions (jj/kk)	acetic-, butanoic-, propanoic-, methylpropanoic-, and methylpentanoic acid (jj/kk), which vary in concentration during the menstrual cycle and which odour is least unpleasant at ovulation (ll/mm)	a synthesised mixture of 5 ovulatory fatty acids enhances ♂ salivary testosterone levels, makes ♂ less discriminative in judging ♀ attractiveness (nn-pp), and encourages ♂ conspecifics to copulate, thus properly timing reproductive behaviour to enhance the chance for offspring (qq/rr)
lactiferous ducts; sebaceous glands (ss); AS (tt/uu)	HLA-proteins	enable individual recognition, and influence sexual orientation and mate choise (vv-aaa)

Legend belonging to Table 14: *, ovulatory women experience the scent as more pleasant than on other days of the menstruation cycle (Grammer 1993). a, Brooksbank et al., 1972; b, Kingsbury and Brooksbank, 1978; c, Smals and Weusten, 1991; d, Brown et al., 2004; e, Cawley et al., 2005; f, Saudan et al., 2006; g, Morofushi et al., 2000; h, Shinohara et al., 2000; i, McCollough et al., 1981; j,Van Toller et al., 1983; k, Cowley and Brooksbank, 1991; l, Kirk-Smith et al., 1978; m, Filsinger et al., 1984; n, Filsinger et al., 1985; o, Maiworm and Langthaler, 1992; p, Labows, 1988; q, Kwan et al., 1992, r, Nixon et al, 1988; s,Kodis et al., 1998; t, Gower and Ruparelia, 1993; u, Grosser et al., 2000; v, Savic et al., 2001a; w, Savic et al., 2005; x, Gulyas et al., 2004; y, Jennings-White, 1995; z, Hummel, 2000; aa, Wyart et al., 2007; bb, Thysen et al., 1968; cc, Jacob and McClintock, 2000; dd, Jacob et al., 2001; ee, Bensafi et al., 2004; ff, Sobel et al.,1999; gg, Berglund et al., 2006; hh, Berliner et al., 1996; ii, Monti-Bloch et al., 1998b; jj, Curtis et al., 1971; kk, Michael et al., 1975; ll, Preti and Huggins, 1975; mm, Doty et al., 1975; nn, Jütte, 1995; oo, Grammer and Jütte, 1997; pp, Jütte, http://anticipation.info/texte/eibesfeldt/evolution.anthro.univie.ac.at/institutes/ urbanethology/ student/html/astrid/femphers. html; qq, Michael et al., 1974; rr, Michael et al., 1975; ss, Murphy et al., 1983; tt, Zavazava et al., 1990; uu, Zavazava et al., 1994; vv, Ober et al., 1997; ww, Ober et al., 1999; xx, Ober, 1999; yy, Jacob et al., 2002a; zz, Martins et al., 2005; aaa, Pause et al., 2006.

of underarm sweat collected from other heterosexuals, lesbians and gay males (Martins et al., 2005). In male-to-female transsexuals, the smelling of odorous steroids, among which EST and ADIO, has a sex-atypical effect on hypothalamus activiation (Berglund et al., 2008). Like ADIO, EST has been demonstrated to act through the MOS and not through the VNO, olfactory mucosa or venous blood (Savic et al., 2009). The men's version of Realm is a commercial pheromone product that contains EST (http:/pherolibrary.com/estratetraenol. htm).

In men, exposed to synthesised pregna-4,20-diene-3,6-dione, a progesteroneic pheromone occurring in human skin extracts, evokes electrical potentials in the VNO (EVG responses). EVGs were obtained when the steroid was delivered in the air stream directed into the lumen of the VNO at a concentration of 10^{-10} to 10^{-9} M, whereas no significant electrical effects were observed when the same applicator delivered identical stimuli to the nasal respiratory epithelium or to the olfactory epithelium of the MOS (Berliner et al., 1996). At a concentration of 10^{-9} M this steroidal vomeropherin (i.e. chemosensory substance whose effect is mediated through the VNO) significantly reduces LH- and FSH pulsatility, plasma LH- and FSH levels as well as testosterone levels in men (*Table 14*), suggesting the existence of a functional vomeronasal-pituitary pathway in adult humans (Berliner et al., 1996; Monti-Bloch et al., 1998b). Additionally, decreased respiratory frequency, increased cardiac frequency, and changes of electrodermal activity and EEG pattern have been observed as a result of pregna-4,20-diene-3,6-dione treatment (Berliner et al., 1996), which could be indicative for functional connections between the VNO and various hypothalamic areas in men. Despite of these findings and those of Monti-Bloch and Grosser (1991) and Monti-Bloch et al. (1998b,c), as remarked before, the adult human VNO is generally considered to be non-functional, and are steroidal vomeropherins also able to activate the nasal non-olfactory respiratory epithelium (Knecht et al., 2003a,b) and brain (Gerber et al., 2005; Witt and Hummel, 2006) in absence of a functional VNO.

Although in slightly different concentrations, a similar oestrogen-based signaling system of volatile C_2-C_5 aliphatic acids (copulins) has been found in the vaginal secretions of women and female nonhuman primates, especially rhesus monkeys (i.e., acetic-, propanoic-, butanoic-, methylpropanoic-, and methylpentanoic acid) (Curtis et al., 1971; Michael et al., 1975). The composition of these odorous short-chained fatty acids varies during the female menstrual cycle (Preti and Huggins, 1975), the vaginal secretion odour at ovulation (like that of axillary odour; Poran, 1994; Singh and Bronstad, 2001) being both the most intense and least unpleasant (Doty et al., 1975). A synthesised mixture of five ovulatory fatty acids enhanced male saliva testosterone levels (to nearly 150% of starting levels) and made males

less discriminative in judging female attractiveness (Jütte, 1995; 2007; Grammer and Jütte, 1997) (*Table 14*). Such compounds seem to function as sex pheromonal signals, which encourage male conspecifics to copulate and thus properly time reproductive behaviour to enhance the chance for offspring (Michael et al., 1974;1975). However, one has to keep in mind that, in contrast to most other mammalian species, human sexual activity is not restricted to the ovulatory phase of the ovarian cycle, because other signals than chemical cues are also involved, and possibly are more important factors to stimulate sexual behaviour (Kohl et al., 2001).

Like various mammalian species (see above, the chapters on sex pheromones in cats, dogs and pigs), lactating women emit odours that release activity in newborns. Nipple, areola and mlk odours appear to be equivalent to the whole breast odour in stimulating oral activity and in delaying crying onset of 3- to 4-days old infants (Doucet et al., 2007). The smells of alveolar secretion and milk both release mouthing, stimulate eye opening, and delay and reduce crying in newborns. Similarly, experiments from Goubet and coworkers (2007) have shown, that newborns display lessened distress and more oral movements when confronted to their mother's odour than when confronted to unfamiliar odour, or no odour. Analysis of the volatile compounds in sweat patch samples, collected from the para-axillary and nipple-areola regions of women during pregnancy and after childbirth, does presume that, at the time of birth and during the first weeks of life, the characteristic pattern of the nipple-areola region is probably useful as a guide to nourishment, whereas the distinctive olfactory pattern of the para-axillary area is probably useful to newborn babies for recognizing and distinguishing their own mother (Vaglio, 2010). Apart from that, social chemosignals from breastfeeding women (and their breastfeeding infants, because breast secretions from the mothers under investigation most likely also contain saliva or other secretions from their infant) increase sexual motivation of other women (Spencer et al., 2004). Those with a partner experienced enhanced sexual desire, whereas those without one had more sexual fantasies.

Although evidence is often poor (Hurst et al., 2005), MHC odours provide the main basis for individual recognition, sexual orientation and mate choice among nonhuman mammals (Beauchamp et al., 1985; Halpin, 1986; Potts et al., 1991; Yamazaki et al., 1979; 1999; Boehm and Zufall, 2006) and humans (Ober et al., 1997; 1999; Ober, 1999; Jacob et al., 2002a; Martins et al., 2005; Pause et al., 2006; Havlicek and Roberts, 2009) (*Table 14*). MHC-linked odour components can be verbally described, but generally it appears difficult to describe odours in sufficient detail to link the description to the allelic specificity of the MHC (Wedekind et al., 2007). It is asserted that men and women are able to distinguish among genetically distinct (MHC-dissimilar), self versus non-self, odours. They prefer the scent of non-self odours, i.e. the scent of genetic diversity, which is produced by a immuno-compatable partner, who thus posesses fitting HLA (Human Leukocyte Antigen is the human MHC)-dependent immune system components (Wedekind et al., 1995; Wedekind and Furi, 1997; Ober et al., 1997; 1999).

In established couples, only one study (Ober et al., 1997) described MHC-dissasortative mating preference in line with that expected based on odour preference studies. Various researchers (Nordlander et al., 1983; Sans et al., 1994; Jin et al.,
1995; Hedrick and Black, 1997), however, found no evidence for a preference for MHC-dissasortative mate choise or even found the opposite, the preference for a MHC-assortative odour scent (Rosenberg et al., 1983). Thus, in married couples, MHC-correlated mating studies did not result in uniform effects. All studies on MHC-correlated odour preferences and MHC-correlated human mate choice were critically scrutinised by Havlicek and Roberts (2009). They pointed to great variations in sample size and ethnical heterogeneity of sample populations, which most likely have biased the results significantly. Other factors, like the

reproductive status of target persons as well as that of raters, the long-term versus short-term mating context and the use of an contraceptive pill, may also have biased the obtained data.

Mothers are able to identify their own newborn infants from the smell of a previously worn T-shirt (Schaal et al., 1980), like MHC-associated odours do in kin recognition of mice (Manning et al., 1992; Yamazaki et al., 2000). In turn, infants prefer breast or axillary pads from their own mother above those of other women (Schaal and Porter, 1991; Goubet et al., 2007). Thus, at least some components of the individual specific odour may be under the control of HLA genes (Preti et al., 1997). The pheromones which provide information about the type of genes one possesses within the HLA complex are examples of signaler pheromones (Wysocki and Preti, 2004). HLA-related proteins have been found in lactiferous ducts of the breast, the intradermal portion of sebaceous glands (Murphy et al., 1983), and human axillary sweat, which is a mixture of sebaceous, apocrine, merocrine and apomerocrine glands secretions (Zavazava et al., 1990; 1994). The MHC contains the most diverse genes known in vertebrates (Klein, 1986), and more than 200 loci have been identified within the human MHC (Beck and Trowsdale, 2000). Polymorphic ownership signals only can provide each individual in the local population from a unique signature. Therefore, MHC-based odours are excellently suitable to attribute to the recognition of familiar scents. Likewise, proteins belonging to the lipocalin family can be put forward for this goal. For, in mice, the relative concentration of the ~15 MUPs in urine varies from male to male, and these urinary substances have been shown to contribute in the individual recognition mechanism (Hurst et al., 2001). To date no information is available about the existence of releaser sex pheromones in humans. The only response ascribed to a human releaser pheromone is the attraction and moving of infants to breast odours of their mother (Varendi and Porter, 2001).

In humans, both OBP and vomerodulin immunoreactivity is localised in the mucus of vomeronasal, nasal olfactory, and nasal respiratory epithelia to function as chemosensory stimulus transporters associated with perireceptor processes in both vomeronasal and olfactory signal transduction (Krishna et al., 1994). More recently, two human OBPs (hOBP-IIa and hOBP-IIb with a molecular weight of 17.8 kDa and 18 kDa, respectively) have been identified, which are differently expressed (Lacazette et al., 2000). hOBP-IIa is strongly expressed in the nasal structures, salivary glands (von Ebner's and submaxilary glands), lachrymal glands, and lung, and hOBP-IIb more strongly in genital sphere organs like the prostate and mammary gland. Both OBPs are furthermore expressed in the male deferent ducts and in the placenta. This may indicate that hOBP-IIs are involved in several functions like olfaction, respiration, taste, lactation and reproduction. Unfortunately, ligands for these odourant and pheromone binding proteins are unknown, which by that leaves the question unanswered whether these lipocalins bind the same ligand to fulfil different physiological functions.

Nonhuman primates

Like humans, nonhuman primates use chemical signals to discriminate individuals (Halpin, 1986; Heyman, 2006; Lewis, 2006; Mertl-Millhollen, 2006; Smith, 2006). Chemical cues have the advantage over other sensory cues in that they remain effective in the absence of the emitter, the message can be long-lasting, and a recipient may receive the cues (and a sender can emit the signals) irrespective of its sleeping/awake state. As many other mammalian species, individual scent signatures are produced by nonmammalian primates and have been demonstrated in a variety of scent sources, like urine, faeces, vaginal secretions, gland secretions, including anogenital, fascial, axillary, brachial, and subcaudal glands (for a review, see Smith, 2006). In these primates scent marking possibly functions to label and defence resources such as territories, and to communicate individual specific information

such as reproductive condition to conspecifics and dominance status within groups (Di Fiore et al., 2006; Lewis, 2006; Smith, 2006). Scent marks thus may contain sex pheromones.

Although 13 proteins have been identified in the scent mark of the common marmoset (*Callithrix jacchus*), results from their behavioural assays suggest that it are volatile rather than nonvolatile cues which play the key signaling role in the scent mark of this primate (Smith, 1994), like they do in many other primate species (e.g., chimpanzees (*Pan tryglodytes;* Fox, 1982), rhesus monkeys (*Macca mulatta;* Keverne and Michael, 1971), ring-tailed lemurs (*Lemur catta;* Hayes et al., 2004), saddle-back tamarins (*Saguinus fuscicollis),* cotton-top tamarins (*Saguinis oedipus;* Epple et al., 1993), and humans (Michael et al., 1974; Zeng et al., 1996b). Chemical information on the volatile compounds that are involved in olfactory signaling of individuality in primate species is, however, scarce. In this regard, research is limited to six species: rhesus monkey (Michael et al., 1971) common marmoset (Smith, 1994; 2006; Smith et al., 2001), ring-tailed lemur (Knapp et al., 2006), coquerel sifika (*Propithecus verrauxi coquereli*; Hayes et al., 2004), saddle-back tamarin (Yarger et al., 1977), and cotton-top tamarin (Belcher et al., 1988).

Vaginal secretions of rhesus monkeys contain short-chain aliphatic acids (identified as acetic, proprionic, isobutyric, butyric, isovaleric and isocaproic acids), which stimulate sexual behaviour (mounting; ejaculations) in males, after daily application of the mixture to the sexual skin of recipient females (Curtis et al., 1971; Michael et al., 1971; 1975). Although the content of acids in vaginal lavages unexpectedly decreases at midcycle when the female's attractiveness is highest, there is an increasing flow of secretions to the outside at this time (Bonsall and Michael, 1980). The findings are, however, criticised by Goldfoot (1981), who remarked that these chemical cues are neither necessary nor sufficient for the co-ordination of fertile matings, and volatile materials other than vaginal products can stimulate sexual activity. Pigtail macaques (*Macaca nemestrina*), common squirrel monkeys (*Saimira sciureus*) and black-handed spider monkeys (*Ateles geoffroyi*) are equally olfactory sensitive for carboxylic acids, acetic esters, aliphatic alcohols and aliphatic aldehydes, and they do not perform more poorly in detecting them than humans (reviewed by Laska et al., 2005). Male stumptailed macaques (*Macaca arctoides*), exposed to vaginal secretions from the late follicular phase of the menstrual cycle, differ from those exposed to menses secretions or saline solution in sustained plasma testosterone concentrations up to 120 min after exposure (Cedra-Molina et al., 2006). This effect is accompanied by a luteinizing hormone surge, occurring 30 minutes after exposure to late follicular phase secretion swabs. Apparently, male stumptailed macaques draw information concerning female reproductive status from the female's vaginal odour.

The marmoset scent mark is a complex mixture of scents from several sources, including secretions from the apocrine and sebaceous glands, secretions from non-specialised circumanal skin glands, urine, genital tract secretions, and faecal material (Sutcliffe and Poole, 1978). GC-MS analysis and behavioural assays have recently demonstrated that each female marmoset (in the luteal phase of their ovarian cycle) has a unique ratio of highly volatile chemicals in their scent mark, which likely affect individual discrimination (the ability to distinguish between two scents) and may play a key role in regulating both female intrasexual competition and intersexual communication (Smith, 2006). In the female marmoset's scent mark, a total of 162 chemicals has been gas chromatographically detected, from which 113 are positively identified with mass spectrometry (Smith et al., 2001). They include short-chained fatty acids (e.g., hydrazoic acid), aromatic nitrogen-containing chemicals (e.g., 2,5-dimethylpyrazine), sulphur-containing compounds (e.g., dimethyl trisulphide), lactones, and a range of 1,2 benzoic esters. A large number of these chemicals have also been found in scent secretions of other animals (e.g., aromatic nitrogen-containing chemicals in white-tailed deer (Gassett et al., 1996), sulphur-containing chemicals in hog-

nosed skunk, *Conepatus moseleucus* (Wood et al., 1993), fatty acids in lion (Andersen and Vulpius, 1999), lactone in striped hyena, *Hyena hyena* (Buglass et al., 1990), and may evoke pheromonal effects (e.g. 2,5 dimethylpyrazine in mice (Novotny et al., 1990b).

The numbers of volatile chemicals detected in the scent marks of other primates than the common marmoset are 16 in saddle-back tamarins (Yarger et al., 1977), 13 in cotton-top mandarins (Belcher et al., 1988), and 50-300 in prosimian species (Hayes et al., 2004; Knapp et al., 2006). In scent marks of male saddle-back tamarins, squalene and 15 *n*-butyric acid esters were identified in all individuals, but in individually unique ratios (Smith et al., 1985). Of the 13 chemicals detected in the scents from cotton-top tamarins, however, only three appear consistently in the scents from all individuals. Individual ring-tailed lemurs possess unique ratios of the most abundant 19 volatile chemicals among the 100 to 300 scent chemicals that are present, indicating both qualitative and quantitative differences between individual scents (Knapp et al., 2006).

Both common marmosets and cotton-top tamarins are able to distinguish odours of peri-ovulatory females from those of non-ovulatory females with increased sexual arousal and testosterone release (Smith and Abbott, 1998; Ziegler et al., 1993, 2005). Functional MRI-studies have shown that peri-ovulatory odours activate the medial preoptic area and anterior hypothalamus in common marmosets (Ferris et al., 2001). Snowdon and allies (2010) proposed from their studies that cues stimulating male marmoset sexual behavior are multivariate and include the male's social condition (single or paired; a father or not a father) and the learnt specific cues related to their own mates (i.e. odour-specific, vocal and visual cues). Studies of several species of marmosets and tamarins have reported individual recognition by odour alone (for review, see Epple (1986)). Snowdon et al. (2010) demonstrate that males can learn to associate arbitrary odour cues with sexual experience, suggesting that males may learn cues identifying their mate through sexual interactions. For more information about such signature compounds in vertebrates, see Wyatt (2010).

Using habituation/ dishabituation tests to recognise individuals and not just individual scents (Johnston and Jernigan, 1994), as first authors, Palagi and Dapporto (2006) have demonstrated olfactory individual recognition (the discrimination of one out of many known individuals by its scent) in a nonhuman species, i.e., the ring-tailed lemur. They show that interindividual odour differences in males appear mainly dependent upon the relative concentrations of the volatile compounds (identified by Hayes et al., 2005) in brachial glands. The composition of the brachial secretions is not affected by social (ranking, stage, age or group provenance of the donors) and environmental (seasonal) situations, but is probably based on the individual uniqueness of the signal rather than on the integration of different information, since secretions belonging to two unfamiliar males with he same age, ranking position and group provenance can be distinguished. Quantitative differences in volatile scent compositions to signal individual identity have furthermore been found in nonprimate species, either alone (Indian mongoose (Gorman, 1976) and giant panda (Hagey and McDonald, 2003)), or in combination with qualitative differences (wolf (Raymer et al., 1985) and European badger (Buesching et al., 2002a,b)). In contrast, it are qualitative and quantitative differences in nonvolatile rather than volatile compounds that characterise mice scent ownership (Nevison et al., 2003).

Using two conditioning paradigms, Laska et al. (2006) have recently shown that pigtail macaques and common squirrel monkeys of both sexes are able to detect the putative human pheromones ADIO and EST at concentrations in the micromolar and mM range, respectively. Male and female black-handed spider monkeys, in contrast, differ markedly in their sensitivity to these two steroids, with males not showing any behavioural response to ADIO and females not responding to EST. These latter data show that a gender-specific influence of ADIO and EST is not restricted to humans. It is unknown, however, whether nonhuman

primates are able to synthesise ADIO and EST, and to release them through secreted or excreted body fluids. Pigtail macaques, squirre monkeys and spider monkeys are furthermore able to detect 5α-androstenone in micromolar concentrations (Laska et al., 2005), which are lower or at least as low as concentrations reported for humans (Wysocki and Beauchamp, 1984; Knecht et al., 2002) and pigs (Dorries et al., 1989; Amor-Frempong et al., 1997), and that in pigs have been shown to induce immediate behavioural responses (Dorries et al., 1997) and oxytocin release (Mattioli et al., 1986). Pigtail macaques, squirrel monkeys and spider monkeys detect 3α-androstenol first in millimolar concentrations, while humans can do that in micromolar concentrations (Brooks and Pearson, 1989; Morofushi et al., 2000), and thus are less sensitive for this steroid than humans. In contrast to humans, of which a substantial proportion (~30%) are anosmic to 3α-androstenol or 5α-androstenone, none of the monkeys and macaques tested is anosmic to these 16-androstenes. This could be due to the considerable loss of the number of functional receptor genes in humans (see next chapter). Interestingly, in contrast to the human, 16-ene-synthetase activity, a prerequisite for the transformation of 5,16-androstadien-3-β-ol (the precursor of the putative human steroid pheromones) into 3α-androstenol, was not measurable in testicular homogenates of two macaque species, the rhesus monkey and the crab-eating macaque (*Macaca fascicularis*) (Weusten et al., 1990). Consequently, the question rises whether nonhuman primates are able to form 3α-androstenol and 5α-androstenone elsewhere in the body to subsequently externalise them. Unfortunately, no further data on this topic are currently available.

Thus far, no study has demonstrated the relationship between olfactory cues and MHC genotype in nonhuman primates as was done for other vertebrate species, including humans (see the paragraphs on rodents and humans, and the next chapter). Recently, a relationship has been suggested between MHC and profiles of volatile compounds obtained from tail and scent gland samples of ring-tailed lemurs (Knapp et al., 2006), of which is known that they are able to distinguish individual scents (Mertl, 1975). However, sample sizes in the study of Knapp and co-workers are relatively small and statistical significance has not been obtained. Therefore, further studies of the MHC and olfactory signals in non-human primates are needed to find out whether MHC has a role in individual or species recognition or mate choice as it has been suggested for other vertebrates. Regarding the importance of scent-marking and pheromone communication in nonhuman primates, a role of pheromone-binding lipocalins or lipocalin pheromones seems likely. Scent marks from the saddle-back tamarin contain a number of water-soluble proteins that have been demonstrated with gel electrophoresis (Belcher et al., 1990). It appears from these studies that the urine of these tamarins includes the major protein (66 kDa), while scent gland secretions contain a second protein (18 kDa). The observations suggest that proteins are a component of what constitutes the scent image. The authors hypothesise that they may serve as carriers and/or reservoirs for more volatile ligands, which encode some of the communicatory messages contained in the material. If so, the 18 kDa protein demonstrated by Belcher and co-workers could be a lipocalin.

The absence or poor development of a VNO, and an efferent anatomical substrate from this organ towards the brain, together with the strong reduction or lack of functional VNO-specific genes that are essential in signal transduction of chemical cues indicate the degeneration of a functional VNO among primates, especially in OW monkeys and hominoids ((Dulac and Torello, 2003; Liman and Innan, 2003; Wysocki and Preti, 2004; Gilad et al., 2004; Liman, 2006; Mast and Samuelsen, 2009; for more details, see the next chapter). In these latter primate taxons, the intranasal olfactory and/or respiratory system thus seem(s) the major site of sensing pheromones.

Olfactory receptor sites, odourant and pheromonal perception, signal transduction, and conduction of evoked action potentials

Mammals

Olfactory chemoreceptors in the MOS

The epithelium of the MOS contains millions of olfactory receptor neurons (ORNs) (Weiss, 2004). The surface of the sensory epithelium in the MOS is composed of knobby terminals of the ORNs, each knob sprouting multiple nonmobile cilia (Silverthorn, 2007). The cilia are embedded in a layer of mucus, and odourant molecules must first dissolve in and penetrate the mucus before they can bind to an olfactory receptor (OR). ORs are G-protein-cyclic nucleotide-linked membrane receptor proteins (Buck and Axel, 1991; Ronnett and Moon, 2002; Silverthorn, 2007).

Nonprimate mammals have around 1-2 thousand different ORs, comprising the largest gene superfamily in mammalian genomes (Glusman et al., 2001; Zozulya et al., 2001; Zhang and Firestein, 2002; Olender et al., 2004; Weiss, 2004). OR genes are classified in two mayor classes and 17 families (Glusman et al., 2001). Although the full repertoire of OR genes is not known in primates other than humans, it appears that there has been a gradual loss of functional OR genes (~700 in pigtail macaques, and ~1000 in common squirrel monkeys, and black-handed spider monkeys (Rouquier et al., 2000; Glusman et al., 2001; Gilad et al., 2004) during anthropoid evolution, which eventually has led to the presence of only ~350 functional ORs in the human (Sharon et al., 1999; Rouquier et al., 2000; Gilad et al., 2003). These human ORs are found on every chromosome except the Y and 20 (Glusman et al., 2001; Zozylya et al., 2001). Approximately 60% and 30% of OR genes are considered pseudogenes in humans (Glusman et al., 2001; Zozulya et al., 2001) and nonhuman apes (Gilad et al., 2003), respectively, which is significantly higher than in mice (Zhang and Firestein, 2002) and dogs (about 20%; Olender et al., 2004). In regard nonhuman primates, four hominoids (common chimpanzee, gorilla (Gorilla gorilla), orangutan (*Pongo pygmaeus*) and Siamang gibbon (*Hylobates syndactylus*), six Old World (OW) monkeys (Guinea baboon (*Papio papio*), rhesus macaque, silver langur (*Trachypithecus auratus*), mona monkey (*Cercopithecus mona*), agile mangabey (*Cercocebus agilis*) and black-and-white colobus (*Colobus guereza*)), and one New World (NW) monkey (black howler monkey (*Alouatta caraya*)) have a significant higher proportion of OR pseudogenes than six other NW monkeys (brown capuchin monkey (*Cebus paella*), (Azara's) southern (night) owl monkey (*Aotus azarai*), spider monkey (*Ateles fusciceps*), common squirrel monkey, woolly monkey (*Lagothrix lagotricha*) and common marmoset, and one prosimian (the crowed lemur (*Eulemur mongoz*)) (Gilad et al., 2004). For a survey of the numbers of potentially intact and nonintact OR genes in human, mouse, rat, dog, cow, opossum, platypus (*Ornithorhynchus anatinus*), chicken, western clawed frog (*Xenopus tropicalis*) and zebrafish, see Grus et al. (2007).

ORs are subdivided into two classes, Class I and Class II (also referred to as the α and γ group of ORs, respectively; Niimura and Nei (2005), based on homology of deduced amino acid sequences (Glusman et al., 2001; Zhang and Firestein 2002; Tsuboi et al., 2006). ORs belonging to Class I form the most ancient group in the olfactory repertoire. They bind nonvolatile odourants like amino acids (Sun et al., 1999), have been detected in fish (Freitag et al., 1995), and have subsequently been found to be intermixed with Class-II (mammalian-type) ORs in amphibian and fish species (Mezler et al., 2001). The striped (blue-white) dolphin (*Stenella couruleoalba*) has both OR classes, but those of class II are all pseudogenes (Freitag et al., 1998). Class-II ORs are specialised for recognizing airborne (volatile) odourants (Sun et al., 1999). The, compared to fish, much larger but less diverse mammalian

OR repertoires will probably do better at discriminating between structurally similar odourants (Kambere and Lane, 2007). Although OR repertoires in teleosts are much smaller than in mammals, based on sequence homology, fish ORs can be divided into more than 5 groups. This may indicate that fish ORs respond to much more divergent kinds of odourants than mammals do. Surprisingly, relative large numbers of Class-I ORs have been identified in human, mouse and dogs, i.e., 120 (Feingold et al., 1999), 147 (Raming et al., 1998) and 175 (18% of 971; Olender et al., 2004), respectively. The, compared to humans and mice, relative more Class-I ORs in dogs may be related with the special olfactory capacities of the latter animals (Olender et al., 2004). Clawed frogs of the species *Xenopus laevis* expresses Class-1 ORs in the epithelium lining the water-filled diverticulum of their nasal cavity, and Class-II ORs in the epithelium lining the air-filled diverticulum of their nasal cavities (Freitag et al., 1995). This phenomenon suggests that the current diversity in mammalian Class-II OR repertoires, necessary to detect airborne odourants, arose at the time vertebrates started to occupy niches on land (Freitag et al., 1995; Glusman et al., 2001).

In rodents, the epithelium of the MOS has several spatial zones of ORNs, that express non-overlapping sets of OR genes (Ressler et al., 1993; Vassar et al., 1993). Each gene is expressed in a small percentage of ORNs that are scattered throughout one zone. It is suggested that *each* of the millions of ORNs contains a *single* type of OR (Chess et al., 1994; Malnic et al., 1999 in Lévai et al., 2006). The current data on odour perception show that a *single* odourant is encoded by using a *combination* of ORs, *each of them* serving as one component of the codes for *many* odourants. Different odourants have different receptor codes, and subtle changes in the structure and concentration of an odourant alter its receptor code. With this mechanism mammals are able to detect and distinghuish an almost unlimited number of chemical compounds. Thus, each OR is sensitive to a variety of substances and one odourant is detected by multiple ORs. For possible mechanisms of OR gene regulation that allow only one gene to be transcribed in an ORN, while keeping the remaining large number of OR genes silenced, see Kambere and Lane (2006) and Capello et al. (2009). In mice, nearly all class-I ORs are expressed in the anterior-dorsal-most zone of the olfactory epithelium (Tsuboi et al., 2006). It is hypothesised that the olfactory epithelium serves as a chromatographic separator of odourants, with ORs responding to fast-sorbing hydrophylic compounds expressed early in the airstream, and ORs responding to slow-sorbing hydrophobic compounds expressed at locations farther along in the airstream (Mozell et al., 1991; Schoenfeld and Cleland, 2006). The finding that class-I ORs prefer polar (hydrophylic) compounds suggests that the location of receptor expression along the olfactory epithelium is related to the ligands that bind the receptor (Saito et al., 2009).

Full or partial OR sequences have been cloned from genomic DNA or olfactory epithelium cDNA not only in mammals (rodents, dog, pig and humans) but also in catfish, chicken and the invertebrates *C-elegans* and *Drosophila* (for a review, see Mombaerts, 1999). Interestingly, OR expression is not limited to olfactory epithelium of the nose but has also been detected in other organs like testis (Thomas et al., 1996), pancreas, spleen and heart (Blache et al., 1998).

Screening of ORs in genetically engineered cell systems, employing olfactory signaling molecules, may lead to the identification of cognate odourant/OR combinations (Krautwurst, 2008). After screening of 93 odourants against 219 mouse ORs and 245 human ORs expressed in heterologous cells, agonists for 52 mouse and 10 human ORs have been identified (Saito et al., 2009). Among a group of 65 odours, the putative male pheromones androstenone and ADIO selectively activate the human odourant receptor OR7D4 *in vitro* (Keller et al., 2007). Commonly occurring genetic variation in this receptor appears to alter odour perception, which may (partly) explain the individual variation in perception of

odorous steroids. In primates, the sensivity of OR7D4 to androstenone and ADIO decreases from the putative catarrhine ancestor to the putative Great Ape ancestor (Zhuang et al., 2009).

Both olfactory and vomeronasal sensory neurons undergo a continuous renewal process throughout adult life at least in the mouse. For neurogenesis of olfactory and vomeronasal sensory neurons, see Halpern and Martinez-Marcos (2003) and Lledo and Saghatelyan (2005).

Signal transduction after odourant-OR binding in the MOS

Binding of an odourant molecule to an OR may activate a special heterotrimeric G-protein (short for guanine nucleotide-binding protein**)**, G_{olf} (also termed $G_{\alpha olf}$ or $G_{olf\alpha}$; www.signaling-gateway.org/molecule/query?afcsid=A000977), that in turn activates adenylyl cyclase* and thus increases intracellular cAMP followed by opening of cyclic nucleotide-gated subunit A2 (CNGA2**; Brunet et al., 1998) cation channels, thereby altering the ion permeability, and hence the excitability, of the membrane (Buck and Axel 1991; Ronnett and Moon, 2002; Dulac and Torello, 2003) (*Table 15*). Depolarisarion of the ORN is strengthened by the opening of the chloride channel Anoctamin 2 (ANO2) by the calcium influx via the opened CNGA2 channel, and the subsequent efflux of chloride (Kurahashi and Yau, 1993; Stephan et al., 2009). ANO2 is a member of the recently identified family of classical Ca^{2+}-activated Cl^- channels (Caputo et al., 2009; Yang et al., 2008; Schroeder et al., 2008).

Together with the cAMP-sensitive CNGA2 channel, transient receptor potential channel M5 (TRPM5***) is coexpressed in a subset of ORNs with components of the PLC pathway (PLC, $G_{\beta 2}$ and G_{y13}), that activate this channel, resulting in release of Ca^{2+} from intracellular stores (Lin et al., 2007). TRPM5-positive glomeruli are localised in an area of the ventral MOB, known to be responsive to mouse urine and putative pheromones (Restrepo et al., 2004; Lin et al., 2005; 2007). Some of these glomeruli respond to stimulation with the male mouse urinare pheromone (methylthio)methanethiol and the female mouse urinary pheromone 2,5-dimethylpyrazine, which are attractive for conspecifics of the opposite sex. TRPM5 is a member of the TRPM subfamily, one from at least 6 existing TRP-subfamilies that form the TRP ion channel superfamily (Clapham et al., 2005; Montell, 2005). The TRP superfamily is grouped into these subfamilies on the basis of amino acid sequence homology and consists of TRPM (‘melastatin’), TRPV (‘vanilloid’), TRPA (‘ankyrin’), TRPML (‘mucolipin’, TRPP (or PKD) (‘polycystin’) and TRPC (‘canonical’). TRPM2 plays an important role in taste receptors. In the MOS epithelium, TRPM5 is preferentially expressed by ORNs located in the ventrolateral zones (Lin et al., 2007). Recently, TRPM5 has also been demonstrated in solitary chemosensory cells located at the entrance duct of the VNO, where it contributes in the regulation mechanisms determining access of chemical fluids to the VNO (Ogura et al., 2010; for further information, see paragraph ‘The trigeminal nerve and odourant/pheromone perception’).

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* There are at least nine known isoforms of adenylyl cyclases (Hanoune and Defer, 2001) of which adenylyl cyclase-3 mRNA is highly enriched in ORNs (Bakalyar and Reed, 1990). Because of their ultrastructural localisation in olfactory cilia, G_{olf} likely mediates activation of adenylyl cyclase-3 (Menco et al., 1992). Besides this latter type of adenylyl cyclase, the isoforms 2 and 4 have also been associated with olfactory epithelium, which may indicate that they are important in different aspects of olfacactory signal transduction (Mons and Cooper, 1995).

** CNG cation channels conduct Na^+, K^+ and Ca^{2+} currents under the control of cAMP and cGMP (Dzeja et al., 1999). The CNG family comprises 5 different members: CNG1-5, which are key elements in olfactory and visual signal transduction (Biel et al., 1999a,b).

*** TRPM5 is a monovalent-specific, nonselective cation channel that carries Na^+, K^+, and Cs^+ ions equally well, but not Ca^{2+} ions (Prawitt et al., 2003).

Various authors have attributed odour adaptation in olfactory receptor neurons to a simple feedback mechanism resulting from Ca^{2+} entry through the transduction channels causing modulation of the transduction machinery (Kurahashi and Shibuya 1990; Kurahashi and Menini, 1997; Leinders-Zufall et al., 1998; Reisert and Matthews, 1998), until evidence was found for the existence of two distinct Ca^{2+}-dependent mechanisms to odour adaptation, i.e., through modulation of cAMP-gated channels and through modulation of adenylyl cyclase (Leinders-Zufall et al., 1999). If nasal olfactory neurons are exposed to a brief (100 msec) odour pulse, all adaptation indeed depends on Ca^{2+} modulation of the cAMP-gated channel. If such neurons are, however, exposed to sustained (8 sec) odour pulses, calmoduline kinase II (CaMKII) inhibition of adenylyl cyclase becomes rate-limiting for recovery from adaptation. CaMKII is abundantly expressed in olfactory cilia and inhibits olfactory adenylyl cyclase via Ca^{2+}/calmodulin-induced phosphorylation (Wei et al., 1996; 1998). Previously, a Ca^{2+}-calmodulin-CaMKII –R2D5 antigen pathway was proposed for modulation of olfactory signal transduction in rabbit OR neurons (Nemoto et al., 1993).

Apart from the two Ca^{2+}- dependent mechanisms described for mice, a third one involving endothelial nitric oxide synthethase (eNOS) has recently been related to (sustained) odourant response adaptation in the MOS (Brunert et al., 2009). These latter authors have demonstrated eNOS in nasal olfactory receptor neurons, and described its functionality and possible physiological role. They have shown that, in mature mouse olfactory sensory neurons, eNOS activation is triggered by Ca^{2+} influx into the cells through the odourant-activated cAMP-signaling cascade as well as through opening of voltage activated Ca^{2+} channels. The difference in EOG amplitudes between wild type and eNOS-deficient mice indicates that eNOS has a role in odourant response adaptation. The presence of eNOS in MOS neurons and its involvement in odourant adaptation implicates nitric oxide (NO) as an important element involved in olfactory signal transduction. The experiments of Brunert and allies (2009) have not focussed on the mechanism by which NO regulates adaptation. Since the major target for NO is soluble guanylyl cyclase, the authors hypothesise that NO could act via this enzyme by increasing intracellular cGMP, especially, the latter compound previously being implicated in a form of long lasting odour adaptation (Zufall and Leinders-Zufall, 1998). Another possible pathway, however, could be S-nitrosylation of olfactory cyclic nucleotide-gated channels, which has been shown to modulate the open probability of the channel (Broillet and Firestein, 1996). Besides its intracellular presence and role, NO appears to be released from mature, functional olfactory neurons. Because NO is a diffusible, gaseous second messenger, it may also have paracrine effects, and thus may have additional functions related to cross adaptation, regeneration, and maintenance of homeostasis in the MOS epithelium. Indeed, NO has been shown to act simultaneously in both an autocrine and a paracrine manner in other cells of the nasal epithelium. (Torroglosa et al., 2007). Therefore, Brunert and coworkers (2009) suggest that NO could function as a mediator in a possible interplay with neighbouring olfactory neurons, sustentacular cells, basal cells, and gland cells. For more information on odour adaptation in ORNs, see Kaupp (2010).

<u>Conduction of action potentials evoked by OR neurons from the MOS to and within the brain</u>

Depolarisation of an OR neuron triggers a signal that is conducted along the olfactory cell axon to the main olfactory bulb (MOB). Each ORN projects a single axon to the ipsilateral MOB, where it forms synapses with second-order neurons, the mitral and tufted cells. The many axons of ORNs with the same receptor converge their axons to two of ~ 2000 glomeruli located in stereotyped positions on the MOB, one on the medial and the other on the lateral surface, creating a stereotyped sensory map of OR input in the MOB, which then can modify the information before sending it further (Ressler et al., 1994; Vassar et al., 1994; Mombaerts

et al., 1996). For more detailed information about the topographic mapping of the MOS and the mechanisms of its formation, see Imai et al. (2010).

In rodents, the primary olfactory cortex consists of a number of different anatomical areas, i.e. the bed nucleus of the lateral olfactory tract, the anterior olfactory nucleus, the piriform cortex, the olfactory tubule, the entorhinal cortex and several amygdaloid nuclei, namely the anterior amygdala and the anterior, medial, anterior cortical and posterolateral cortical nuclei of the amygdala (Shipley and Ennis, 1996; Tirindelli et al., 2009). Olfactory-evoked action potentials are conducted from the MOB, through mitral/tufted cells, directly to these primary olfactory cortex areas. Various feed back mechanisms modulate the processing of MOB stimuli. Direct connections from MOB mitral cells to the medial amygdala have also been observed in sheep (Jansen et al., 1998) and humans (Price et al., 1987).

The amygdala receives direct projections not only from the MOBs, but also from the AOBs. The part of the amygdala that receives direct projections from the MOBs and/or the AOBs is recently termed the chemosensory amygdala (Pro-Sistiaga et al., 2007; Martinez-Marcos, 2009; Gutiérrez-Castellanos et al., 2010). It can be subdivided into (i) the olfactory amygdala, which consists of the posterolateral cortical nucleus and the amygdalo-piriform transition area, (ii) the vomeronasal amygdala, which comprises the anygdaloid posteromedial cortical nucleus and the posteromedial bed nucleus of the stria terminalis, (iii) the olfactory predominance part of the mixed chemosensory amygdala, which includes the amygdaloid anterior cortical nucleus, the corticoamygdaloid transition area and the nucleus of the lateral olfactory tract, and (iv) the vomeronasal predominance part of the mixed chemosensory amygdala, consisting of the medial amygdala, the bed nucleus of the accessory olfactory tract and the anterior amygdaloid area (*Figure 9*).

Thus, apart from inputs from the MOB and AOB into the chemosensory amygdala, which are supposed to play different and independent functional roles in the detection of odours and pheromones, respectively, there are interrelationships between the two olfactory systems which manifest in the mixed chemosensory amygdala. This points to integration of olfactory information from the MOS and the VNO at these sites (Licht and Meredith, 1987; Meredith, 1998; Brennan and Kendrick, 2006; Brennan and Zufall, 2006; Pro-Sistiaga et al., 2007; Baum and Kelliher, 2009; Baum, 2009; Martinez-Marcos, 2009; Touhara and Vosshall, 2009; Kang et al., 2009; Tirindelli et al, 2010; Gutiérrez-Castellanos et al., 2010). Such an integration of pheromonal inputs not only regulate heterosexual mate recognition, courtship, and sexual arousal in both sexes (Brennan and Zufall, 2006; Shephard, 2006), but also aggressive behaviour (Siever, 2008; Chudasama et al., 2009), rewarding phenomena and motivated responses (Cador et al., 1989; Everitt et al., 1991; 1999).

Projections from the olfactory amygdala are directed to the hippocampus and the parahippocampal cortices as well as to the ventral striatum (Ubeda-Bañon et al., 2007; Pro-Sistiaga et al., 2007; Martinez-Marcos, 2009; Gutiérrez-Castellanos et al., 2010). Amygdala and hippocampus both are part of the limbic system of the brain, which is involved in memory, emotion, motivation and sexual behaviour. The ventral striatum is closely related to the limbic system and functionally linked to reward, risk and motivated responses. The chemosensory memories containing brain areas not only receive projections from the olfactory amygdala, but also from the vomeronasal amygdala. This latter part of the amygdala and both parts of the mixed chemosensory amygdala all act directly and, via the stria terminalis, indirectly on the hypothalamus to control its activity, which may neurally or neurohormonally affect the endocrine activity of the hypophysis (Pro-Sistiaga et al., 2007; Martinez-Marcos, 2009; Gutiérrez-Castellanos et al., 2010). From the hypothalamus, efferent signals can be conducted to the mammilary corpuscle, the cerebral peduncles and lower motor neurons in the central nervous system, which may evoke a behavioural response (Dyce et al., 2002).

For more detailed information on the brain areas engaged in the processing of olfactory cues, and that can be activated to elicit integrated behavioural, endocrine and autonomic responses, see Savic (2001), Dulac and Torello (2003), Weiss (2004), Keverne (2004), Yoon et al. (2005), Brennan and Zufall (2006), Ubeda-Bañon et al., 2007 ; Pro-Sistiaga et al., 2007; Touhara (2008), Murata et al. (2009), Baum (2009), Martinez-Marcos (2009), Tirindelli et al. (2009), Gutiérrez-Castellanos et al. (2010) and Mucignat-Caretta (2010). For detailed information on separate neural circuits of individual and different forms of sexual recognition in Syrian hamsters, see Petrulis (2009).

Neuronal projections from the MOB to the primary olfactory cortex transfer receptor inputs, generating different stereotyped maps of discrete clusters of cortical neurons that permits the integration of inputs from combinations of receptors (Buck, 2004). Thus, single cortical neurons receive combinatorial input from different ORs, while (as mentioned before) individual neurons in the epithelium of the MOS appear each to be equipped with one type of OR, and those in the MOB each receive information from one OR.

Although most odourants that stimulate ORNs are volatile, nonvolatile MHC class-I peptides may also function in the mammalian MOS as olfactory cues, and carry information about individuality (see the introduction of the chapter on mammalian pheromones). Evidence for such a role is, however, not conclusive (Hurst et al., 2005). These immune system molecules activiate subsets of ORNs and may affect social preference of male mice (i.e. their choice for a particular same-strain female), or more likely may contribute to the recognition of familiar scents such as the recognition of a familiar mate or neighbour competitor (Spehr et al., 2006). The effect is brought about through activation of the G_{olf}-cyclic nucleotide-gated channel gene GNGA2 in ORNs. Pheromonal MHC class-1 peptides are detected by ORNs with detection thresholds near or below 10^{-10} M. The MHC-dependent signal transduction mechanism in ORNs is distinct from that employed by vomeronasal neurons (see below). MHC peptides thus are able to stimulate olfactory sensory neurons from both the vomeronasal (Leinders-Zufall et al., 2004) and main olfactory epithelium (Spehr et al., 2006) in mice and thus may directly function as chemosignals in the two sensory organs. Although it may contribute to MHC distinctions, the VNO is, however, not a necessary sensor of it, since vomeronasalectomised mice are able to detect chemical signals among conspecific strains (Wysocki et al., 2004). Apart from MHC peptides, OBPs may bind odourants and pheromones in the MOS. Indeed, apart from odourants (Scaloni et al., 2001), OBPs bind a large series of lipophilic ligands (maternal fatty acids and paternal steroids) in the nasal mucus of pre-pubertal pigs (Guiraudie et al., 2003). OBP is not only expressed in the nasal mucosa but also in the VNO of these farm animals, and is likely to be associated with the coding of pheromonal appeasing signals (Guiraudie et al., 2003). Except the binding of a porcine OBP to a human OR (Matarazzo et al., 2002), potential recognition between OBPs and ORs has not yet been clearly established, so that their precise role in olfactory reception remains unclear (Tegoni et al., 2000). As remarked above, it may involve odourant transport, its delivery to receptors, and/or its sequestration. Thus, the function of OBPs, as their name indicates, is related to binding odourants, which may include pheromones (Tegoni et al., 2000). Apart frrom mice and pigs, OBPs have been isolated from various other mammals like cattle, elephants and porcupines (see introduction of the chapter on mammalian pheromones).

The VNO

The VNO, formerly termed the organ of Jacobson, has been often shown to play an active role in most amphibians, reptiles and mammals in the perception of chemical signals, including sex pheromones, which a.o. elicit attraction, aggressive, parental and reproductive behaviour, and affect the time of ovulation and puberty (Trotier and Døving, 1998; Keverne,

1999; Zufall et al., 2002; Stowers et al., 2002; Cooper and Pèrez Mellado, 2002). However, because available data on the function of the VNO are conflicting and other sensory systems could also respond to pheromones, it can be questioned whether the VNO is really specialised for detecting pheromones (Baxi et al., 2006). Indeed, in amphibians and reptiles, the VNO is also involved in foraging (Graves, 1993; Kardong and Berkhoudt, 1999; Placyk and Graves, 2002), a function which could also hold for mammals, but has not been well-investigated yet (Baxi et al., 2006). An indication for such a VNO role in mammals could be the high sensititvity of mouse vomeronasal neurons to low concentrations (10^{-10} M) of both odourants and pheromones (Sam et al., 2001). From their findings, these latter authors suggested that, through the VNO, certain odourants in the natural habitat of this species may arouse instinctive behaviours, like feeding and nesting behaviour. The VNO is absent in teleosts, lungfish, crocodiles, birds and marine mammals (Stoddard, 1980; Eisthen, 1992; Witt and Hummel, 2006). Evidence of VNO development in larval amphibians and neotenic salamanders does presume that the VNO is not an adaptation to terrestrial life (Eisthen, 2000; Jermakowicz et al., 2004).

In terms of anatomical organisation, three different complexity levels of the VNO have been described for mammals, rodents and opossums having the most complex type with a thick layer of sensory epithelium, dogs and cows having a less complex type with a much thinner layer of sensory epithelium, and humans having the least complex type characterised by either the absence of a VNO or the presence of a nonfunctional VNO (Takami, 2002). Additionally, the latter authors has described literally and figuratively two more types of VNO in nonmammalian vertebrates: one for amphibians and turtles, in which nonsensory epithelium is absent and the vomeronasal lumen is a part of the nasal cavity, and one for squamate reptiles, particularly snakes, in which the thick sensory cell layer is divided into hundreds of connective tissue septi that contain blood vessels. Among vertebrates, snakes thus possess the most complex anatomical organisation, some species containing more sensory neurons in the olfactory epithelium of the VNO than in that of the MOS (Gabe and Saint Girons, 1976). Based on the anatomical structure of the VNO, and neuroanatomical and behavioural features, either snakes (Halpern, 1992) or gekkotan lizards (Schwenk, 1993b) are considered as olfactory specialists.

In nonprimate mammals and most amphibians and reptiles, the VNO is distinctly separated from the nasal cavity (for illustrations, see Baxi et al., 2006). It is enclosed in a bony or cartilaginous capsule and located at the base of the nasal cavity, and consists of two tubules, which are divided from each other by the nasal septum (Døving and Trotier, 1998). The VNO is blind posteriorly, and species-dependently opens anteriorly indirectly into either the nasal cavity or the oral cavity (Dyce et al., 2002). To reach the VNO, urine, saliva or other glandular secretions containing pheromones enter the nasal cavity by the nostrils after direct contact of the snout. Subsequently, chemical compounds are transported through an opening in the bottom of the nasal cavity to an nasopalatine duct (incisive duct), and then to the VNO which is connected with the latter duct. In various species (e.g. dogs and cows) the two nasopalatine ducts connect the oral and nasal cavities, as a result of which chemical substances that have been taken up by the mouth (for example by licking) may also reach the VNO.

In primates, vomeronasal function, along with its genome, has been maintained within prosimians (strepsirrhines and tarsiers), reduced in platyrrhines, and nearly extinguished in catarrhines and homonoids (Evans, 2006). Among humans, 6% to 100% have a VNO (Witt and Hummel, 2006), the percentages being dependent on the research techniques used, the swelling condition of the nasal mucosa, the exchange of the VNO with other structures, and the hugh variation of the size and form of the VNO (Knecht et al., 2003b).

The crescent-shaped lumen of the VNO is on its medial side lined with olfactory receptor neurons, which a.o. receive sex pheromones eliciting behavioural, reproductive and neuro-endocrine responses among individuals of the same species (Thompson et al., 1994; Keverne, 1999). In contrast to the cilia on the neurons of the their main olfactory system, the VNO neurons in terrestrial species possess up to 100 apical microvilli (Zufall et al., 2002). The morphology of the lubricatory system of the VNO varies among vertebrate classes, being either intrinsic (cecilian amphibian and mammalian vomeronasal glands) or extrinsic (anuran and urodele nasal glands and reptile Harderian gland) (Rehorek et al., 2000). Although the precise function of the VNO fluid is still largely unknown, it most likely is a medium for airborne (votile) chemicals and by sniffing and licking perceived non-votile compounds to dissolve before they can stimulate olfactory neurons. Apart from that, the fluid may contain stimulus binding proteins which transport the chemical stimulus to the sensory epithelium, or enzymes which break down the chemicals to smaller units that bind to the vomeronasal receptor neurons. The mucosa of the VNO contains an extensive network of blood sinusses, which is surrounded by a band of cavernous erectile tissue, forming a vomeronasal pump that may aid in the delivery of odourants (Meredith et al., 1980). VNO access of chemicals is furthermore controlled by solitary chemosensory cells at the entrance of the VNO (Ogura et al., 2010; for further information, see paragraph 'The trigeminal nerve and odourant/ pheromone perception'). Another mechanisms by which a chemosensory stimulus may reach the sensory epithelium of the VNO is often associated with the special facial mimics termed flehmen (Marchlewska-Koj, 1984).

Generation of two-dimensional response heat maps from live neurons in VNO slices perfused with oxygenated cerebrospinal fluid, provides virtual representations of the activity of large numbers of vomeronasal neurons and reveals how these neurons code for gender, reproductive condition and individual recognition (He et al., 2008). Such studies with male VNO slices have shown that either male or female mouse urine activates a substantial proportion of vomeronasal neurons, and that only a small proportion of these receptors is exclusively responsive to the sex of the producer. These male neurons were also differentially regulated by urine collected at different stages of the oestrous cycle. In addition to *gender*, generated heat maps also show the presence of urinary signals that enable *individual* recognition. Besides, individual AOB neurons are often highly selective for the sex of the urine donor (Hendrickson et al., 2008). Examination of both explicitly inhibitory responses, as well as responses to mixtures of male and female urine, have shown that laterally connected inhibition is both prevalent and of large magnitude. Furthermore, a behavioural response (pregnancy block) evoked by the presence of unfamiliar male urine can be suppressed by the addition of female urine to the stimulus, demonstrating that this system displays a behavioural opponency consistent with neural inhibition. The results of Hendrickson and coworkers indicate that laterally connected inhibitory circuitry in the AOB plays an important role in shaping neural selectivity for natural stimuli. Lateral modulation of incoming AOB signals can be brought about by collaterals from the mitral/tufted cell axons that may recruit adjacent intrinsic neurons which, in turn, interact with the dendrites of adjacent mitral cells (Larriva-Sahd, 2008). Some AOB neurons immunoreact with hypothalamic releasing factors like LHRH**,** thyrotropin releasing hormone and somatostatin (Dluzen and Ramirez, 1983), indicating that these factors may modulate the AOB response to pheromones and its subsequent physiological and behavioural effect.

In vertebrates, vomeronasal neurons express at least 2 different types of chemoreceptors (VRs), which are unrelated to ORs and members of the G protein-coupled receptor family. The first type of VRs (V1Rs; 308 genes in mice of which 187 are intact) is located in the apical neurons of the VNO epithelium and has been shown to mediate volatile pheromone perception in mice and teleost fish (Krieger et al., 1999; Thompson et al., 2004;

Zhang et al., 2004; Pfister and Rodrigues, 2005; Silvotti et al., 2005; Touhara, 2007; Shi and Zhang, 2007). Rodent V1R genes are further classified into 15 distinct families, based on amino acid sequence identity and phylogenetic relationships (Rodriguez et al., 2002; Grus et al., 2005). For a phylogenetic reconstruction of putatively functional V1Rs, see Grus and Zhang (2006) and Shi and Zhang (2007). V1R receptors are involved in (i) the detection of sulphated steroids (Nodari et al., 2008; Hsu et al., 2008; the detection being dependent on the presence of TRPC2 channels) and small volatile pheromones, like 6-hydroxy-6-methyl-3-heptanone, *n*-pentylacetate, isobutylamine (Del Punta et al., 2002) and 2-heptanone (Boschat et al., 2002), (ii) axon guidance processes (Belluscio et al., 1999; Rodrigues et al., 1999), and (iii) the regulation of their own expression through a negative feedback mechanism, whereby the expression of a particular V1R evokes an unknown signal that prevents the potential transcription of other V1R genes (Roppolo et al., 2007). Capello and coworkers (2009) have even concluded from their results that a common gene exclusion mechanism is used by both pheromone and odourant receptor genes.

The second type of VRs (V2Rs; ~280 genes in mice of which ~120 are intact (Young and Trask, 2007)) is located in the more basal neurons of the VNO epithelium, is expressed in various vertebrate species (Thompson et al., 2004; Zhang et al., 2004; Pfister and Rodrigues, 2005; Silvotti et al., 2005; Grus and Zhang, 2006; Shi and Zhang, 2007) and, at least in teleosts (Pfister and Rodrigues, 2005; Bjarnadóttir et al., 2005) and African clawed frogs (Hagino-Yamagishi et al., 2004), mediates the perception of amino acids. Based on the amino acid sequence and phylogenetic relationships, V2Rs are divided into three families (A-C) (Yang et al., 2005). For phylogenetic reconstruction of teleost, amphibian and rodent V2Rs, see Grus and Zhang (2006). Information on the distribution of V2Rs among mammals is limited, putatively functional V2Rs being identified in mice, rats and opossum only (Grus and Zhang, 2006; Shi and Zhang, 2007). In the neurosensory epithelium of the rat VNO, one of the V2Rs, VN2, is expressed in a sexually dimorphic pattern, i.e. in the most apical portion of the basal zone in males and in the central portion of this zone in females (Herrada and Dulac, 1997). In mammals, V2Rs may (like V1Rs) bind sulphated steroids (Nodari et al., 2008; Hsu et al., 2008), but additionally bind watersoluble, nonvolatile peptide pheromones such as MUPs, MHC peptides, and ESPs (Krieger et al., 1999; Touhara, 2007), which are larger compounds than the volatile ones bound by V1Rs. Further intracellular signaling is dependent on the presence of TCRP2 channels. In agreement with ORs (Spehr et al., 2006), V2Rs (but not $V2R_2$) are most likely activated by MHC peptide ligands (Boehm and Zufall, 2006; Leinders-Zufall et al., 2009) and other urinary pheromonal components of proteinaceous nature, like the rat MUP α_{2u}-globulin (Cavaggioni and Mucignat-Caretta, 2000) and the mouse MUPs (Beynon and Hurst, 2003). These compounds may contribute to diversity and specificity of the V2R neurons, possibly by having a role in the recognition of the part of the peptide component in the pheromone that carries the individual identity (Beynon et al., 2002; Hegde, 2003; Boehm and Zufall, 2006). *Table 16* shows the different forms of olfactory receptors and their ligands in mammals. Apart from ESPs, MUPs and MHC molecules, VNBPs and vomerodulin may play a role in pheromone signaling within the VNO (Miyawaki et al., 1994; Krishna et al., 1994; Mechref et al, 1999; Guiraudie et al., 2003; Leinders-Zufall et al., 2009). The existence of specific receptors for these locally synthesised binding proteins is, however, still obscure. There are no reports of MHC loci being expressed in the primate VNO, and V2R genes have not been isolated in any primate (Rodriguez et al., 2000; Rodriguez and Mombaerts, 2002).

A third type of VRs (V3Rs; > 100) has been demonstrated in rodents in the apical part of the VNO epithelium, the V3R genes being distantly related to V1R genes (Pantages and Dulac, 2000; Thompson et al., 2004). There is, however, no direct evidence that V3Rs recognise pheromone molecules (Wakabayashi et al., 2002).

Table 15: Olfactory receptors in main olfactory system (MOS) and vomeronasal organ (VNO) neurons of mammals, and putative pathways of olfactory signal transduction leading to electric signaling. The data are based on information given by Buck and Axel (1991), Ronnett and Moon (2002), Spehr et al. (2002), Breer (2003), Dulac and Torello (2003), Rodriguez, (2003), Prawitt et al., 2003), Bigiani et al. (2005), Zufall et al. (2005), Selvatici et al (2006), Grus and Zhang (2006), Grus et al. (2007), Lin et al.(2007), Leinders-Zufall (2007), Munger et al. (2009), Rivière et al. (2009), Liberles et al., 2009 and Knapp (2010).

Neuronal receptors in the MOS			**Neuronal receptors in the VNO**		
OR and TAAR	**OR**	**GC-D•**	**V1R**	**V2R**	**FPR**
↓	↓	↓	↓	↓	↓
G_{olf} protein activation	$G_{\beta 2}$ and $G_{\gamma 13}$ proteins	activation guanylyl cyclase	$G_{\alpha o}$ protein activation	$G_{\alpha i2}$ protein activation	activation of $G_{\alpha i2}$ or $G_{\alpha o}$ ptotein**
↓	↓	↓	↓	↓	↓
activation adenylyl cyclase	PLC activation	cGMP formation from GTP	PLC activation		activation of o.a., PLC#
↓	↓	↓	↓	↓	↓
cAMP formation from ATP	IP3 generation from PIP2 hydrolysis	PDE2	DAG production and IP3 generation from PIP2 hydrolysis		generation of DAG, IP3 and PKC isoforms
↓	↓	↓	↓	↓	↓
CNGA2 gating	TRPM5 gating	CNGA3 gating	TRPC2, IP_3R3 and (via arachidonic acid) Ca^{2+}-dependent ion channel gating##		intracellular Ca^{2+} transients
↓	↓	↓	↓	↓	↓
influx of extracellular Na^+/Ca^{2+}	Ca^{2+} release from intracellular ER	influx of extracellular Na^+/Ca^{2+}	influx of extracellular Na^+/Ca^{2+} or* intracellular Ca^{2+} release from ER		influx of extracellular Ca^{2+}
↓	↓	↓	↓	↓	↓
depolarisation of cilium membrane			membrane depolarisation along the dendrite		
↓	↓	↓	↓	↓	↓
activation of voltage-gated Na^+ and K^+ channels					
↓	↓	↓	↓	↓	↓
generation of action potentials in neuron					
↓	↓	↓	↓	↓	↓
transport of nerve impulses along the axon to the brain					

Legend belonging to Table 15: ER, endoplasmic reticulum; OR, odourant receptor; V1R, vomeronasal receptor type 1; V2R, vomeronasal receptor type 2; TAAR, trace amine-associated receptor; PLC, phospholipase C; PIP2, phosphoinsositol-4,5-biphosphate; DAG, diacylglycerol; IP3, inositol-1,4,5-triphosphate; CNGA2, cyclic nucleotide-gated channel type A2; CNGA3, cyclic nucleotide-gated channel type A3; TRPM5, transient receptor potential channel type M5; TRPC2, transient receptor potential channel type 2; FPR, formyl peptide receptor; GC-D, guanylyl cyclase receptor type D; PDE2, phosphodiesterase-2; G_{olf} protein, guanine nucleotide-binding protein type olf; $G_{\alpha i2}$ protein, guanine nucleotide-binding protein type αi2; $G_{\alpha 0}$ protein, guanine nucleotide-binding protein type α0; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; ATP, adenosine triphosphate; • Sensory neurons in the Grüneberg ganglion (not shown in this Table) contain GC-D and GC-G receptors, which both evoke influx of extracellular Na^+/Ca^{2+} through cGMP, PDE2 and CNGA3- gating (Liu et al., 2009; Fleischer et al., 2009; Mamasuew et al., 2010; Chao et al., 2010); * in case of IP3 generation; ** based on findings of Liberles et al. (2009); # based on observed signal transduction pathways in human neutrophils (Selvatici, 2006); ## based on findings of Mast et al. (2010) with rats and Zhang et al. (2010) with mice.

Per neuron only one V1R, one V2R or one V3R is expressed. All basal neurons, however, express supplementary and divergent V2Rs, namely $V2R_2$ (Martini et al., 2001; Silvotti et al., 2005) and $V2R_x$ (Kannan and Krishnan, 2006; Kannan et al., 2008). Each odourant activates only 0.3-0.7% of the vomeronasal neurons, which suggests that some pheromones may be detected by only a single receptor type, rather than by a combination of receptors as described for the MOS (Buck, 2004). This, along with the finding that vomeronasal neurons are concentration invariant at least for the tested mice pheromones, indicate that they are ultrasensitive and highly-selective pheromone detectors (Holy et al., 2000; Zufall et al., 2002). Neurons in the MOS show lower sensitivity and broader specificity.

Neurons in the apical and basal zone of the VNO are ultrasensitive (up to a concentration of 10^{-11} M) to volatile pheromones and nonvolatile MHC class-I peptide pheromones, respectively (Leinders-Zufall et al., 2000; 2009).

Like ORs, VRs have the seven-transmembrane domain structure of G protein-coupled receptors, and members of each family vary in protein sequence, suggesting an ability to recognise a variety of different chemicals (Buck, 2004). Each receptor gene is expressed in a small percentage of neurons. As mentioned before, VRs are found in spatial zones in the VNO. This suggests that the zones process different types of chemosensory information. This opinion is strengthened by findings of Zufall et al. (2002), that show restricted activation of V1R or V3R neurons by the urinary metabolites 2,5-dimethylpyrazine, 2-*sec*-butyl-4,5-dihydrothiazole, 2,3-dehydro-*exo*-brevicomin, and farnesene, which are pheromonally active in female mice (*Table 8*). Furthermore, the VNO of mutant mice, lacking a cluster of 16 V1R genes, are defective in detecting three (6-hydroxy-6-methyl-3-heptanone, *n*-pentyl acetate and isobutylamine) out of eight urinary V1R ligands tested (Del Punta et al., 2002). These mice are fertile but the drive to initiate sexual encounters and maternal aggression are reduced. In mouse and rat, V1Rs exhibit no sequence homology to any known protein except a weak similarity to taste receptors (Pfister and Rodrigues, 2005). There is an extreme variability among mammalian V1R families (Young et al., 2009). Dog, human and chimpanzee have very few intact V1R genes (8, 5 and 0, respectively) compared to sheep (21), goat (23), cow (40), opossum (98), rat (106), mouse (187) and platypus (270) (Young et al., 2005; Grus and Zhang, 2006; Shi and Zhang, 2007; Grus et al., 2007; Ohara et al., 2009). The small numbers in the dog genome is remarkable, given the presence of a functional VNO in dogs (Dennis et al., 2003) and the presumption of a complex system of pheromone-based behaviour. The relative small numbers of V1Rs in dogs may point to a small contribution of V1Rs in signal transduction.

Table 16: Olfactory receptors and their ligands in vertebrates.

Receptor type	Ligands
OR	Odours
V1R	Sulphated steroids
	Small volatile molecules
V2R	Sulphated steroids
	MUPs, ESPs, VNBPs, Vomerodulin
	MHC peptides
TAAR	Amines
FPR	Supposed pathogen- and inflammation-related compounds
	Supposed food-related compounds
GC-D	Guanylin, Uroguanylin (extraxellular)
	Ca2+, Neurocalcin δ, Bicarbonate (intracellular)
GC-G	Unknown

Legend belonging to Table 16: OR, odourant receptor; V1R, vomeronasal receptor type 1; V2R, vomeronasal receptor type 2; TAAR, trace amine-associated receptor; FPR, formyl peptide receptor; GC-D, guanylyl cyclase receptor type D; GC-G, guanylyl cyclase receptor type G; MUPs, major urinary proteins; ESPs, exocrine gland-secreting peptides; VNBPs, vomeronasal binding proteins; MHC, major histocompatibility complex.

In mammals, thus far, at most five putative functional V1R genes (designated as V1RL1 to V1RL5) among several tens to at least 120 (mouse) of V1R pseudogenes have been identified only (Rodriguez et al., 2000; Rodriguez and Mombaerts, 2002; Giorgi and Rouquier, 2002; Zhang and Webb, 2003; Young et al., 2005; Young and Trask, 2007; Shi and Zhang, 2007), from which V1RL1 is the single human putative VNO receptor gene reported to be expressed at the mRNA level in the main olfactory mucosa (Rodriguez et al., 2000). Allelic differences in the human V1R1 gene are unlikely to be associated with gender and hence to contribute to distinct gender-specific behaviour (Mitropoulos et al., 2007).Thus, it remains to be shown, whether V1RL1 is a VNO receptor or simply an odourant receptor with pheromone-like ligand properties. In-vitro cultured HeLa cells (an immortal cell line used in scientific research, which has been derived from cervical cancer cells taken from Henrietta Lacks, who died from cancer on October 4, 1951; Sharrer, 2006) functionally express all 5 V1RL receptors at the plasma membrane and respond differentially to 19 of 140 tested odourants in a combinatorial way (Shirokova et al., 2008). The best agonists for these receptors are C9-C10 aliphatic alcohols and aldehydes which, when added in μM concentrations, surprisingly activate the G_{olf} -ACIII-CNGA2-pathway. Tested steroids (androstenone, androstenol, epiandrosterone, androsterone, testosterone) did not activiate signaling through V1RL1-5. It can be concluded from the results, that human V1RL receptors in HeLa cells have similar functional characteristics as odourant receptors, sense certain odourants but not (putative steroidal) pheromones. It still has to be demonstrated, however, if such receptors also bind odourants in vivo in the human nasal olfactory epithelium, and whether the concerned V1R project to specialised brain areas. In the nonhuman primate vomeronasal system,V1RL1 is absent in lar gibbons (*Hylobatus lar*), olive baboon (*Papio anubis*), ebony langur (*Trachipethicus auratus*) and De Brazza's monkey (*Ceropithecus neglectus*), a pseudogene in common chimpanzee, urangutans, common marmoset, saddle-backed tamarin, night monkey (*Aotus* sp.), white-fronted capuchin (*Cebus albifrons*), golden lion tamarin (*Leontopithecus chrysomelas)* and Goeldi's monkey (*Callicimo goeldii*), but has an intact open reading frame, indicating a putative functional gene, in gorillas, pygmy

marmoset (*Cebuella pygmaea*) and three species of howler monkey (*Alouatta sara, A. seniculus* and *A. paliata mexicana*) (Giorgi and Rouquier, 2002; Mundy and Cook, 2003) as in humans. From the common marmoset, Giorgi and Rouquier (2002) isolated five V1R genes, and these were all pseudogenes.

A main feature of V2Rs is their large and highly variable extracellular domain, which is responsible for binding with their respective agonists, and which share sequence similarity with metabotropic glutamate receptors, Ca^{2+} sensing receptors, and the putative taste receptors T1R1 and T1R2 (Hoon et al., 1999; Grus and Zhang, 2009). In mammals, varying numbers of V2R genes are expressed, varying from 0 (human) to 270 (platypus) intact genes and 30 (opossum) to 121 (mouse) pseudogenes (Grus et al., 2007; Shi and Zhang, 2007; Grus and Zhang, 2009). V2R genes are also expressed in fish and frogs, but not in reptiles and birds. V2R neurons express two families of non-classical MHC class 1b molecules, M1 and M10 (Loconto et al., 2003; Ishii et al., 2003), the individual neurons expressing only one or a few MHC class 1b molecules. Specific M1 and M10 family proteins are expressed with different V2Rs, which suggests that they may be involved in specificity to different pheromones. In rodents, V2R, M10 and β2-microglobulin form a multimolecular complex that is localised to the dendritic tips of VNO neurons at the site of pheromone detection (for illustration, see Dulac and Torello, 2003), and that is likely involved in the process of pheromone detection. Outside rodents (i.e. in dogs, cows, and humans), the M10 family ofMHC proteins is, however, absent (Shi and Zhang, 2007). Likewise, ESPs, which activate mouse V2R-expressing vomeronasal neurons (Kimoto et al., 2005), are absent outside rodents (Shi and Zhang, 2007).

Signal transduction after pheromone-VR binding in the VNO

Unlike ORNs that express G_{olf}, vomeronasal neurons express two other types of membrane associated G-protein-subunits: $G_{\alpha i2}$ or $G_{\alpha o}$. After binding of a pheromone to a VR, the pheromonal signal is transduced through $G_{\alpha i2}$ (in case of V1R and V3R family members) or $G_{\alpha o}$ (in case of V2R family members) proteins, followed by phospholipase C-induced production of diacylglycerol (DAG) (Zufall, 2005; Zufall et al., 2005; Boehm and Zufall, 2006) and (Dulac and Torello, 2003)/or (Sasaki et al., 1999; Takami 2002; Thompson et al., 2004) inositol triphosphate (IP3), where after Na^+/Ca^{2+} ion channels are opened (*Table 15*). A few VNO neurons express the taste-specific G protein α-gustducin, which may point to a similarity with the processing of chemosignals by taste receptor cells (Zancanaro et al., 1999).

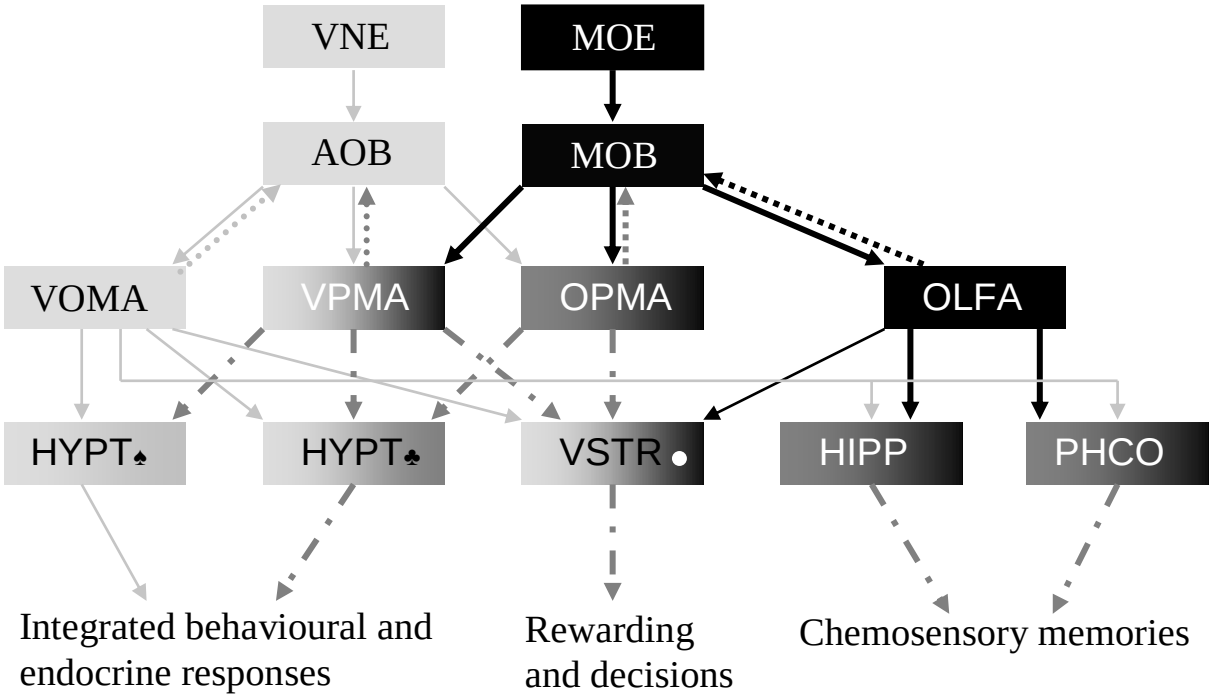
The epithelium of dog, goat, horse, musk shrew (*Suncus marinus*) and common marmoset VNO immunoreacts only to $G_{\alpha i2}$ antibodies, which suggest the presence in these species of V1Rs only (Takigami et al., 2004; Hagino-Yamagishi, 2008). In goats there is an unusual dual expression of the V1R1 gene in the epithelium of both the VNO and the MOS (Wakabayashi et al., 2002). It has been demonstrated for rodent vomeronasal neurons that the cation channel gene TRPC2 is unique, at least for the V1R or V3R containing neurons located in the apical zone of the VNO, and that it plays a fundamental role in the neuronal signal transduction mechanism engaged in the sensing of pheromonal signals (i.e., those that stimulate male-male aggression, establishment of dominance and inhibit sexual behaviour of males towards other males) (Zufall, 2005; Zufall et al., 2005). Because the signaling of MHC-peptides in V2R-expressing neurons is intact in *Trpc2*$^{-/-}$ mice, other signaling mechanisms than that involving TRPC2 may exist (Zufall and Leinders-Zufall, 2007; Kaupp, 2010). TRPC2 is one of seven members of the TRPC subfamily with classical, canonical, or short transient receptor potentials (the C in TRPC stands for canonical or classical), belonging to the large superfamily (~30) of mammalian TRP ion channels (for reviews, see Freichel et al., 2004; Vazquez et al., 2004; Wu et al., 2010), which can be subdivided into 6

(Clapham et al., 2005) or 7 (Montell, 2005) subfamilies (see also the paragraph '*Signal transduction after odourant-OR binding in the MOS*').

Gating of TRPC2 ion channels is generated by a pheromonally triggered V1R/V2R-G_{α} protein-PLC-DAG/IP_3 cascade (Dulac and Torello, 2003; *Table 15*). In the sensory area of the rat VNO, scaffolding-associated proteins from the Homer family (particularly Homer 1b/c and Homer 3) and chaperone-associated proteins, i.e., receptor transporting protein 1 (RTP1) and receptor expression enhancing protein 1 (REEP1), are expressed which form protein-protein interactions with TRPC2 channels and regulate TRPC2 expression and channel activity, thereby modulating the transduction of chemosignals (Mast et al., 2010). Besides, TRPC2 and Homer 1b/c form a complex with IP_3R3 ion channels to allow Ca^{2+}-influx. As a result of the rise in intracellular calcium, a calcium-activated non-selective ion channel can amplify the chemosignal-induced current. It furthermore activates calcium-activated big conductance potassium ion channels as well as calmodulin, which may bind to both TRPC2 and IR_3P3. Ca^{2+} transients in VNOs can be elicited by application of polyunsaturated fatty acids, including linoleic acid and arachidonic acid (Spehr et al., 2002). Indeed, it has been demonstrated in mouse vomeronasal neurons that odours, after activation of the V1R/V2R-G_{α}-PLC-DAG pathway, may open Ca^{2+}-dependent ion channels via arachidon acid (a metabolite of DAG) (Zhang et al., 2010) (*Table 15*). See also Dulac and Torello (2003), Mast et al. (2010), Zhang et al. (2010) and Kaupp (2010) for schematic presentations of proposed signal transduction of pheromone responses in the VNO.

By analyzing sequence data from the TRPC2 gene of 22 primate species, i.e., two prosimians (black and white ruffed lemur (*Varecia variegate*) and ring-tailed lemur), nine NW monkeys (squirrel monkey, spider monkey, (Azara's) southern (night) owl monkey, three-striped night (owl) monkey (*Aotus trivirgatus*), titi monkey (*Callicebus moloch*), red howler monkey (*Alouatta seniculus*), cotton-top tamarin, Rio tapajós saki (*Pithecia irrorata*) and common marmoset), five OW monkeys (rhesus macaque, Hamadryas baboon (*Papio hamadryas*), black-and-white colobus monkey (guereza; *Colobus guereza*), langur (*Semnopithecus* sp.) and drill (*Mandrillus leucophaeus*)), and six huminoids (sumatran orangutan (*Pongo pygmaeus*), Siamang gibbon, white-cheeked gibbon (*Hylobates leucogenys*), western lowland gorilla, common chimpanzee and human), the presence of an intact TRPC2 open reading frame has been demonstrated in the prosimian species (Strepsirrhines) and the NW monkey species (Platyrrhines), and its absence (complete pseudogenisation) in all OW monkeys and hominoids (Catarrhines) surveyed (Liman and Innan, 2003; Zhang and Webb, 2003). Together, the V1R and TRPC2 results indicate degeneration of the VNS transduction pathways in OW monkeys and hominoids, whereas the specific signal transduction molecules for VNO function are present in prosimians and NW monkeys. The findings correspond with the absence of a distinct accessory olfactory bulb (AOB) and the lack of a VNO in many species of OW monkeys and hominoids (Wysocki, 1979). The loss of OR, V1R and TRPC2 genes coincides with the acquisition of full trichromatic vision in primates (Liman and Innan, 2003; Zhang and Webb, 2003; Gilad et al., 2004), and the enhanced reliance on vision may have led to a reduced reliance on chemical signaling in mediating social interactions (Liman and Innan, 2003). In this connection, it is questioned why several Cattarhine species possess well developed scent glands (Dixon, 1998). Apart from the red howler, for two other species of NW howler monkeys (i.e., the mantled howler, *Alouatta palliata*, and the red-handed howler, *A. belzebul*) evidence was obtained for the coexistence of pheromone perception and full trichromatic vision by demonstrating that the TRPC2 gene is functional in these monkeys and not a pseudogene without an open reading frame (Webb et al., 2004) as is the case in all hominoids and OW monkeys (Zhang and Webb, 2003). This finding in howler monkeys is supported by their marking, sniffing, nibbing and licking behaviours (Milton, 1975; Glander, 1980; Cortés-Ortiz 1998), which are rarely seen in OW monkeys and hominoids (Webb et al.,

Figure 9: Schematic presentation of the processing of olfactory information from the MOE in and VNE to the chemosensory amygdala and further brain centres in rodents that leads to integrated behavioural and endocrine responses, rewarding and decisions, and chemosensory memories (adapted from Gutiérrez-Castellanos et al., 2010).



Legend belonging to Figure 9: Fully black boxes, areas processing olfactory stimuli originated in the main olfactory epithelium (MOE); fully grey boxes, areas processing olfactory stimuli originated in the vomeronasal epithelium (VNE); black-grey boxes, areas processing olfactory stimuli originated in the MOE or the VNE; MOB, main olfactory bulb; AOB, accessory olfactory bulb; OLFA, olfactory amygdala; VOMA, vomeronasal amygdala; OPMA, olfactory predominance part of the mixed chemosensory amygdala; VPMA, vomeronasal predominance part of the mixed chemosensory amygdala; HYPT, hypothalamus; VSTR, ventral striatum; HIPP, hippocampus; PHCO, parahyppocampal cortices; ♠, the dorsomedial part of the ventromedial nucleus of the hypothalamus, the anterior hypothalamic nucleus and the dorsal premammillary nucleus; ♣, the ventrolateral part of the ventromedial nucleus of the hypothalamus, medial preoptic area and ventral premammillary nucleus; ○, nucleus accumbens, olfactory tubercle and islands of Calleja; dotted arrow, modulatory feedback; black arrow, projection of main olfactory chemosensory stimuli; thinner (light-gray) arrow, projection of vomeronasal chemosensory stimuli; dash-dotted arrow, projection of mixed chemosensory area.

2004). The latter authors furthermore suggested that, besides the development of full trichromatic vision, ecological differences, particularly habitat selection, may have also affected the evolution of pheromone perception in primates. Indeed, OW monkeys and hominoids are generally terrestrial and live in more open forests and savannahs, while NW monkeys generally live in more dense tropical rainforests and are arboreal (Fleagle, 1999).

Female TRPC2-knockout mice show a reduction in female-specific behaviour, including maternal aggression and lactating behaviour (Kimchi et al., 2007). Such homozygote knockout females display characteristics of male sexual and courtship behaviours such as mounting, pelvic thrust, solicitation, anogenital olfactory investigation, and emission of complex ultrasonic vocalisations towards male and female conspecific mice. The same behavioural phenotype is observed after VNO surgical removal in adult animals, and is not accompanied by disruption of the oestrous cycle and sex hormone levels. VNO-mediated pheromone cues thus seem to repress male behaviour in female mice and activate that of females.

Patch-clamp and field recordings together with immunohistochemical studies, have recently pointed to the presence of a Ca^{2+}-calmodulin feedback mechanism, mediating sensory adaptation and inhibition of pheromone-sensitive TRPC2 channels in the VNO (Spehr et al., 2009). In contrast to olfactory neurons in the MOS (Wei et al., 1996; 1998; Leinders-Zufall et al., 1999), pheromone-sensitive VNO neurons do not express CaMKII (Menco, 2005), while application of a specific peptide inhibitor of CaMKII does not prevent CaM-mediated channel inhibition (Spehr et al., 2009). Consequently, these observations exclude an involvement of the concerned kinase in this effect.

Conduction of action potentials evoked by VR neurons from the VNO to and within the brain

As a consequence of intracellular cation inflow in vomeronasal neurons, the neuron membrane is depolarised, which may result in an axonal action potential. These vomeronasal axons coalesce to form the vomeronasal nerves and conduct evoked action potentials to secondary sensory neurons in the AOB, which then processes the incoming information. The AOB contains vomeronasal nerves, glomeruli, mitral/tufted cells and granular cells (Nakajima et al., 1998; Salazar et al., 2003; Kelliher et al., 2001), which in goats are structurally organised in layers (Mogi et al., 2007). In rodents, projecting axons from these neuronal populations remain segregated into 2 zones of the AOB. V1R-$G_{\alpha i2}$ and V2R-$G_{\alpha o}$ expressing vomeronasal neurons respectively project to the anterior and posterior portion of the AOB (Inamura et al., 1985; Ichikawa et al., 1994). In contrast, goats lack an anterior-posterior segregation in the projection patterns of their (only V1R-$G_{\alpha i2}$ expressing) vomeronasal neurons in the AOB (Takigami et al., 2000; Hagino-Yamagishi, 2008).

By combining multi-electrode recording in the AOB of anaesthetised mice and an unique noninvasive *in-vivo* experimental preparation for studying vomeronasal functioning that engages the natural pumping mechanism, requires small volumes of test stimuli, and allows many cycles of stimulus presentation, not only high selectivity of vomeronasal activation by male and female mouse urinary and salivary cues has been demonstrated, but also that AOB neurons can achieve multilevel distinctions, namely among animals from different strains, among animals from the same strain, and among distinct samples from an individual mouse (Ben-Shaul et al., 2010). This discriminating potency of the AOB enables individual recognition important to social and sexual behaviour. Besides, a significant fraction of AOB neurons responds robustly and selectively to predator cues, indicating a role for the AOB in both intraspecific and interspecific recognition.

From the AOB, pheromonally evoked action potentials are conducted through mitral cells to areas of the limbic system, more precisely to (i) the posteromedial cortical nucleus, (ii) the posteromedial bed nucleus of the stria terminalis (which together have been termed

the vomeronasal amygdala), (iii) the medial nuclei of the amygdala, (iv) the bed nucleus of the accessory olfactory tract, (v) the anterior amygdaloid area (which areas form the vomeronasal predominance part of the mixed chemosensory amygdala) and, to a lesser extent, to (vi) the anterior cortical nucleus, (vii) the corticoamygdaloid transition area and (viii) the nucleus of the lateral olfactory tract (which form the olfactory predominance part of the mixed chemosensory amygdala) (Pro-Sistiaga et al., 2007; Martinez-Marcos, 2009; Gutiérrez-Castellanos et al., 2010; *Figure 9*; see also chapter '*Conduction of action potentials evoked by OR neurons from the MOS to and within the brain*'). From the vomeronasal amygdala and the vomeronasal predominance part of the mixed chemosensory amygdala, projections are successively directed to various hypothalamic centres (like the medial preoptic area; with possible effects on hypophyseal hormone release, thereby determining the endocrine state of the animal), the mammilary corpuscle and lower motor neurons from the central nervous system (with possible behavioural effects) (Scalia and Winans, 1975; Kevetter and Winans, 1981a,b; Halpern, 1987; Von Campenhausen and Mori, 2000. Petrovic et al., 2001; Halpern and Martinez-Marcos, 2003; Keverne, 2004; Gutiérrez-Castellanos et al., 2010). Partially different projections have been described in the opossum (Martinez-Marcos and Halpern, 1999) and in the rat (Mohedano-Moriano et al., 2007), which form a warning for making careless extrapolations between species. Various feed back mechanisms modulate the processing of AOB stimuli (Raisman, 1972; Fan and Luo, 2009).

In contrast to the situation in the AOB, segregation of afferent nerve signals originating from V1R and V2R neurons is not completely maintained in the amygdalic regions, because clusters of amygdalic neurons may not only project to specific areas of the amygdala and hypothalamus, but (at least in some species) also combine both vomeronasal signals (Martinez-Marcos and Halpern, 1999; Mohedano-Moriano et al., 2007; Mohedano-Moriano et al., 2008; Von Campenhausen and Mori, 2000).

Although significant advances have been made in isolating and characterizing several sex-specific olfactory ligands, neural mechanisms that enable a gender dimorphic response to these odours were largely unknown. There are now, however, several indications for sexual dimorphism in olfactory signaling.

Based on findings with ferrets, it was concluded that peripheral processing of pheromonal inputs from the MOS/MOB and/or VNO/AOB may be similar in the two sexes, whereas the motivational salience of these signals differ in males and females, because of sexual dimorphic morphological features of the medial preoptic area and anterior hypothalamus (Baum, 2009).

In rats, immunohistochemical studies on the distribution of cFos (a cellular proto-oncogene belonging to the immediate early gene family of transcription factors and a marker of neuronal activity in response to several sensory stimuli; Collado et al., 1990; Boilleret et al., 2000; Cooke and Woolley, 2005; VanElzakker et al., 2008; Dall'Oglio et al., 2008; Touhara and Vosshall, 2009) and dual immunohistochemistry for cFos and phenotypes, showed that, after their triggering by a pheromonal stimulus (exposure to the air-borne volatiles emanating from male-soiled bedding), females have a greater number of activated neurons than males in the the VNO, AOB and medial extended amygdala (Pereno et al., 2010), which is made up of the medial amygdaloid nucleus and the medial division of the bed nucleus of the stria terminalis (Dall'Oglio et al., 2008). This amygdaloid structure participates in the processing of pheromonal signals concerned with the control and modulation of neuroendocrine, appetitive, reproductive, and emotional behaviors (Keller et al., 2009). The finding of Pereno et al. (2010) is indicative of the existence of sex differences in cFos immunoreactivity in neurons of the vomeronasal amygdala, which supports previous studies that demonstrated different aspects of functional sex differences in this brain area (Jia et al., 1999; Boilleret et al., 2000; Larriva-Sahd, 2008).

After exposure to male urinary volatiles, females mice have a greater number of activated neurons than males in the AOB (Kang et al., 2010). Following ESP1 exposure, cFos-induction patterns in sub-cortical brain regions showed various sexual dimorphisms in neural activation, such as an increase of cFos in the ventromedial hypothalamus of females and in the medial preoptic area of males (Stowers and Logan, 2010).

In humans, the volume of the central subdivision of the bed nucleus of the stria terminalis is larger in men than in women, which may have implications for (olfaction-related) sexual behaviour (Zhou et al., 1995), transsexuals having female neuron numbers in this brain area (Kruijver et al., 2000). Furthermore, structural and functional sex differences have been described for the human hypothalamus (Swaab et al., 1995; 2001). Garcia-Falgueras et al. (2006) also found sexual dimorphism in gray matter concentration of several olfactory regions. Women have a higher concentration in certain orbitofrontal cortex areas and in their temporomedial cortex (i.e. bilateral hippocampus and right amygdala), as well as in their left basal insular cortex. In contrast, men show a higher gray matter concentration in the left entorhinal cortex, right ventral pallidum, dorsal left insular cortex and a region of the orbitofrontal cortex. The mammalian olfactory system thus seems to be a sexually dimorphic network. For more olfaction-related sex differences in human brain areas, see paragraph '*Human brain responses to putative pheromones*'.

Exposure of mice to odourants elicits a rapid change in firing frequency in the MOB, while exposure to pheromones evokes responses with differential, slower kinetics in the AOB (Luo et al., 2003). Exposure of oestrous rat to male pheromones induces intense exploratory acrivity in the females, which is followed by (an approximately two hours) delayed activation of the (posteromedial cortical nucleus of the) amygdala, while exposure to control odours only elicits immediate exploration behaviour (Mucignat-Caretta et al., 2006). It is concluded that, in addition to fast responses, stimulation of the rat VNO may result in long-lasting modifications to the firing rate of the AOB and in slow-onset activity of the amygdala, suggesting the involvement of vomeronasal projection areas in the long-term modulation of the hypothalamus axis, which affects gonadal hormone output and reproductive activity (Mucignat-Caretta, 2009).

Several key structures of the rat vomeronasal system, such as the AOB, the posteromedial cortical and medial nuclei of amygdala, the bed nuclei of the accessory olfacyory tract and the bed nucleus of the stria terminalis, express high levels of nitric oxide synthase (Rodrigo et al., 1994). Augustin-Pavón et al. (2009) demonstrated that, in mice, nitric oxide indeed has a role in pheromone-mediated intraspecific communication by influencing the processing of the pheromonal signal through the vomeronasal system. In rats, Pereno and coworkers (2010) observed a great colocalisation of cFos with GABA, calretinin, and calbindin in neurons of the VNO, AOB and medial extended amygdala, and concluded from their findings that in amygdaloid areas, neuronal excitability is controlled by GABAergic neurons that contain different calcium-binding proteins, indicating the important role of inhibitory control on the incoming sensory pheromonal and olfactory inputs, which are controlled and processed by the vomeronasal system.

It is interesting to note that leptin receptor neurons in the hypothalamic ventral premammillary nucleus of the mouse directly innervate GnRH neurons and stimulate GnRH release not only after sensing leptin but also after sensing odourant of the opposite sex (Leshan et al., 2009). These leptin-binding receptor neurons additionally signal the energy status of an individual, thereby permitting the expenditure of resources on energy-intensive processes such as reproduction (Cohen et al., 2001; deLuca et al., 2005; Gao and Horvath, 2007; Berthoud, 2007). Apparantly, leptin receptor neurons in the ventral premammilary nucleus integrate sexual cues with leptin-mediated signals of energy status, and so regulate the reproductive axis in response to metabolic and odourant stimuli.

Functional relation between the MOS and the VNO

The VNO is physically but not completely functionally separated from the MOS, since all species without a VNO are sexually active, and species with a VNO not only sense specific vomeronasal stimuli but also other chemical cues through the vomeronasal epithelium (for reviews, see Dulac and Terello, 2003; Halpern and Martinez-Marcos, 2003; Restrepo et al., 2004; Witt and Hummel, 2006; Wang et al., 2006; Keller et al., 2009). Indeed, it has been reported that (i) a small number of mouse VNO cells responds to volatile compounds, which also elicit distinctive smells (Sam et al., 2001), (ii) odorous compounds can be detected in transgenic mice with a nonfunctional MOS (as a result of the knockout of adenylyl cyclase-3 (Wang et al., 2006), (iii) certain odours elicit electrovomeronasogram (EVG) responses in mice (Trinh and Storm, 2003), and (iv) certain OR subtypes are expressed in small populations of VNO neurons, while certain VRs are expressed in the neuro-epithelium of the MOS (Rodriguez, 2004; Karunadasa et al., 2006; Wakabayashi et al., 2007; Date-Ito et al., 2008).

Lévai et al. (2006) have demonstrated the expression of a subset of ORs in the apical layer of the mouse VNO. At this site, they have identified 44 different OR genes. The respective OR genes are also expressed in neuro-epithelial cells of the MOS. Although the ORNs in the MOS are zonally distributed, no such pattern is displayed by the OR expressing VNO neurons. Cells expressing ORs in the VNO do not express the typical transduction elements of the MOS epithelium, like adenylyl cyclase-3 and G_{olf} but, in stead, positively stain in double in situ hybridisation experiments for TRPC2 and $G_{\alpha i}$, the markers for neurons in the apical layer of the VNO. Furthermore, the authors have shown that VNO cells expressing distinct ORs project to the AOB. The MOS can mediate pheromone-induced behaviour in rabbits, mice (Schaal et al., 2003; Mandiyan et al., 2005), golden (= Syrian) hamsters (Swann et al., 2001) and pigs (Dorries et al., 1997), while certain known mice pheromones excite both the MOB and the AOB in mice (Xu et al., 2005). Besides, in female (Swiss Webster) mice, MOS-medial amygdala-AOB neural signaling of gender-specific (i.e., male) urinary volatiles has been demonstrated (Martel and Baum, 2009), while there is anatomical evidence from the rat, which shows that the AOB may receive axon collaterals directly from mitral cells of the MOB (Larriva-Sahd, 2008). Moreover, male VNO-ectomised male mice are still able to distinguish urine odours from males and oestrous females, and from mice of both sexes that are in different endocrine states (Pankevich et al., 2004), while TRPC2-knockout male mice mate normal with female mice (demonstrating that the male VNO is not required for initiating male sexual behaviour (Stowers et al., 2002)), and mutant mice lacking CNGA2 show deficits in sexual and aggressive behaviours (Mandiyan et al., 2005), which may point to their mediation through pheromone signaling in the MOS. This corroborates reports on the mouse MOB and its response to volatile, biologically significant pheromones (Ma et al., 2003; Xu et al., 2005; Martel et al., 2007; Kang et al., 2009).

Findings with mice and ferrets have shown complementary roles of the MOS and VNO in mate recognition. The MOS appears involved in the detection of volatile pheromones that are impotant for sex discrimination and mate recognition, while the VNO contributes to motivational aspects of mate recognition, including attraction to opposite-sex pheromones (Baum and Kelliher, 2009). The male votile pheromonal signals, conveyed in female mice through the MOS-medial amygdala-AOB neural pathway, may motivate approach behaviour to opposite-sex pheromonal signals that ensure successful reproduction (Martel and Baum, 2009). A synergistic role of the MOS and VNO has furthermore been demonstrated in regard the detection of oestrus by male mice, the MOS being involved primarily in the attraction from a distance, and the VNO playing a major role in close proximity (pre-copulatory behaviour) (Achiraman et al., 2010). The currently collected data strongly indicate the

existence of functional relations between and complementary roles for the MOS and the VNO, and an overlap in the chemosignals that can be detected by the MOS and the VNO.

Different from the situation in rodents, all (32) identified intact caprine V1R genes are expressed in both the MOS and the VNO (Ohara et al., 2009). This overall V1R expression in the goat's MOS and VNO might be indicative of a dual system for perceiving pheromonal cues, like the induction of a flehmen response through MOS-V1R, followed by a VNO-V1R mediated stimulation of the gonadotropin-releasing hormone pulse-generator activity in the hypothalamus. Ohara and coworkers (2009) discovered that a surprisingly high percentage (over 70%) of the bovine V1Rs have orthologs in goat and/or sheep, which make species-specific V1Rs in ruminants scarce and which may indicate that the role of V1Rs in defining species specificity in ruminants is relatively poor. The high amino acid sequency identity of ruminant ortologous V1R pairs suggests that these ortologous V1Rs detect the same or closely related chemical compound(s), and may explain the induction of out-of-season ovulation in anoestrous ewes by a buck pheromone and that of anoestrous does by a ram pheromone (Over et al., 1990; Ichimaru et al., 2008).

Human brain responses to putative pheromones

Although the existence of a VNO has been demonstrated in variable percentages of the humans that have been studied (Knecht et al., 2003b) and pheromone-like compounds can elicit a local response in the VNO epithelium in a gender-related manner (Monti-Bloch and Grossner, 1991; Jennings-White, 1995; Berliner et al., 1996; Grosser et al., 2000), no neurons running from the adult human VNO have hitherto been identified, while the AOB exists only in the human foetus (Savic, 2001). Therefore, most noncommercially allied scientists are of opinion that the VNO is not functional or question the role of the VNO in chemical communication (e.g., Trottier et al., 2000; Meredith, 2001; Liman and Innan, 2003; Keverne, 2004; Wysocki and Preti, 2004; Witt and Hummel, 2006; Mast and Samuelsen, 2009). Despite of that, it still has recently been hypothesised that loss or damage of the VNO, resulting from orthognatic surgery, influences the post-operative social life of humans in terms of a loss of negative feed-back, which is important for exclusion of inappropriate mates (Foltán and Sedý, 2009). However, these authors did not provide data to support their opinion, while the cited research literature is mischaracterised (Mast and Samuelson, 2009). More likely, the observation that, after orthognatic surgery, people become less committed to an existing mate or even become promiscuous is the result of the cosmetic intervention for which it is aimed, i.e. the correction of congenital or acquired jaw deformation, which significantly increases the patient's self confidence (Nurminen et al., 1999), their psychological-psychiatric profile (Flanary et al., 1990) and their physical attractiveness (Jacobson, 1984).

The human show various morphological sex differences in regard the gray matter of the olfactory system within the brain (Zhou et al., 1995; Kruijver et al., 2000; Swaab et al., 1995; 2001; Garcia-Falgueras et al., 2006; see paragraph '*Conduction of action potentials evoked by VR neurons from the VNO*'). Furthermore, using positron emission tomography to study the brain response to ADIO and EST, striking sexually dimorphic neural response patterns to these steroidal metabolites have been observed (Savic et al., 2001). EST induces activity primarily in the hypothalamic region of men but olfactory region of women. In contrast, ADIO induces primarily the hypothalamic region in women but olfactory region of men. Studies of this group show that, in humans, the preferred pathway for transporting pheromone-like cues is associated with the responder's sexual orientation rather than to the biological sex (Savic et al., 2005; Berglund et al., 2006). Pheromonal effects in humans thus seem to be mediated by intranasal sensory epithelia and not by the extranasal epithelium of the VNO. More recent data from positron emission tomography brain activation experiments,

in which the human VNO was either occluded or left open, have confirmed that the VNO is not involved in the perception of endogenous odours like ADIO (Frasnelli et al., 2010). The intranasal olfactory and respiratory epithelia have previously been proposed as pheromone mediating tissues (Hummel, 2000; Knecht et al., 2003a,b; Gerber et al., 2005; Witt and Hummel, 2006). The MOS may realise such pheromonal communication, since androstenone and ADIO have been shown to selectively activate a specific human odourant receptor (OR7D4) *in vitro* (Keller et al., 2007). It has to be remarked that, by using functional magnetic resonance imaging and lower steroid concentrations, Zhou and Chen (2008) were not able to repeat the hypothalamus response to putative steroid pheromones in heterosexual women and gay men and thus could not confirm the link between sexual orientation and hypothalamic neuronal processes as described by Savic et al. (2001; 2005). The former authors have shown that the right orbitofrontal cortex, right fusiform cortex and right hypothalamus respond to airborne natural sweat, and conlude from their findings and existing literature (see references in Zhou and Chen's paper) that the right orbitofrontal cortex, along with the hypothalamus, processes the emotional value of natural human sexual sweat, and that the chemosensory information of the sexual sweat is encoded holistically in the brain rather than specifically for its sexual quality.

Few functional MRI-studies on human brain activity reported that, relative to body odour when viewing a neutral film clip, a person's body odour is perceptively altered when watching film clips that elicit anxiety or fear versus clips that contain comedic scenes, or when they are exposed to sexually explicit videos (Ackerl et al., 2002; Zhou and Chen, 2008; 2009). These changes in body odour may point to the presence of signaler and/or modulator pheromones in human sweat that inform other humans about immediate environmental situations, and which may influence the mood of persons.

Olfactory chemoreceptors different from ORs and VRs

In addition to ORs and VRs, there may be other as yet undiscovered sensory receptors in detecting vertebrate pheromones. Indeed, $GABA_A$ receptors could represent a target for 5α-androstenol (or other steroids that are structurally similar to endogenous A-ring reduced neurosteroids, acting as positive modulators of these receptors) as a pheromone, for which it is well suited because of high volatility and lipophilicity, or as a conventional hormonal neurosteroid (Kaminski et al., 2006). $GABA_A$ receptors are ionotropic receptors and ligand-gated ion channels, and have γ-aminobutyric acid (the major inhibitory neurotransmitter in the central nervous system) as their endogenous ligand.

Trace amine-associated receptors (TAARs), bind and are activated by nanomolar concentrations of biogenic amines that are present in mammalian tissues (Zucchi et al., 2006; *Table 16*). Fifteen TAAR genes have been detected in mice in the epithelium of the MOS, and can be activated by pheromonal chemicals present in their urine (Lindemann et al., 1995; Liberles and Buck, 2006; Liberles, 2009). In these studies, three mouse TAARs have been found to respond to volatile amines present in mouse urine, one of them detecting 2-phenylethylamine, which is associated with stress, and the two others (trimethylamine and isoamylamine) detecting amines present in greater abundance in male than in female urine. It is suggested that TAAR expressing ORNs are involved in the detection of pheromonal cues that elicit innate behaviors (Liberles and Buck, 2006). Interestingly, different TAAR genes code for similar receptors in humans, fish (Liberles and Buck, 2006) and domestic chickens (Hashiguchi and Nishida, 2007), which could indicate a function for TAARs in the detection of olfactory signs also in these diverging species. Frequent gene gains/losses and high non-synonymous and synonymous nucleotide substitution rates of the species-specific teleost TAAR genes suggest that, in fish, these receptors are used for detecting some species-specific chemicals such as pheromones (Hashiguchi et al., 2008). TAARs have furthermore been

detected as nasal chemosensory receptor genes in rat (Lindeman et al., 2005), dog, cow, opossum, platypus, domestic chicken and western clawed frog (Grus et al., 2007). In vertebrates thus far under investigation, the number of intact TAAR genes varies from 2 (dog) to 57 (zebrafish), and that of disrupted TAAR genes from 0 (opossum and chicken) to 40 (zebrafish) (Grus et al., 2007). TAARs can be subdivided into 3 classes, of which class III does not have an aminergic ligand motif and thus probably responds to ligands other than amines (Hussain et al., 2009). Like ORs, TAARs are bound to G_{olf}, which is activated when ligands bind to the receptor, resulting in an increase of cAMP levels, followed by the opening of a CNG ion channel that is specific for the MOS (Liberles and Buck, 2006; *Table 15)*. Apart from the MOS, TAAR's have also been identified in the Grüneberg ganglion (Fletcher et al., 2007).

The olfactory epithelium of the MOS does not only express G-protein-coupled receptors to detect chemosensory stimuli, since a small number of olfactory sensory neurons in the epithelium of the MOS expresses an orphan receptor guanylyl cyclase (GC) (Fülle et al., 1995; Walz et al., 2007). The GC receptor family contains seven plasmamembrane forms, which include peptide and orphan receptors expressed in various tissues and species, and involved in diverse functions different from chemoreception (Gibson and Garbers, 2000; Kuhn, 2009). For only four of them, GC-A through GC-D, specific ligands have been found. GC receptors consist of an extracellular receptor domain, a short transmembrane region, and an intracellular catalytic domain. Peptide binding to the extracellular receptor domain results in activation of the intracellular cyclase domain followed by the elevation of intracellular cGMP. The activity of GC receptors is modulated by intracellular Ca^{2+} (Duda et al., 2001; 2004; Sharma and Duda, 2010), intracellular proteins such as Ca^{2+}-inhibited guanylyl cyclase activating proteins (Palczewski et al., 2004; Kuhn, 2009), neurocalcin δ (Duda et al., 2004) and bicarbonate (Chao et al., 2010). The GC-receptor in olfactory neurons is termed GC-D (guanylyl cyclase 2d). Intact GC-D genes have been found in rodents, canines, and some prosimians (lemurs and bushbabies), but not in the human, apes, OW- and NW monkeys and tarsiers (Young et al., 2007). In rodents, the GC-D receptor gene is exclusively expressed in the olfactory epithelium, and has chemosensory functions (Kuhn, 2009). The receptor has been shown to detect and transduce certain peptide stimuli (Leinders-Zufall et al., 2007; Duda and Sharma, 2008) such as the natriuretic peptide hormones uroguanylin and guanylin (Cockerham et al., 2009; *Table 16*). Although all GC-D-expressing neurons are highly sensitive to these peptide hormones, individual cells are differentially tuned to either one or both of the peptides. Activation of a GC-D receptor, most likely stimulates a cGMP-phosphodiesterase-2-CNGA3 pathway (Luo, 2008; Munger et al., 2009; Spehr and Munger, 2009; Chao et al., 2010; *Table 15*). Axons of GC-D neurons project to the necklace glomeruli, which reside between the MOB and AOB (Walz et al., 2007; Kaupp, 2010).

Expression of a novel class of olfactory receptor genes, i.e. formyl-peptide receptor (FPR)-related genes, has been detected in the vomeronasal sensory neurons of rodents which, similar to the OR, VR, and TAAR gene classes, encode seven-transmembrane proteins, and are characterised by monogenic transcription and a punctuate expression pattern in the sensory neuroepithelium (Rivière et al., 2009; Liberles et al., 2009). In mice, five from seven transcripts, corresponding to members of the FPR gene family, have been detected by these latter authors in vomeronasal neurons. FRP agonists are present in bodily fluids, like urine, in which various peptides and proteins can be found in situations associated with inflammation or deseases. Therefore, the identified FPR receptors are linked to various biochemical responses which contribute to physiological defence against bacterial infection and cell disruption. Apart from the mouse, FPR family members have furthermore been detected in platypus, rat, dog, and a few primates, inclusive the human (Liberles et al., 2009). Neurons with the same FPR uniformly coexpress either the $G_{\alpha i2}$ protein or the $G_{\alpha o}$ protein (Liberles et

al., 2009). Based on the signal-transduction pathways triggered in human neutrophils, FPR binding may lead to activation of one of these two G proteins, followed by activation of phospholipase C (PLC), PLD, PLA2, and phosphatidylinositol-3-kinase, and triggering of tyrosine phosphorylation (Selvatici et al., 2006). In human neutrophils, the second messengers resulting from FPR interaction act on various intracellular kinases, including protein kinase C and mitogen-activated protein kinases. Activation of PLCβ in neutrophils results in hydrolysis of phosphatidyl inositol-4,5-biphosphate, generating DAG, which on its turn activates PKC isoforms and IP3. This results in Ca^{2+} release from intracellular stores, which then induces the opening of Ca^{2+} channels in the plasma membrane, causing an influx of Ca^{2+}. Such a transduction mechanism could also be present in vomeronasal neurons, since various FPR agonists have been demonstrated to induce cytosolic Ca^{2+} transients in single dendritic knobs of isolated vomeronasal neurons (Rivière et al., 2009). Although the functional role for FPR receptors in olfactory sensory neurons is unknown, it is suggested that they signal the edibility of specific plants or the decay in a potential food source, or enable the identification of unhealthy conspecifics through evaluation of bodily secretions (Kaveliers et al., 2004; 2005a;b; 2006; Liberles et al., 2009; *Table 16*).

<u>The septal organ and Grüneberg ganglion as possible odourant/pheromone detection sites</u>
As mentioned in the Introduction chapter, the MOS, the VNO, the septal organ and the Grüneberg ganglion may receive olfactory input.

The area occupied by the septal organ is highly variable among individuals and may vary between contralateral surfaces of the same animal (Adams and McFarland, 1971). The sensory epithelium of the septal organ resembles that of the MOS. They both contain ciliated olfactory neurons as well as basal and sustentacular cells, but the septal organ comprises only one to three layers of sensory neurons, while most regions of the MOS have six to eight layers (Schoenfeld et al., 1994; Weiler and Farbman, 2003). Neurons of the septal organ, express only about 50 to 80 of the large repertoire of OR genes, which are found in the epithelium of the MOS (Kaluza et al., 2004; Tian and Ma, 2004). These exclusively class-II OR neurons, like those in the MOS but unlike those in the VNO, express adenylyl cyclase type 3 and G_{olf} as transduction elements. Most ORs are expressed only in a few septal organ neurons; a few receptors are found in several hundred cells. However, two receptors, *OR244-3* (Kaluza et al., 2004) and *OR256-3* (Tian and Ma, 2004), are expressed in 20% and 50% of all septal organ neurons, respectively, and thus may have a special role in this olfactory structure. There is no evidence for expression of more than one receptor type per cell. Like the MOS neurons, those of the septal organ have axons that project to the MOB (Ma et al., 2003). The septal organ responds to a broad range of odour stimuli (Marshall and Maruniak, 1986). Due to its location directly at the opening of the nasopalatine duct, the septal organ is perfectly suited to sample odorous compounds from the oral cavity. These substances could be volatile, but also nonvolatile compounds that are transferred by licking activities. Consequently, it is conceivable that the septal organ may have a dual functional role: being involved in surveying food odours, as well as in detecting social-sexual signal molecules (Breer et al., 2006).

The clustered collection of neurons of the Grüneberg ganglion, like the GC-D neurons (Walz et al., 2007), project their axons to the glomeruli from the necklace area, which reside between the MOB and AOB (Fuss et al., 2005). The majority of these neurons express V2R83 (which is also manifest in certain VNO neurons) (Fleischer et al., 2006), together with the vomeronasal G proteins $G_{\alpha o}$ and $G_{\alpha i}$. In their in-situ hybridisation- and RT-PCR studies, the latter authors have furthermore demonstrated that, during prenatal and perinatal stages, few neurons of the Grüneberg ganglion express ORs, G_{olf} proteins, and adenylyl cyclase-3, characteristic for MOS neurons. It indicates that this compartment of the complex

olfactory system comprises cells with either a VNO-like or a MOS-like phenotype, and that it might serve as an additional chemosensory system to detect pheromones and odourants. It has additionally been found that TAARs are expressed in small subsets of Grüneberg ganglion neurons (Fleischer et al., 2007), though also resticted to fetal and perinatal stages. Based on the projection of their axons to the region of the 'necklace glomeruli' (characterised by Shinoda et al., 1989; 1993) in the olfactory bulb, which are active during suckling behavior of pups, it has been suggested that the Grüneberg ganglion may be involved in the detection of important cues for newborns (Fuss et al., 2005; Koos et al., 2005). However, the significance of the transient receptor expressions in the Grüneberg ganglion is unclear, since associated signal transduction molecules are not expressed (Roppolo et al., 2006). Instead, it has recently been demonstrated that, in rodents, subsets of sensory Grüneberg ganglia express GC-D or GC-G receptors and the cGMP-associated signaling proteins PDE2A, cGMP-dependent kinase II, and cyclic nucleotide gated channel subunit A3, coupled to a chemoreceptor repertoire of cilia-localised particulate guanylyl cyclase receptors (GC-D and GC-G) (Liu et al., 2009; Fleischer et al., 2009; Mamasuew et al., 2010; Chao et al., 2010). It is suggested that the Grüneberg ganglion may detect signal molecules, which do not readily reach other olfactory compartments situated in more posterior regions of the nasal cavity, or may operate as primary device for the VNO triggering the vomeronasal pump mechanism through downstream neuronal circuits. Indeed, the Grüneberg ganglion has been found to recognise alarm pheromones (Brechbühl et al., 2008). Using alert pheromones, isolated from mice, calcium imaging techniques and behavioural analysis, these latter authors observed calcium responses in Grüneberg ganglion neurons kept *in vitro* and induction of freezing behaviour *in vivo*. Based on ultrastructural features, small gaseous or lipid-soluble molecules are proposed candidates for detection by the Grüneberg ganglion (Liu et al., 2009).

The trigeminal nerve and odourant/pheromone perception

The olfactory system is not only innervated by olfactory and vomeronasal nerves, but also by branches of the trigeminal nerve. A prominent branch of this fifth brain nerve enters the nasal capsule ventrolaterally to the olfactory nerve and then curls up around it, splaying out in numerous branches distributed to the dorsal and medial nasal mucosa and to tissues external and anterior to the capsule (Tucker, 1963). At this site, trigeminal activation is related with profuse flow of nasal secretions. Increase in the rate of mucous secretion from the olfactory mucosa and in the rate of flow of mucus over it would likely reduce the accessibility of odorous molecules to the receptor. Conversely, most odours have the tendency to stimulate free nerve endings of the trigeminal nerve located within the lining of the nasal vestibule, and produce sensations like irritation, tickling, cooling, warming, burning, and stinging (Hummel, 2000). Putative steroidal pheromones elicit electro-physiological responses not only in the VNO (Knecht et al., 2003/a;b; Monti-Bloch and Grosser, 1991; Grosser et al., 2000; Jennings-White, 1995), but also in the respiratory epithelium at a distance of at least 1-1.5 cm from the VNO (Knecht et al., 2003a;b; Witt and Hummel, 2006), which may indicate that trigeminal afferents play a role in transporting nasal electrical signals that are evoked by these steroids. A role of the nasal mucosa in pheromone reception is supported by the observed similarity in cortical responses to ADIO in intact humans and in those, in which the entrance to the VNO was occluded (Gerber et al., 2005; Witt and Hummel, 2006). Studies with (due to nasal polyposis) chronically anosmic men have shown that ADIO and EST act through the nasal olfactory mucosa and not through trigeminal nerve activation in the respiratory mucosa (Savic et al., 2009). There is, however, an interaction between olfactory and trigeminal pathways. These pathways converge on the same neural elements within the brain, and blocking of the trigeminal pathway enhances odour-induced activity in the olfactory bulb,

while electrical stimulation of the trigeminal nerve decreases bulbar activity (Stone, 1969; Savic, 2001).

Although free nerve endings of the trigeminal nerve fibres in the nasal epithelium are generally believed to react with chemical stimuli (Bryant and Silver, 2000), at least in mice, they are also able to do this indirectly through the abundant solitary chemosensory cells (SCCs), which reside preferentially at the entrance duct of the VNO (Ogura et al., 2010). These SCCs have apical microvilli reaching the luminal surface of the VNO and lack an axon, but in stead are innervated by sensory trigeminal nerve endings. Ogura and allies (2010) furthermore observed that the amount of stimulus fluid that entered the VNO is inversely correlated to the concentration of odorous and bitter substances in the fluid, which means that chemical access to the VNO is regulated by the concentration of odorous irritants and harmful substances in the arriving fluid most likely to protect the vomeronasal sensory neurons. Besides, the authors demonstrated that SCCs express key chemosensory-signaling proteins, like bitter taste receptors, α-gustducin (a key element in taste sensation; Zancanaro et al., 1999; Margolskee, 1993), PLCβ2 and γ13 (a G-protein γ subunit required for PLCβ2 activation; Huang et al., 1999) and the transient receptor channel TRPM5 (which has also been detected in a subset of MOS neurons; see paragraph '*Signal transduction after odourant-OR binding in the MOS*') , as well as choline acetyltransferase and vesicular acetylcholine transporter (i.e. two critical elements for synthesis and packaging of acethylcholine, which is a potential transmitter in the nervous system). Based on their findings on SCC- and trigeminal nerve immunolabeling, trigeminal innervation of SCCs, Ca^{2+}-imaging and fluorescent dye assays, Ogura and coworkers (2010) conclude that signal transduction in SCCs primarily involves the PLC signaling pathway, in which activation of PLC results in either an increase in inracellular Ca^{2+} levels via the internal Ca^{2+} stores, leading to activation of TRPM5 or activation of unknown effectors. PLC-independent pathway(s) may also be involved in chemical reception. For sensory transduction of bitter compounds, the increase in intracellular Ca^{2+} opens TRPM5 ion channels. Activation of SCCs probably leads to release of the neural transmitter acetylcholine, which causes an action potential in afferent branches of trigeminal nerve fibres. This finally may lead to an efferent trigeminal nerve response that evokes a reduction of irritating and harmful chemicals accessing to the VNO. It has to be remarked that not all the irritating and harmful chemical compounds that threatens to enter the VNO are detected by SCCs and that other sensory tissue units, such as the trigeminal free nerve fibres, are likely involved. Future studies have to unravel a possible further significance of trigeminal activation for odourant and/ or pheromone perception and resulting signal transduction, transport and interpretation.

<u>Direct stimulation of the brain by odourants/pheromones</u>

Apart from perception in the MOS and VNO, odourants and pheromones may directly stimulate the brain by diffusion into the blood stream via nasal capillaries (Krzymowska et al., 1999; Stefanczyk-Krzymowska et al., 2000b) and, as has been suggested for therapeutical agents, direct access to the cerebrospinal fluid through transport across the cribriform plate (Hanson and Frey, 2008). Possible mechanisms of such a transport may involve bulk flow and diffusion within perineuronal channels, perivascular spaces, or lymphatic channels directly connected to brain tissue or cerebrospinal fluid (Thorne and Fey, 2001).

Nonmammalian vertebrates

The organisational principles of detecting and discriminating a hugh number of different odourant stimuli and the anatomical organisation of the olfactory system in mammals are quite similar in insects (Imai et al., 2010). Detailed information on olfactory organisation in

insects is, however, beyond the scope of this review. For other reviews on odourant and pheromone sensing and olfactory systems in insects, see De Bruyne and Baker (2008); Touhara and Vosshall (2009); Kaupp (2010) and Galizia and Rossler (2010). Compared to insects and mammals, little is known about olfactory receptor sites, odourant and pheromonal perception, signal transduction, and conduction of evoked action potentials in nonmammalian vertebrates, particulary in reptiles and birds.

Fishes

Unlike the situation in mammals, fish have three different types of ORNs within the olfactory epithelium of the nose: ciliated, microvillous and crypt neurons (Nikonov and Caprio, 2001). Microvillous and crypt-type ORNs are heterologously distributed in the olfactory epithelium (Hansen et al., 2005), but in goldfish the crypt cells are preferentially located along the dorsal margin of the epithelium and near the midline raphe (Hansen et al., 2004). In the crucian carp (*Carassius carassius*), the number of crypt cells varies dramatically throughout the year: at any location within the olfactory epithelium during winter, deep in the epithelium not yet exposed to the environment in spring, and at the epithelial surface during summer spawning season (Hamdani et al., 2007). Ciliated ORNs are also heterogeneously distributed in catfish (Hansen et al., 2005), but more or less homogeneously in goldfish (Hansen et al., 2003). In the channel catfish, ciliated ORNs project to the medial area of the olfactory bulb (OB) that respond to bile acids, while microvillous ORN projections to the posterior dorsal area of the OB responds to nucleotids (Nikonov and Caprio, 2001; Hansen et al., 2003). Other ciliated and microvillous ORNs project to the anterior ventral areas and anterior dorsal areas of the OB, respectively, which both respond to amino acids. Crypt ORNs project to very small distinct ventral areas of the OB (Nikonov and Caprio, 2001). From here, secondary odour neurons project to the lateral part of the medial olfactory tract, which mediates reproductive behaviour (Hamdani and Døving, 2006). According to Hamdani and Døving (2002) axons of ciliated ORNs project to the medial part of the medial olfactory tract, which mediates alarm reactions, whereas those of the microvillous ORNs project to the lateral olfactory tract, which mediates feeding behaviour (Hamdani et al., 2001a). The described topical ORN projections are similar in channel catfish, *Ictalurus punctatus* (Hansen et al., 2003) and zebrafish (Sato et al., 2005; Yoshihara, 2009). Hence, ORNs in fish detect sex pheromones and certain other chemical signals and then, after depolarisation, conduct the evoked action potential through their axons to different regions of the olfactory bulb.

Using anterograde labeling of the axons of olfactory receptor neurons with the voltage-sensitive dye Di8-ANEPPQ and optical recording of the activity induced by diverse natural odourants in afferent axons and across the array of glomeruli in zebrafish, Friedrich and Korsching (1998) have shown that certain subregions of the OB are preferentially activated by defined chemical odourant classes. Within these subregions, amino acids, bile acids and nucleotides induce overlapping activity patterns involving multiple glomeruli, indicating that they are represented by combinatorial activity patterns. In contrast, PGF2α and 17α, 20β-dihydroxy-4-pregnene-3-one-20-sulphate each induce a single focus of activity, at least one of which comes from a single, highly specific and sensitive glomerulus. The results indicate that the OB is organised into functional subregions processing classes of odourants. Similar findings have been described for several other fish species (Nikonov and Caprio, 2001; Hamdani and Doving, 2003; Lastein et al., 2006; 2008). From the various subregions in the olfactory bulb, various regions in the forebrain are innervated, among which are regions that control reproductive processes like sexual behaviour, ovulation and sperm release (Resink et al., 1989d; Dulka and Stacey, 1991; Sorensen et al., 1991b).

In several fish species, OR genes have been identified *(river lamprey*: Freitag et al., 1999; *zebrafish*: Weth et al., 1996; Barth et al., 1997; Dugas and Ngai, 2001; *goldfish*: Cao et

al., 1998; *channel catfish*: Ngai et al., 1993; *Japanese medaka ricefish*: Sun et al., 1999; Kondo et al., 2002; *Japanese loach*: Irie-Kushiyama et al., 2004; various *salmonoids*: Wickens et al., 2001; Dukes et al., 2004; 2006; Morinishi et al., 2007). As mentioned above, ORs belonging to Class I have been detected in fish (Freitag et al., 1995), and have subsequently been found to be intermixed with Class-II (mammalian-type) ORs in both fish and amphibian species (Mezler et al., 2001). Although the exact numbers of fish OR genes are unknown, molecular cloning and genomic DNA-blot hybridisations suggest an approximately five-fold to ten-fold smaller OR repertoire size than that of mammalian species (Alioto and Ngai, 2005; Niimura and Nei, 2005). Despite OR repertoires in teleosts are much smaller than in mammals, based on sequence homology, fish ORs can be divided into more than 5 groups. This may indicate that fish ORs respond to much more divergent kinds of odourants than mammals do. For a survey of the numbers of potentially intact and nonintact OR genes in zebrafish, see Grus et al. (2007).

In fish, a strong correlation between ORN morphology, type of odourant receptor and G-protein expressed has been found:
(i) *ciliated* ORNs express the OR-type (Class I; Sun et al., 1999) of odourant receptor and G_{olf},
(ii) *microvillous* ORNs express V2R-like receptors (in fish also termed olfactory receptors related to class C G-protein coupled receptors, abbreviated OlfCs; Alioto & Ngai, 2006) and $G_{\alpha o}$, $G_{\alpha q}$ or $G_{\alpha i3}$, and
(iii) *crypt* ORNs express $G_{\alpha o}$ and $G_{\alpha q}$ receptor molecules (Hansen et al., 2004). However, these teleost receptors cluster with the tetrapod V2Rs and, thus, on the molecular level are vomeronasal receptors (Grus and Zhang, 2006).

V2R and OR-type receptor molecules do not co-localise in one cell, and only crypt-type ORNs express more than one G-protein. Zebrafish, fugu and green spotted pfufferfish respectively have 44, 18 and 4 intact V2R genes, and 8, 29 and 21 V2R pseudogenes (Shi and Zhang, 2007). No V2R genes have been found in the sea lamprey genome (Grus and Zhang, 2009). In contrast, the latter authors detected 32 unique V2R genes in that of the elephant shark. TRP2 expression in the teleost olfactory epithelium is limited to the regions that also express V2Rs and, thus, was not found in regions were ORs are expressed (Sato et al., 2005), which may indicate that the VNO-specific signal transduction pathway existed before the emergence of a VNO in tetrapods. TRP2 has also been demonstrated in the MOS of the sea lamprey and the elephant shark (Grus and Zhang, 2009) and in the VNO of the musk turtle (*Sternotherus odoratus*) (Murphy et al., 2001).

The three types of teleost ORNs employ either adenylyl cyclase/cAMP or PLC/IP3 as second messenger systems (Hansen et al., 2003). Goldfish detect pheromonal signals by microvillous or crypt-type ORNs expressing $G_{\alpha 0}$, $G_{\alpha i3}$ or $G_{\alpha q}$ (Hansen et al., 2004).
Fish steroidal and PG sex pheromones are mediated by ORNs, which employ the cAMP transduction cascade (Sorensen and Sato, 2005). Responses to amino acids (feeding stimuli) appear mediated by at least two other types of ORNs, one using cAMP, the other IP3 as second messenger. IP3 also functions in frog, snake and turtle VNO neurons, and thus possibly is also a component of the amphibian and reptilian VNO (Taniguchi et al., 2000; Cinelli et al., 2000; Gjerstadt et al., 2003). Besides, in VNO neurons of reptiles (i.e., turtles and snakes), cyclic nucleotide-mediated transduction components like $G_{\alpha i}$, $G_{\alpha o}$, adenylyl cyclase and cyclic nucleotide-gated channels have been identified (Luo et al., 1994; Okamoto et al., 1996; Taniguchi et al., 1996a;b).

Although, in fish, expression of two V1R-types of receptors (in fish also termed olfactory receptors related to class A G-protein coupled receptors, abbreviated ORAs; Saraiva and Korsching, 2007) has been demonstrated (Pfister and Rodrigues, 2005; Pfister et al., 2007; Shi and Zhang, 2007), it is unclear which type of ORN(s) contains these receptors.

Pfister and coworkers (2007) have identified two different V1R gene sequences in the MOS of 10 different *Danio* species, the threespine stickleback and the medaka (*Oryzias latipes*), one of them corresponding to the previously described zebrafish V1R gene (Pfister and Rodrigues, 2005). A single V1R gene has been found in two tetradontidae species, i.e. the green spotted pufferfish *(Tetraodon nigroviridis)* and the fugu *(Takifugu rubripes)*. The V1R gene common to all tested species is named *V1r1* and the one missing in the tetraodontidae lineage *V1r2*. No pseudogenes have been found in these fish species. Conserved repertoires of V1R (and V2R) families in teleost fishes may imply that these receptors perceive common odourants for teleosts, such as amino acids (Hashiguchi et al., 2008). In the genomes of a catilagenous fish, the elephant shark (*Callorhinchus milii*), and a jawless fish, the sea lamprey, 2 and 3 putatively functional V1R genes have been identified, respectively (Grus and Zhang, 2009). Because of an evolutionary shift of VR gene repertoires in the vertebrate transition from water to land, V1Rs and class-II ORs have been suggested to bind to small airborne chemicals, whereas V2Rs and class-I ORs recognise water-soluble molecules (Shi and Zhang, 2007). Olfactory receptor related to Class A, Type 2 (*V1r-like Ora2*) genes are conserved between five species of distantly related rockfishes (Genus *Sebastes*) (Johansson and Banks, 2010). The authors conclude that this strong sequence conservation is indicative of a functional significance of this gene, but that, the *V1r-like Ora2* gene, in isolation, would be unlikely to differentiate species during mating season, because of shared alleles among species.

As mentioned before in this chapter, compared to other vertebrates, the MOS of fish express many functional and non-functional TAAR genes (Grus et al., 2007), and fish TAARs could very well be implicated in the detection of certain pheromones (Hashigushi et al., 2008). It is, however, unclear which pheromonal compounds are recognised by fish TAARs. For more detailed information on the molecular evolution of teleost TAAR-, OR- and VR-gene families, see Korsching (2009).

Odour information conveyed from the ORNs to the olfactory bulb is further transmitted via mitral cell axons to multiple higher olfactory target regions in the forebrain, including the bilateral hemispheres of the telencephalon and the diencephalic right habenular nucleus, where the odour is translated to elicit appropriate cognitive, emotional, hormonal and behavioural responses (Miyasaki et al., 2009) through various brain centres, including the hippocampus, the hypothalamus and the midbrain (Bianco and Wilson, 2009). In our studies with African catfish, effects of steroidal pheromones are conveyed to higher brain centres through the medial olfactory tract which, like the lateral olfactory tract, sends projections to various corresponding telencephalic centres but, unlike the lateral olfactory tract, does not send projections to the habenula (Resink et al., 1989d).

Amphibians

In-situ hybridisation studies revealed Class-II ORs in the MOS epithelium of the tiger salamander (*Ambystoma tigrinum*) (Marchand et al., 2004) and both Class-I and Class-II ORs in that of the axolotl (*Ambystoma mexicanum*) (Zhou et al., 1997) and that of the mudpuppy (*Necturus maculosus*) (Eisthen, 1997; Zhou et al., 1997). The G-protein G_{olf} has recently been demonstrated in the MOS of the red-legged salamander *Plethodon shermani* (Woodley, 2010). 1452 G-protein-coupled receptors have been identified in the western clawed frog, *Xenopus (Silurana) tropicalis*, of which 70% are chemosensory receptors, i.e., ORs, V1Rs, and V2Rs (Ji et al., 2009). With that, this frog shares a more similar repertoire of such chemoreceptors with mammals than with fish. Class-II ORs have been localised in the epithelium of the MOS of the edible frog, *Rana esculenta* (Freitag et al., 1998). As mentioned above, the African clawed frog, *Xenopus laevis*, expresses Class-I ORs in the epithelium lining the water-filled diverticulum of their nasal cavity, and Class-II ORs in the epithelium

lining the air-filled diverticulum of their nasal cavities (Freitag et al., 1995). This phenomenon suggests that the current diversity in mammalian Class-II OR repertoires, necessary to detect airborne odourants, arose at the time vertebrates started to occupy niches on land (Freitag et al., 1995; Glusman et al., 2001). For a survey of the numbers of potentially intact and nonintact OR genes in clawed frogs, see Grus et al. (2007). Western clawed frogs have 66 genes in Class-I ORs and 599 genes in Class-II ORs (Ji et al., 2009), of which a large proportion (over 53%) consists of pseudogenes (Niimura and Nei, 2005). The number of 665 ORs, identified in *Xenopus tropicalis* by Ji and allies (2009), is approximately 62% more than previously predicted for this species (Niimura and Nei, 2005).

In amphibians, the VNO is, like that of mammals (Zufall et al., 2002), lined with microvillar receptor neurons only (Eisthen, 1992). Distinct from that, the amphibian MOS is lined with ciliated receptor neurons in salamanders, and with both ciliated and microvillar receptor neurons in frogs. The olfactory systems of some amphibians, such as clawed frogs, is characterised by the division of the olfactory epithelium into a primary chamber, in which volatile olfactory compounds are detected, and a middle chamber, in which water-soluble chemicals can be sensed (Saito and Taniguchi, 2000). In the red-legged salamander, V2Rs could be demonstrated in the VNO epithelium together with the ion channel protein TRPC2 (Woodley, 2010). Apart from mammals and fish, 21 intact V1R genes (and 2 pseudogenes), as well as a very large V2R gene repertoire (249 intact genes and 408 pseudogenes) have been detected in clawed frogs (Shi and Zhang, 2007; Date- Ito et al., 2008). 12 V1Rs and more than 330 V2Rs have been found in the western clawed frog, *Xenopus tropicalis* (Ji et al., 2009). Although amphibians are the first vertebrates to possess a VNO, expression of the V1R genes in frogs was detected in the MOS epithelium and not in that of the VNO (Date-Ito et al., 2008). The findings with fish, frogs and mammals do suspect the presence of V1Rs in reptiles and birds, in which thus far, however, no V1R has been reported. Whereas, in *Xenopus laevis*, V2Rs are expressed throughout the epithelium of the VNO, expression of V1Rs appears restricted to that of the primary and middle chambers of the MOS (Date-Ito et al., 2008; Hagino-Yamagishi , 2008). Some V2R genes are expressed in the middle chamber of the MOS epithelium (Hagino-Yamagishi et al., 2004). Like in mammals, V1Rs and V2Rs are co-localised with G_{i2} (Hagino-Yamagishi, 2004) and G_o (Date-Ito et al., 2008), respectively.

No intact V2R genes are detected in the chicken, dog, cow and human. It is unclear, why V1R and V2R repertoires in frogs have substantially expanded and why intact V2R genes are lost in chickens and different mammalian species. It is possible (i) that new gene family members arose frequently by gene duplication, because of lower selective constraints on these receptors (Ji et al., 2009), or (ii) that the taste system replaced the V2R-mediated detection of nonvolatile (water-soluble) peptides, because water-soluble taste molecules are sensed by T1Rs, which have weak homology with V2Rs (Touhara, 2007), and such peptides commonly enter the nasal and oral cavity (either or not via the incisive duct) through sniffing and licking. TAAR transcripts have been demonstrated in the epithelium of the MOS in *Xenopus laevis* (Hashigushi and Nishida, 2007; Gliem et al., 2009). The western clawed frog *Xenopus laevis* expresses 2 intact (and 1 disrupted) TAAR genes in their MOS (Grus et al., 2007; Grus and Zhang, 2008). Examination of all putatively functional MOS-expressed TAARs and ORs and VNO-expressed V1Rs and V2Rs in 7 tetrapods (mouse, rat, dog, opossum, platypus, chicken, and frog) has led to the conclusion that the majority or all MOS receptors are broadly tuned generalists, whereas the studied VNO receptors are narrowly tuned specialists (Grus and Zhang, 2008).

Reptiles

Thus far, Huang et al. (2006) have found that the neurons of male, but not female, red-sided gartner snake (*Thamnophis sirtalis parietalis*) VNOs respond to a purified female sex pheromone mixture of 13 long-chain (C29–C37) saturated and monounsaturated methyl-ketones, suggesting that the discriminated response to this pheromone originates in the VNO and not further centrally in the brain. Furthermore, it has been shown that VNO stimulants bind to G-protein–coupled receptors on snake VN neurons (Luo et al., 1994), while sexually dimorphic expression and localisation of the Ga1–3 subunit of GTP-binding proteins has been reported in the musk turtle *Sternotherus odoratus* (Murphy et al., 2001). Brann and Fadool (2006) have found evidence for the existence of multiple transduction cascades in the vomeronasal neurons of the stinkpot/musk turtle *Sternotherus odoratus*, one of which being mediated by a non-selective cation conductance that is not gated by IP3 but may be modulated by the interaction of its receptor with the TRPC2 channel. Despite these data, to date, no VNO receptor has been identified a in a reptile. In contrast, 156 OR genes were identified, including 42 pseudogenes, in a lizard, termed the green anole (*Anolis carolinensis*) (Steiger et al., 2009).

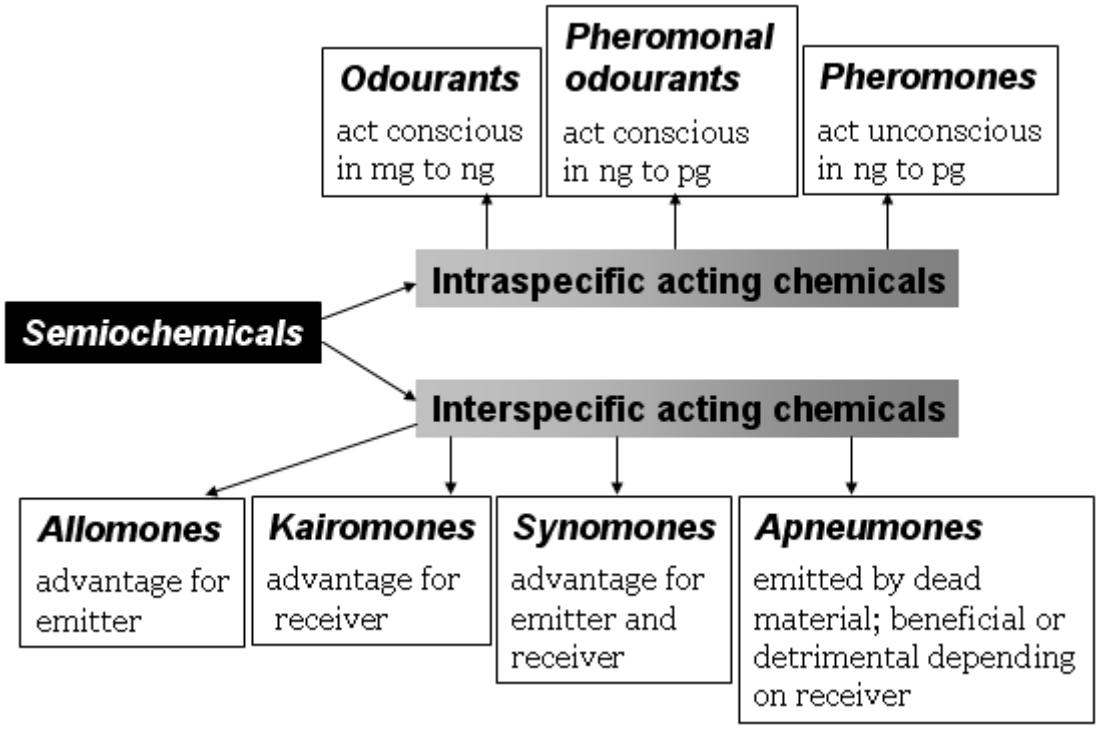
Birds

Birds do have a MOS, that projects to a MOB (Bang and Cobb, 1968; Gomez and Celii, 2008), but lack a VNO and a AOB (Hagelin, 2007). The MOS epithelium contains OR neurons. The number of OR genes on 9 species of birds correlates with the size of the bird (Steiger et al., 2008). Depending on the species, birds express 100 to 650 diverse OR genes, of which a surprisingly large number is functional (Steiger et al., 2009; 2010; Castro et al., 2010). This may indicate that avian olfactory potency is excellent, better than previously thought (see the chapter ‘Sex pheromones in birds’. The MOB projects to multiple brain areas that are homologous to olfactory projection regions in mammals (Rieke and Wenzel, 1978; Reiner and Karten, 1985; Bingman et al., 1994). For revised nomenclature for avian telencephalon and some related brainstem nuclei, see Reiner et al.(2004). Neuronal transduction cascades in MOS neurons of birds, leading to axon depolarisation of olfactory nerves, have not been described yet.

Concluding remarks and future perspectives

The hitherto given definitions of a pheromone are not uniform, often confusing, and only vaguely make distinction with odourants. In an attempt to make terminology in this respect less confused, I propose to subdivide intraspecific semiochemicals or intraspecific odorous chemical substances into three classes: odourants (which act conscious in milligrams to nanograms), pheromonal odourants (which also act conscious but in nanograms to picograms) and pheromones (which act unconscious, commonly in nanograms to picograms). This makes *Figure 2A* change into *Figure 10*.

Figure 10: Semiochemicals in the surrounding of a vertebrate (proposed view).



Vertebrates produce (sex) pheromones through their genital tract (inclusive the gonads and gonadal derivatives), their intestinal tract (inclusive derivatives like the liver, the gal bladder and the anal glands), and their skin or special skin glands. These pheromones often are excreted superfluous compounds from general metabolism or steroid metabolism. Such compounds are used, either directly or after their conversion by resident mico-organisms, for chemical communication to inform conspecifics about the (reproductive) status of an individual, or to stimulate behavioural and/or physiological changes in conspecifics among which potential reproductive partners. In this way, released sex pheromones form a specific signal which is especially developed for mate choice and to optimalise the reproductive success. The method of efficient signaling is possibly the result of a ritualisation process, i.e. some degree of evolutionary development or specialisation of the stimulus.

Teleost fish excrete superfluous steroidal hormones, steroid metabolites, glucuronidated and sulphated steroid conjugates and prostaglandines, which may act as sex pheromones. In primitive jawless fishes bile compounds may have such a role and are also used to lead adult fish to their spawning grounds. The pheromonal blend changes in composition depending of the season and reproductive status of the emitter. The ratio's and concentrations of the

pheromonal blend components have to exceed threshold values to evoke an effect. Although the current data point to the secretion of species-specific mixtures of olfactory components, of which the concentration and relative proportion is appropriate to attract a sexual partner and to stimulate sexual behaviour and subsequent release of matured germ cells, it has not yet been studied in detail how fish recognise and use these discontinuous cues. In particular, their role in the expression of sexual behaviour is unclear.

Because of the restriction of EOG-recordings that only positive responses may indicate a putative pheromone, such studies have to be supplemented by other ones, like those using electrical recording from the olfactory bulbs, and in vitro binding of or endocrine bioassays for questionable compounds, to confirm olfactory specificity. Such an approach has thus far only been done for certain steroid compounds in goldfish (Stacey et al., 1991; Sorensen et al., 1992) and thus deserves imitation. EOG-recordings, showing similar patterns of pheromone detection among closely related species, are not in support of selection for specificity in this respect (Stacey et al., 2003; Narayanan and Stacey, 2003). However, different dynamics of pheromone release together with other sensory cues may minimise the problem of triggering maladaptive interspecific responses, which could be due to the use of similar pheromonal cues by related sympatrical living species. Indeed, it has been reported, that pheromonal mixtures are excreted pulsatile in a species-specific rhythm. Besides, the distance over which the pheromonal plume is spread probably is short, since this increases the chance for attraction of only conspecifics or related fishes. Thereby the pheromonal component(s) with the highest concentration may have the best attractive effect, because of the bigger chance to exceed their threshold value needed for detection. The ones with lower concentration may be additionally important for further sexual arousal and display of typical sexual behaviour patterns. Nevertheless, interspecific spawning does occur in closely related species (carps: Sorensen et al., 1992; cichlids: Streelman et al., 2004; trouts: Bettles et al., 2005, sticklebacks: Gow et al., 2006). Studies on a wider variety of fish species are necessary to further prove the existence of species-specific pheromonal blends and excretion rhythms. In this regard, information on related, reproductively sympatric species is of special interest, because of the great chance for heterospecific interactions.

It can be speculated that released chemical cues primarily evoke attraction of mating partners, and will then prime the formation of appropriate hormones and further activity of the nervous system, which will lead to enhanced milt production, ovulation and motivation to court. Under appropriate environmental circumstances (like suitable water temperature, flooded spawning fields, presence of adequate pheromones), courtship and spawning behaviour will be exhibited through an imprinted ritualised program that is started upon the observation of appropriate sensory cues other than chemical signs. Possibly, induction of courtship and spawning need the presence of similar pheromonal mixtures but with different ratio's and concentrations of the components of which it is composed. Future studies, however, have to be done to confirm this hypothesis.

Additional information on the nature and function of pheromones and the dynamics of their secretion will enhance our understanding of the regulation of fish reproduction and how it has evolved. It furthermore, may have considerable impact on fish culturing and fish management, since fish handling, selection of suitable individuals and possible induction of abnormal endogenous processes can be avoided. Concerning applied aspects of sex pheromones in fish reproduction, one has, however, to wonder whether such an approach can compete in terms of costs and effectiveness with hormonal injection techniques for induced ovulation of cultured teleosts.

Relatively little is known about the nature of sex pheromones in amphibians, reptiles and birds. In amphibians, a specific peptide or protein may function as sex pheromones, while in snakes and ducks such a function has been attributed to mixtures of specific methyl

ketones and mixtures of specific fatty acid diesters, respectively. In these vertebrates, visual, auditory and tactile signs are additional essential cues that control the initiation and completion of adequate reproduction behaviour. Far more studies have to be done to increase our knowledge on the nature and specific function(s) of sex pheromones in these vertebrate classes and what, in regard to the stimulation of reproductive processes, these chemical signs add to existing other sensory stimuli. It is recommended to investigate in such studies the effects on behaviour and reproductive processes of two or more sensory modalities in combination, since stimuli from two or more sensory modalities may produce a greater response in the receiver than either cue alone. In nonmammalian vertebrates, information on the identification and characterisation of pheromone receptors is scarce but gradually growing, and needs further attention to elucidate the mechanisms and evolution of chemical communication during reproduction of vertebrates.

Despite the tremendous volume of chemical information on released semiochemicals by vertebrates, information on the actual compounds that are, either or not in a specific cocktail, involved in specific behaviours or physiological changes is relatively scarce, the conclusions drawn often being contradictory or questionable. One of the most reliable findings is the role of particular steroidal compounds in specific reproductive aspects of fish and pigs. Steroids have also been claimed or suggested to function as human pheromones and steroids and sulphated steroids as mouse pheromones. Because of the obvious pheromonal function of steroids in divergent vertebrate classes as fish and pigs and their putative role in humans and mice, it is surprising that studies on semiochemicals in other vertebrates did not reveal or were not focused on the presence of steroidal compounds in excretions, nor on their possible function as (sex) pheromones. Therefore, it should be encouraged to pay more attention in future studies to the importance of excreted steroids for the reproduction process or for the introductory actions that may lead to such a process in various vertebrates.

In mammals, apart from steroids, many types of chemicals have been put forward as possible or true pheromones or components of pheromonal blends. Examples of such semiochemicals are alcohols, ketones, alkanes, amino acids, amines, terpenes, fatty acids or their esters, and proteins. Proteins may in this regard serve either as pheromones or carriers for pheromones. For most studies carried out at this field counts that much work still has to be done to identify the active components and to determine the concentrations in which they are effective. The identification, characterisation and synthesis of pheromonal compounds or mixtures is of enormous commercial interest for livestock management especially, for instance to hasten the onset of puberty or to detect oestrus in female animals, or to shorten the postpartum period in lactating specimens. When deciphered, pheromones could be used in practical protocols for the management of reproduction, the reduction of environmental stress and aggressive behaviour, and the stimulation of feeding behaviour of domestic and livestock animals. Such pheromones could also be of help in the stimulation of reproduction in captive or feral endangered species like bears, elephants and urangutans. The extent to which sexual and social odours play a role in human community is another intriguing challenge for future research in the field of chemical communication and its role in the choice of a sexual partner, reproduction and social behaviour, as is the interaction among various sensory signals.

Because of the available conflicting data on the role of the VNO in tetrapods (Baxi et al., 2006), further studies on its putative mediating role in the behaviour and physiology of these animals have to be done to find out whether this organ indeed is used for more than just pheromone detection as has been claimed by Sam et al. (2001). Further microchemical analysis of VNO fluid in both nonmammalian and mammalian species is required before either the nature and function of the vomeronasal fluid components can be ascertained and the mechanisms of odourant or pheromone binding to olfactory receptors can be understood. Thus far our knowledge on the nature of the sensory stimuli that are detected by vomeronasal

neurons is limited. Systemic functional mapping studies of semiochemical-induced neuronal activity by optical imaging together with gene expression mapping studies of vomeronasal receptors are needed to determine the precise repertoire of chemosensory cues that are detected and processed by vomeronasal neurons in each of the two anatomical zones (Zufall et al., 2002). This could lead to the prediction of the interaction of specific ligands with subsets of vomeronasal neurons and their receptors or type of response elicited by a certain ligand (e.g., reproductive *vs* feeding behaviour). Such imaging studies can also be used to investigate whether male and female vomeronasal neurons respond differentially to chemosignals. Because of the limited number of receptors and the narrow tuning in the vomeronasal neurons, it seems possible in the future to define the complete set of stimuli that are detected by the VNO. This will be more difficult for the numerous and broadly tuned olfactory neurons. Apart from such neural studies, the demonstrated resorption in pigs of signaling pheromones from the nasal cavity into the circulatory system and their subsequent transport to the brain and hypophysis (Krzymowska et al., 1999; Stefanczyk-Krzymowska et al., 2000b) may have hugh consequences for the current knowledge on the semiochemicals' mode of action. In this regard, it will be of special interest to find out whether an uptake of putative pheromonal steroids or other odourants is also possible in the MOS or in the vestigial VNO of humans, and if such compounds may find their way to the brain through subsequent humoral distribution. Furthermore, to explain nasal pheromonal transport, the finding that intranasal delivery bypasses the blood-brain barrier to target therapeutic agents to the central nervous system and treat neurodegenerative disease (Hanson and Frey, 2008) is interesting. Possible mechanisms of transport may include direct access to cerebral spinal fluid via movements across the cribriform plate by bulk flow and diffusion within perineuronal channels, perivascular spaces, or lymphatic channels directly connected to brain tissue or cerebrospinal fluid (Thorne and Frey, 2001).

It is believed that MHC class-I molecules do not function as peptide receptors and that V2R family members are the most likely candidates for specific peptide receptors (Boehm and Zufall, 2006). MHC class-I molecules are associated with V2Rs and β2-microglobulin (Loconto et al., 2003). However, despite the many speculations about their function in mating preference and social behaviours particularly in fish, mice and humans, it is still unclear what the exact role of these MHC molecules is and how MHC molecules do interact with V2Rs and influence signal transduction by these receptors (Hedge, 2003). It has been shown that, apart from the VNO, MHC class-I peptides are also able to activate subsets of olfactory neurons in the MOS of mice at remarkably low concentrations (Spehr et al., 2006). Likewise, the MOS can mediate pheromone-induced behaviour apart from odourant-induced behaviour in various species (Dorries et al., 1997; Mandiyan et al., 2005 Schaal et al., 2005; Kelliher, 2007; Hurst, 2009). Future studies have to focus on the deciphering of the tuning properties of both peptide sensitive olfactory and vomeronasal neurons, and the identification of the receptors that recognise the MHC peptides as well as those that recognise their ligands. As counts for these MHC peptides, it is necessary in future experiments to elucidate the precise role of the various types of internally and externally formed lipocalins and other binding proteins within the nasal and vomeronasal system of vertebrates.

In the past three years, much information has become available on the expression of TAAR genes in the MOS. Hopefully, the recent discovery of FPR gene expression in the VNO will also lead to increased interest in and studies on the significance and spreading of these latter genes over the olfactory systems in various vertebrate classes.

Although in the last years substantial progress has been made to uncover the brain centres involved in transporting, judging, and memorizing of intraspecific olfactory information coming from the MOS and VNO (Pro-Sistiaga et al., 2007; Martinez-Marcos, 2009; Baum and Kelliher, 2009; Baum, 2009; Touhara and Vosshall, 2009; Kang et al., 2009;

Fan and Luo, 2009; Tirindelli et al., 2009; Gutiérrez-Castellanos et al., 2010), far more studies have to be done to learn how the different intraspecific sexual, individual and other social olfactory chemical signs are exactly processed within the brain of both mammalian and nonmammalian species to evoke an behavioural or endocrine response.

As can be concluded from the foregoing, more and more evidence is obtained (i) that the MOS and the VNO both can perceive odourants and pheromones, (ii) that they both contain a variety of proteins to bind olfacory signals, and (iii) that there are functional overlaps of the two olfactory systems. Additionally, the concept that the MOS and VNO are neuronally connected with the MOB and AOB, respectively, has recently become more complex because of the finding of odourant receptors in the VNO that project to the AOB (Lévai et al., 2006). Apart from this, there are new anatomical findings, which advocate a reorganisation of the recipient cortex to include olfactory, vomeronasal and mixed chemosensory cortices (Martinez-Marcos, 2009). These recent findings make it even more difficult than before to unravel the routes followed by odourants or pheromones that lead to an effect in the brain and possible behavioural or physiological action.

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Epilogue

In 2010, Richard L. Doty published a book entitled ‘The great pheromone myth’ (The Johns Hopkins University Press, Baltimore, Maryland U.S.A.; 296 pp.). I do not subscribe his denial of the existence of mammalian pheromones. My book reviews numerous papers that show conclusive and lesser conclusive evidence for (i) priming effects of released intraspecific semiochemicals on the hypothalamus-hypophyseal-gonadal axis of both non-mammalian and mammalian species, which results in elevated (gonadotropic and steroid) hormone secretion, and (2) the releasing effects of such compounds on the ovarian cycle, the occurrence of puberty and the behaviour of many vertebrates.

The opinion of Doty that mammalian pheromones are a myth is a consequence of the lack of an appropriate and uniformous pheromone definition. In my opinion, pheromones are excreted, intraspecific working semiochemicals that (at least initially) act unconscious and in concentrations of nanograms to picograms. If a semiochemical is effective only in larger concentrations, it isn’t a pheromone, but an odorant. When administered in higher concentrations, pheromones often result in no or a repulsive behavioral effect. For further information on the term pheromone, see the *Introduction* and the last chapter (*Concluding remarks*) of my book.

The conclusion in Doty’s book that Chanel 5 can serve as an attractant for mice and thus can be seen as a pheromone for this species is incorrect; it only shows that animals are able to learn to associate an artificial odourant with a specific behaviour. For, Chanel 5 is not excreted by mice and thus is not acting intraspecifically. Furthermore, most likely, the attractive ingredient(s) of Chanel 5 does/do not work as attractant(s), when offered in concentrations of nanograms to picograms. In other words, Chanel 5 cannot be termed a pheromone.

About the author

Dr. Robert van den Hurk is a retired biologist. As Associate Professor he worked at he Utrecht University, where he was appointed from 1968 till 1989 at the Department of Zoology (Faculty of Biology) and from 1989 till 2008 at the Department of Pathobiology (Faculty of Veterinary Medicine).

His teaching program comprised anatomical, histological, celbiological and physiological aspects of the reproduction system, the endocrine system, the respiration system, the circulation system, the (central) nervous system, the digestive system, the excretory system, the locomotion apparatus and vertebrate embryos, and courses on comparative anatomy of vertebrate skulls, immunohistochemistry and pheromones.

Until 1989, his research progam comprised the endocrine and exocrine regulation of teleost reproduction, with special focus on annual gonadal cycles, gonadal sex differentiation and intraspecific communication through sex pheromones.
From 1989 until 2008, his research was focussed on the regulation of mammalian ovarian follicle development.

After his retirement, he continued his collaboration with several Brazilian scientists with whom he up to now studies the *in-vitro* regulation of ruminant ovarian follicle development. His ongoing interest in sex pheromones and their significance for the reproduction of vertebrates brought him to write the current book.