ELSEVIER

Physiology & Behavior 79 (2003) 441–449

PHYSIOLOGY & BEHAVIOR

Parasite manipulation of the proximate mechanisms that mediate social behavior in vertebrates

Sabra L. Klein*

W. Harry Feinstone Department of Molecular Microbiology and Immunology, Johns Hopkins Bloomberg School of Public Health, 615 North Wolfe Street, Baltimore, MD 21205-2179, USA

Received 4 April 2003; accepted 17 April 2003

Abstract

Paul MacLean was instrumental in establishing the brain regions that mediate the expression of social behaviors in vertebrates. Pathogens can exploit these central mechanisms to alter host social behaviors, including aggressive, reproductive, and parental behaviors. Although some behavioral changes after infection are mediated by the host (e.g., sickness behaviors), other behavioral modifications are mediated by the pathogen to facilitate transmission. The goal of this review is to provide examples of parasite-mediated changes in social behavior and to illustrate that parasites affect host behavior by infecting neurons, causing central nervous system (CNS) inflammation, and altering neurotransmitter and hormonal communication. Secondarily, a comparative approach will be used to demonstrate that the effects of parasites on social behavior are retained across several classes of vertebrates possibly because parasites affect the phylogenetically primitive structures of the limbic system and related neurochemical systems.

Keywords: Aggression; Endocrine-immune; Limbic system; Mating; Neurotransmission; Parental behavior; Parasite–host coevolution; Reproduction

1. Introduction

Within the central nervous system (CNS), the hypothalamus and limbic system have been most closely implicated as mediators of social behaviors, such as aggressive, reproductive, and parental behaviors. The limbic system, including the hippocampus, cingulate cortex, fornix, olfactory bulb, mammillary body, and amygdala, is phylogenetically primitive and as such modulates behaviors that are present in terrestrial vertebrates from lizards and birds to mammals [1]. Papez [2] was the first to suggest that the neural circuitry connecting the limbic system, hypothalamus, and cerebral cortex forms the anatomical basis of emotion. During this time, Klüver and Bucy [3] demonstrated that damage to the limbic system and cerebral cortex causes pronounced changes in aggression and sexual behavior in primates. Paul MacLean expanded the Papez circuit of emotion to include the hypothalamus, septal area, nucleus accumbens (NAcc), and amygdala and demonstrated that the phylogeny of these brain structures could be used to predict the expression of social behaviors in vertebrates.

The hypothalamus, in particular, integrates endocrine and autonomic responses to stimuli and therefore plays a central role in coordinating the neuroanatomical and chemical correlates of social behavior. Several neurotransmitters and hormones, including dopamine (DA), norepinephrine (NE), serotonin (5-HT), opioids, γ-aminobutyric acid (GABA), glutamate, vasopressin, oxytocin, glucocorticoids, sex steroids, and nitric oxide, are involved in the expression of social behaviors [4]. These chemicals synchronize physiological and behavioral responses and influence the probability that social behaviors will be exhibited in response to the appropriate stimuli.

Parasites, broadly defined to include microparasites (e.g., viruses and bacteria) and macroparasites (e.g., protozoan, helminth, and arthropod parasites), can exploit the proximate mechanisms that modulate social behaviors in vertebrates to increase the likelihood of transmission. Parasites can modify the expression of social behaviors by infecting cells (e.g., neurons, endothelial cells, and glial cells) and inducing apoptosis within the CNS, causing inflammatory immune responses in the CNS, and altering the chemical signals that underlie the expression of behavior (see Table 1). Because

* Tel.: +1-410-955-8898; fax: +1-410-955-0105.
E-mail address: saklein@jhsph.edu (S.L. Klein).

0031-9384/$ – see front matter © 2003 Elsevier Inc. All rights reserved.
doi:10.1016/S0031-9384(03)00163-X

Table 1
Examples of infection-induced changes in social behaviors and the mechanisms that mediate these effects in vertebrates

Host	Pathogen	Behavioral effects	Proximate mechanisms[a]	References
Viruses				
Rats (*R. norvegicus*)	BDV	↑ Aggression	Loss of DA neurons in VTA, ↓ DA receptor binding in NAcc, ↑ DA metabolism in cortex, infection of neurons in limbic cortical areas, vomeronasal organ, and olfactory bulb	[5–7]
Tree shrew (*Tupaia glis*)	BDV	↑ Aggression, ↑ physical contact, ↑ sexual behavior	Infection of neurons in frontal cortex	[5,8]
Mice (*Mus musculus*)	Herpes simplex virus	↑ Aggression	↑ Synthesis of 5-HT and DA, ↑ HVA and 5-HIAA concentration	[9]
Several primate species	SIV[b]	↑ Aggression and wounding	No infection of neurons, CNS inflammation, infection of glia in basal ganglia, thalamus and midbrain, ↓ DA activity, ↑ somatostatin mRNA in frontal cortex, apoptosis	[10–12]
Cats (*F. catus*)	FIV[b]	↑ Wounding	No infection of neurons, CNS inflammation, infection of glial cells and macrophages in midbrain and thalamus	[13,14]
Several mammalian species	Rabies virus	↑ Aggression	Infection of neurons in limbic cortical areas, ↓ 5-HT and opioid receptor binding, ↓ 5-HT release, ↓ GABA uptake in cortical neurons, apoptosis	[15–19]
Rats	Seoul virus	↑ Wounding, ↑ aggression, ↓ subordination	No infection of neurons	[20,21]
Mice	Tick-borne encephalitis virus	↑ Aggression, ↑ sexual interest	↑ Testosterone, infects CNS	[22]
Protozoa				
Mice	*E. vermiformis*	↓ Sexual interest	↑ Opioid activity	[23]
Western fence lizard (*Sceloporus occidentalis*)	*Plasmodium mexicanum*	↓ Aggression, ↓ social displays, ↓ dominance, ↓ territoriality	↓ Testosterone, ↑ corticosterone, ↓ glucose	[24–26]
Sage grouse (*Centrocercus urophasianus*)	*Plasmodium pediocetii*	↓ Lek attendance, ↓ mating behavior	NE	[27]
Great tit (*Parus major*)	*Plasmodium* spp.	↑ Paternal behavior	NE	[28]
Mice/rats	*T. gondii*	↑ Aggression, ↑ dominance, ↑ social exploration, ↓ defensive behavior	Infection of neurons, glial, and endothelial cells in limbic areas, frontal cortex, and basal ganglia, ↓ NE, ↑ DA and HVA concentrations in brain	[29–32] but see Ref. [33]
American kestrel (*Falco sparverius*)	*Trichinella pseudospiralis*	↓ Aggression, ↓ parental care	NE	[34,35]
Mice	*T. spiralis*	↓ Dominance, ↑ subordination, ↓ mating behavior, ↓ social investigation	No infection of CNS	[36–39]
Mice	*Trypanosoma cruzi*	↓ Social rank	CNS inflammation	[40,41]
Red-spotted newt (*Notophthalmus viridescens*)	*Trypanosoma diemyctyli*	↓ Reproduction	NE	[42]
Pied flycatcher (*Ficedula hypoleuca*)	*Trypanosoma* spp.	↑ Late arrival date to breeding sites, ↓ mating opportunities	NE	[43]
Sedge warbler (*Acrocephalus schoenobaenus*)	Protozoan spp. (*Haemoproteus* spp., *Plasmodium* spp., and *Trypanosoma* spp.)	↓ Song repertoire, ↓ paternal behavior	NE	[44]
Helminth				
Red jungle fowl (*Gallus gallus*)	*Ascaridia galli*	↓ Social rank, ↓ mating success	NE	[45,46]
European minnows (*Phoxinus phoxinus*)	*Diplostomum phoxini*	↑ Tubercles, ↑ competitive ability	Infects brain	[47]
White-tail deer (*Odocoileus virginianus*)	*Fascioloides magna*	↓ Body size, ↓ antler points, ↓ social rank	NE	[48]
Guppies (*Poecilia reticulata*)	*Gyrodactylus turnbulli*	↓ Courtship behavior	NE	[49]

Table 1 (*continued*)

Host	Pathogen	Behavioral effects	Proximate mechanisms[a]	References
Helminth				
Mice	*Heligmosomoides polygyrus*	↓ Aggression, ↑ subordination, ↓ conspecific odor discrimination	↓ Opioid-mediated analgesia	[50,51]
Rats	*H. diminuta*	↓ Latency to retrieve pups	NE	[52]
Sticklebacks (*Gasterosteus aculeatus*)	*Pomphorhynchus laevis*	↓ Paternal behavior	NE	[53]
Spadefoot toad (*Scaphiopus couchii*)	*Pseudodiplorchis americanus*	↓ Mate preference	NE	[54]
Sticklebacks	*Schistocephalus solidus*	↓ Competitive ability	NE	[55]
Mice	*S. mansoni*	↓ Mating behavior	↑ β-endorphin, ↓ testosterone, ↓ estradiol	[56,57]
Mice (males only)	*T. crassiceps*	↓ Mating behavior	↑ Estradiol, ↓ testosterone	[58,59]
Rats	*T. taeniaeformis*	↓ Mating behavior, ↓ fertility	↓ Testosterone	[60]
Upland bullies (*Gobiomorphus breviceps*)	*Telogaaster opisthorchis*	↓ Mate preference	NE	[61]
Mice	*T. canis*	↓ Aggression, ↑ defensive behaviors, ↓ social investigation	↑ Larvae in brain	[62,63]
Arthropods				
Sleepy lizard (*T. rugosa*)	*A. limbatum* and *A. hydrosauri*	↑ Mating success, ↑ likelihood to form monogamous pairs	NE	[64]
Great tit	*Ceratophyllus gallinae*	↑ Nestling begging, ↑ nestling competition, ↑ paternal behavior	NE	[65]
House sparrows (*Hirundo rustica*)	*Ornithonyssus bursa*	↓ Song and mating success	↑ Anemia	[66]

Social behaviors include only behaviors exhibited by infected individuals toward conspecifics; therefore, predator–prey relations are not included.
NE = not examined; 5-HIAA = hydroxyindoleacetic acid.

[a] Proximate mechanisms include only chemical and neuroanatomical mechanisms.

[b] For immunodeficiency viruses, there is a correlation between aggression and likelihood of being infected. Whether this association is caused by parasite-mediated changes in behavior has not been determined.

social behaviors facilitate interactions between conspecifics, these behaviors can increase the transmission of parasites from infected to susceptible individuals. The primary goal of this review is to illustrate that pathogen-mediated changes in social behavior are caused by pathogens altering the neuroanatomy and chemistry that underlie the expression of social behaviors in vertebrates. To better understand the relationship between infection and host social behavior, both the proximate mechanisms and the adaptive function of these relationships will be considered.

2. Parasite-mediated changes in social behavior: manipulation or side effect?

During host–parasite coevolution, host populations have evolved adaptations to evade infection and pathogens have evolved counteradaptations to overcome host defense mechanisms. In many cases, these counteradaptations involve direct manipulation of host behavior to increase contact between infected and susceptible individuals [67,68]. There are several examples of changes in host social behavior following infection that are mediated by pathogens (see Table 1). If pathogens are transmitted through social contact, then natural selection should favor those that affect the physiological mechanisms mediating the expression of social behaviors. Presumably, pathogen-mediated changes in social behavior serve to increase transmission and hence reproduction of the pathogen [67–69].

The outcome of pathogen-mediated changes in behavior may depend on the life cycle of the pathogen. If a pathogen has a direct life cycle (i.e., there is no intermediate host, only a definitive host population), then survival and reproduction may be increased through social contact among conspecifics. Viruses that have direct life cycles, such as Borna disease virus (BDV), rabies virus, and hantaviruses, typically cause increased aggression and physical contact in host populations (see Table 1) [5–21]. Conversely, if a pathogen has an indirect life cycle (i.e., undergoes development in one host population and moves to another host population to complete the life cycle), then survival and reproduction may be increased primarily through predation [68,70]. To increase the probability of predation, pathogens can affect social behaviors in the intermediate host. For example, rodents infected with *Toxoplasma gondii* exhibit increased exploratory behavior and aggression, which may make them more conspicuous to and less fearful of the definitive host, the cat (*Felis catus*) [29,32,33]. Other pathogens, such as *Eimeria vermiformis* and *Trichinella spiralis*, can have either direct or indirect life cycles and can reduce social interactions among conspecifics [23,36–39]. Because social grouping is an effective defense against

predation, reduced social interactions also may increase the risk of predation [71].

Pathogens often alter physiology and behavior without causing mortality in host populations. Whether pathogens induce mortality in their hosts can depend on the life cycle of the pathogen [68]. In most cases, however, if infection causes mortality in the host (i.e., the pathogen is highly virulent), then survival and reproduction is hindered for the pathogen as well as for the host [69]. Anderson and May [69] present a model of host–parasite coevolution that illustrates that parasite virulence, parasite transmissibility, and host survival following infection must be balanced for successful parasite reproduction to ensue. Whereas highly virulent pathogens can kill a host, less virulent pathogens have low transmissibility because host immune responses suppress parasite replication. Natural selection should favor parasites that evolve to have intermediate levels of virulence.

For example, myxoma virus was introduced in Australia in the 1950s to control rabbit populations and the initial strain of virus was highly virulent, killed many rabbits, and ultimately reduced transmissibility of the virus [69]. Over the years, less virulent strains of myxoma virus coevolved with increased resistance against infection in the rabbits [72]. When viral strains were subdivided based on virulence, reproduction rates were highest for strains of myxoma virus that produced intermediate levels of virulence (i.e., the virus was virulent enough to evade host immune responses and to be transmitted to new hosts but not so virulent that it killed the host before transmission could occur) [72]. Intermediate levels of virulence evolved because host resistance is a selection pressure for increased virulence in the pathogen [69]. Thus, the effects of parasites on host populations may result in more subtle changes in host physiology and behavior that increase the probability of social contact and parasite transmission.

Additional studies illustrate that the virulence of a pathogen can depend on the behavioral route of transmission. For example, among cats, feline leukemia virus (FeLV) is more virulent than feline immunodeficiency virus (FIV) [13]. FeLV is transmitted in both saliva and blood and transmission can occur through many social behaviors including sexual contact, biting, grooming, and food sharing [73]. In contrast, FIV is transmitted in saliva through bite wounds. Consequently, although similar rates of FeLV infection are reported for male and female cats, male cats are more likely to be infected with FIV than females [13]. Thus, the relationship among virulence, transmission, and host behavior can be pathogen specific and can determine who, within a population, is most likely to be infected with a pathogen.

Not all behavioral modifications following infection are mediated by pathogens [67]. If the behavioral changes following infection are beneficial to the survival and reproduction of the host, then the behavioral modifications may be host mediated as opposed to pathogen mediated. Infected animals often exhibit a repertoire of adaptive behavioral responses that aid in recovery and survival following infection. These behaviors have been collectively termed "sickness behaviors" and include reduced interest in social, parental, and sexual interactions [71]. Sickness behaviors may appear maladaptive because they limit social contact and can potentially reduce opportunities for reproductive success. Animals that can successfully overcome infection by engaging in sickness behaviors, however, may achieve higher lifetime reproductive success than individuals that do not engage in these restorative behaviors. Natural selection should favor individuals that engage in these recuperative behaviors.

Other host-mediated social behavioral responses to infection involve the use of parasite infection to avoid contact with infected individuals. Behavioral responses of susceptible (i.e., uninfected) individuals toward infected individuals and subsequent effects on mate selection have received considerable attention [70,74–78]. Also, whether certain individuals within a population are physiologically predisposed to engage in social behaviors like aggression that increase exposure or even susceptibility to a pathogen has been considered elsewhere (reviewed in Refs. [79,80]).

Hypotheses regarding pathogen- and host-mediated changes in behavior imply that behavioral changes are adaptive for the survival and reproduction of the pathogen or host, respectively. Alternatively, because infection causes pathology in the host, behavioral changes following infection may be a side effect of the pathology associated with infection and have no adaptive function [63,67,68]. If the pathological state of the host increases the reproductive success of the parasite, host, or both, then it will not be selected against [67–69].

Taken together, these data illustrate alternative hypotheses for why host behavior changes after infection. The life cycle of the pathogen, pathogen virulence, transmissibility, and host immunity interact to influence the effects that pathogens have on host behavior. Whether behavioral changes following infection are adaptive to the host, the parasite, or both or are a side effect of infection depends on the host–parasite system. Several studies, however, demonstrate that parasites can cause pronounced changes in host social behavior to increase transmission. As illustrated in Table 1, pathogens alter host behavior via effects on the CNS and neurochemical systems.

3. Proximate mechanisms of parasite-mediated changes in social behavior

The mechanisms that pathogens use to alter the behavior of vertebrate hosts vary. Several pathogens, including viruses, such as BDV and rabies, and macroparasites, such as *T. gondii* and *Toxocara canis*, can infect neurons in the CNS to cause changes in the brain regions that mediate the expression of social behaviors [5,29,63,68,81,82]. In addi-

tion to infecting cells within the CNS, pathogens can alter the social behavior of vertebrate hosts by inducing immune responses and inflammation of the CNS and altering neurochemical communication (reviewed in Ref. [81]).

Among mammals, rabies virus infects and kills neurons in brain regions (e.g., hippocampus, hypothalamus, and amygdala) that modulate host behaviors, including aggression, and causes reductions in 5-HT and GABA neurotransmission [15–19]. Decreased 5-HT neural communication has been linked to elevated aggression in rodents [83]. Presumably, by exploiting the 5-HT system and causing increased levels of aggression, salivary transmission of rabies between infected animals and other individuals within a population may be increased [81,82,84]. BDV infects neurons in limbic and cortical areas of the brain, including the hippocampus, hypothalamus, olfactory bulb, septum, amygdala, thalamus, basal ganglia, and frontal cortex [5]. Also, dopaminergic neurons in the ventral tegmental area (VTA) and DA receptors in the NAcc are reduced by BDV infection [7]. Infection of neurons within the limbic system and changes in the DA pathway may explain the increased aggressive and sexual behaviors that are characteristic of animals infected with BDV [5–8].

Macroparasites, such as *T. gondii*, infect neurons, glial cells, and endothelial cells throughout the CNS [30]. *T. gondii* also alters several neurochemical pathways in the brain. Concentrations of NE are reduced whereas concentrations of DA and its metabolite, homovanillic acid (HVA), are increased in infected mice [31]. These neurochemical changes as well as the formation of cysts in the brain may underlie the elevated aggressive and exploratory behaviors reported in rodents infected with *T. gondii* [29–33].

Macroparasites can alter the social behavior of vertebrate hosts by altering neurochemical communication (reviewed in Ref. [81]). Neurochemical changes associated with infection appear to underlie reduced pain sensitivity following infection [70]. Rodents infected with the protozoan parasite *E. vermiformis*, the nematode *Nippostrongylus brasiliensis*, or the trematode *Schistosoma mansoni* exhibit increased opioid-mediated analgesic responses (i.e., reduced sensitivity to pain) (reviewed in Ref. [70]). During the early phase of *E. vermiformis* infection, infection of males increases analgesia and reduces preference for odors from estrous females [23]. Conversely, during the infective phase of infection, analgesia is reduced and responsiveness to estrous odors is increased in male mice [23]. Male responsiveness to the odors of estrous females can be reversed by administration of opioid receptor antagonists, suggesting that endogenous opioids mediate the effects of infection on responses to sexual cues [23]. Changes in opioid-mediated analgesia are hypothesized to increase social interactions between infected and uninfected conspecifics [70].

Viruses also can alter behavior through mechanisms other than infection of neurons. For example, although infection of primates, including mandrills (*Mandrillus sphinx*) and rhesus macaques (*Macaca mulatto*), with simian immunodeficiency virus (SIV) and cats with FIV does not cause neuronal infection, behavioral modifications, including changes in cognition and aggression, are observed [11,13,81]. Viral infection causes inflammation (i.e., induction of cytokine and chemokine responses), apoptosis of microglia, and changes in neurotransmitter (e.g., somatostatin) synthesis in the brain that are associated with virus-induced pathology [10,12,14]. Although behavioral changes following infection may be a pathological side effect of infection, because virus transmission is enhanced by increased aggression, the effects of infection on behavior still benefit the reproduction of the parasite.

In common with rabies, SIV, and FIV, hantaviruses are directly transmitted and are hypothesized to be propagated through bite wounds [20,85–87]. Intraspecific transmission of hantaviruses appears to occur through contact with saliva during aggressive encounters [20]. In natural populations of Norway rats (*Rattus norvegicus*), adult males are more likely to have severe wounds and be infected with hantaviruses than either females or juvenile males [20]. Male rats with more severe wounds also are more likely to shed virus in saliva than males with less severe wounds (E.R. Hinson et al., unpublished data). Whether engaging in aggressive behavior increases exposure to hantaviruses (i.e., host-mediated hypothesis) or whether infection increases the propensity to engage in aggression (i.e., parasite-mediated hypothesis) remains unclear.

Laboratory studies of male Norway rats infected with Seoul virus (i.e., the naturally occurring hantavirus of Norway rats) reveal that during the persistent phase of infection (i.e., 30 days after inoculation with Seoul virus) males spend more time engaged in aggression, during resident–intruder tests, than either uninfected males or males tested during the acute phase of infection (i.e., 15 days after inoculation) (Fig. 1) [21]. Males that engage in aggression for a longer duration of time have more virus present in lung, kidney, and testis than males that engage in less aggression [21]. Virus is not present in the brains of infected males. Thus, the changes in host aggressive behavior may be a by-product of elevated virus replication in peripheral target tissues. The effects of hantaviruses on neurotransmitters as well as on cytokines in the CNS require additional investigation.

Parasites can have pronounced effects on peripheral tissues that can in turn alter chemical signals sent from peripheral organs to the CNS. For example, the tapeworms *Taenia crassiceps* and *Taenia taeniaeformis* inhibit the expression of reproductive behavior in male mice through effects on testosterone, as opposed to through direct effects on the brain areas that mediate behavior. Female mice are more susceptible to infection with *T. crassiceps* and *T. taeniaeformis* than males because estradiol enhances parasite reproduction [58–60]. Infection of male rodents with *T. crassiceps* or *T. taeniaeformis* reduces both serum and testicular testosterone concentrations, increases estradiol concentrations, and inhibits mating behavior (Fig. 2) [58–

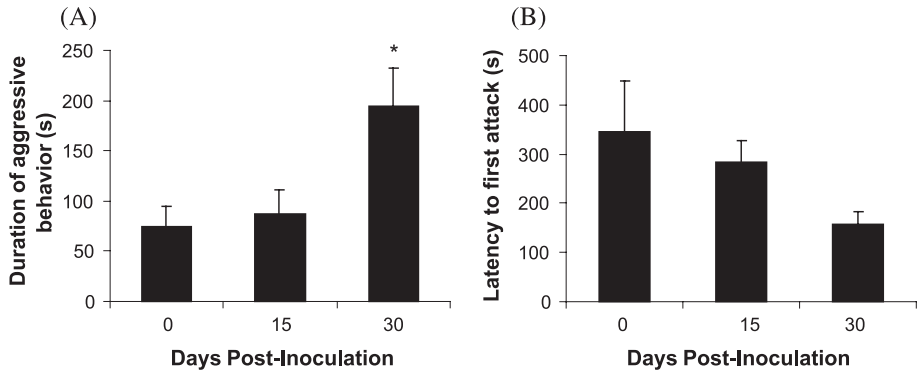

Fig. 1. Mean ± S.E.M. duration of aggressive behavior exhibited by resident male laboratory rats (A) and mean ± S.E.M. latency for the resident male to begin attacking the intruder male (B) during a 20 min resident–intruder aggression test. Resident males were tested for behavior 0, 15, or 30 days after inoculation with Seoul virus (i.e., the naturally occurring hantavirus in Norway rats). Male rats tested during the persistent phase of infection (i.e., 30 days after inoculation) spend more time engaged in aggression than uninfected males or males tested during the acute phase of infection (i.e., 15 days after inoculation). * $P < .05$ [21].

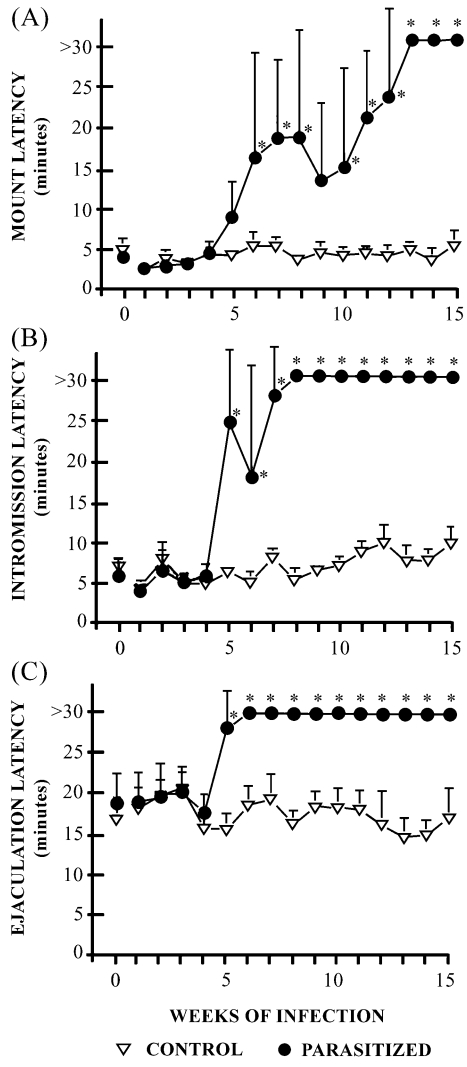

Fig. 2. Mean ± S.D. latency for male mice to begin mounting (A), intromitting (B), and ejaculating (C) with a stimulus female during a 30 min mating behavior test. Male mice were either uninfected (control) or infected with *T. crassiceps* (parasitized) 15 weeks prior to behavioral testing. Infected male mice take longer to mount, intromit, and ejaculate with the stimulus female than uninfected males. * $P < .05$ [59].

60]. Reduced mating behavior in infected male rodents can be restored to normal levels by exposure to exogenous testosterone, suggesting that suppressed testosterone, and not pathology caused by infection, underlies the reduced sexual behavior [59]. Because testosterone concentrations in testicular tissue are reduced, infection may alter Leydig cell production of testosterone, responsiveness of Leydig cells to gonadotropins, or feedback mechanisms within the hypothalamic–pituitary–gonadal axis. These parasites do not infect the CNS; therefore, the behavioral changes following infection are due to the effects of the parasites on peripheral tissues and hormones. Because tapeworm reproduction is enhanced in a female-typic hormonal milieu, the endocrinological and behavioral changes in male rodents following infection are beneficial for parasite reproduction [69].

Although much of MacLean's [1] research focuses on the role of the limbic system and cerebral cortex in parental behavior, the effects of parasites on the expression of parental behavior have been less well studied than the effects of parasites on aggressive and reproductive behaviors (see Table 1). To ascertain the effects of maternal infection on offspring, studies typically focus on congenital infection of the fetus and transmission of maternal immunity to offspring. Presumably, the effects of infection on maternal behavior may vary depending on whether there is horizontal (i.e., transmission from infected to susceptible individuals), vertical (i.e., transmission from mother to offspring), or both modes of transmission within a host–parasite system.

During tests of maternal behavior, female rats infected with the tapeworm *Hymenolepis diminuta* retrieve pups faster than uninfected females, suggesting that infection may increase parental investment in current offspring [52]. The effects of infection on parental behavior may vary depending on whether the host species exhibit biparental or uniparental care. Female prairie voles (*Microtus ochrogaster*) injected with lipopolysaccharide from *Escherichia coli* and male lizards (*Tiliqua rugosa*) infested with ticks (*Aponomma hydrosauri* and *Amblyomma limbatum*)

are more likely to form monogamous pairs than uninfected conspecifics, suggesting that infection may increase the need for biparental care [64,88]. The precise mechanisms mediating the effects of infection on parental behavior remain elusive but may involve neuropeptides, including vasopressin and oxytocin, that modulate the expression of parental behaviors in vertebrates [89].

4. Conclusions and future directions

Taken together, these data illustrate that social behaviors in vertebrates change following infection. The data presented in this review provide several examples of parasites exploiting the proximate mechanisms that mediate the expression of social behaviors to increase transmission. Pathogens can affect behavior not only by infecting cells (e.g., neurons, glial cells, and endothelial cells) within the CNS but also by causing apoptosis, inducing inflammation, and altering neurotransmitter and hormonal communications. The role of cellular apoptosis in behavioral changes following infection requires further investigation. Viruses, including rabies virus and BDV, can cause apoptosis of neurons, which may underlie the elevated aggressive and sexual behavior observed in animals infected with these viruses [17]. Whether infection-induced apoptosis is mediated by the pathogen or by the host to eliminate infected cells requires further investigation. The role of cytokines in mediating changes in social behaviors following infection has been most well studied with regard to sickness behaviors. Whether parasites exploit cytokine-mediated processes to alter behavior has not been reported. Although the proximate mechanisms that pathogens use to alter host behavior are well characterized in mammals, the effects of pathogens on the CNS and neurochemical systems in other vertebrate species require additional investigation. Presumably, the effects of parasites on social behavior are retained across several classes of vertebrates because parasites affect the phylogenetically primitive structures of the limbic system and related neurochemical systems.

Like parasites manipulating their hosts, neuroscientists have exploited the fact that parasites can infect and replicate in neurons. Neurotropic viruses, including rabies and herpes simplex viruses, have been used as transneuronal tract tracers to uncover the connections of several neuroanatomical pathways [90,91]. Utilization of these neurotropic viruses for answering questions about the proximate mechanisms mediating behavior may provide further insights into the biology of social behavior.

Future studies must continue to explore the adaptive function of host–parasite interactions. Although the examples provided (see Table 1) illustrate that parasites can induce changes in the expression of social behaviors to increase transmission, other behavioral modifications following infection may be mediated by the host or be a by-product of host–parasite relations. Consideration of the route of transmission, pathogen life cycle, and pathogen virulence will be important to fully understand why parasites manipulate social behaviors in host populations. Additionally, the behavioral outcome of infection may depend on several host factors including the sex, age, and immune status of the individual.

Finally, we often assume that if a parasite infects the CNS, then it is the infected brain areas that cause subsequent changes in behavior. Alternatively, changes in social behaviors following infection may be caused by neurochemical changes (as illustrated in Table 1) or by changes in the neural functioning of unaffected brain areas. Studies of parasite-mediated selection should utilize what MacLean and others have uncovered about the role of the CNS, particularly the limbic system and related structures, in social behavior and should use this information to formulate hypotheses about how parasites affect the expression of social behavior in vertebrates.

Acknowledgements

I thank Thaddeus Graczyk for useful comments on an earlier draft of this manuscript, Amy Cernetich for help with the table, and Lance Kriegsfeld for graphics assistance.

References

[1] MacLean PD. Brain evolution relating to family, play, and the separation call. Arch Gen Psychiatry 1985;42:405–17.
[2] Papez JW. A proposed mechanism of emotion. Arch Neurol Psychiatry 1937;38:725–43.
[3] Klüver H, Bucy PC. An analysis of certain effects of bilateral temporal lobectomy in the rhesus monkey, with special reference to "psychic blindness". J Psychol 1938;5:33–54.
[4] Nelson RJ. An introduction to behavioral endocrinology. Massachusetts: Sinauer; 2000.
[5] Solbrig MV, Fallon JH, Lipkin WI. Behavioral disturbances and pharmacology of Borna disease. Curr Top Microbiol Immunol 1995; 190:93–101.
[6] Solbrig MV, Koob GF, Fallon JH, Reid S, Lipkin WI. Prefrontal cortex dysfunction in Borna disease virus (BDV)-infected rats. Biol Psychiatry 1996;40:629–36.
[7] Solbrig MV, Koob GF, Joyce JN, Lipkin WI. A neural substrate of hyperactivity in Borna disease: changes in brain dopamine receptors. Virology 1996;222:332–8.
[8] Sprankel H, Richarz K, Ludwig H, Rott R. Behavior alterations in tree shrews (*Tupaia glis*, Diard, 1820) induced by Borna disease virus. Med Microbiol Immunol 1978;165:1–18.
[9] Lycke E, Roos BE. Influence of changes in brain monoamine metabolism on behaviour of herpes-simplex-infected mice. J Neurol Sci 1974;22:277–89.
[10] Da Cunha A, Rausch DM, Eiden LE. An early increase in somatostatin mRNA expression in the frontal cortex of rhesus monkeys infected with simian immunodeficiency virus. Proc Natl Acad Sci USA 1995;92:1371–5.
[11] Nerrientet E, Amouretti X, Müller-Trutwin MC, Poaty-Mavoungou V, Bedjebaga I, Nguyen HT, et al. Phylogenetic analysis of SIV and STLV type I in mandrills (*Mandrillus sphinx*): indications that intra-

colony transmissions are predominantly the result of male-to-male aggressive contacts. AIDS Res Hum Retrovir 1998;14:785–96.
[12] Sopper S, Koutsilieri E, Scheller C, Czub S, Riederer P, ter Meulen V. Macaque animal model for HIV-induced neurological disease. J Neural Transm 2002;109:747–66.
[13] Fromont E, Courchamp F, Artois M, Pontier D. Infection strategies of retroviruses and social grouping in domestic cats. Can J Zool 1997; 75:1994–2002.
[14] Gardner MB, Dandekar S. Neurobiology of simian and feline immunodeficiency virus infections. Curr Top Microbiol Immunol 1995; 202:135–50.
[15] Bouzamondo E, Ladogana A, Tsiang H. Alteration of potassium-evoked 5-HT release from virus-infected rat cortical synaptosomes. NeuroReport 1993;4:555–8.
[16] Ceccaldi P-E, Fillion M-P, Ermine A, Tsiang H, Fillion G. Rabies virus selectively alters 5-HT1 receptor subtypes in rat brain. Eur J Pharmacol 1993;245:129–38.
[17] Dietzschold B, Morimoto K, Hooper DC. Mechanisms of virus-induced neuronal damage and the clearance of viruses from the CNS. Curr Top Microbiol Immunol 2001;253:145–55.
[18] Koschel K, Münzel P. Inhibition of opiate receptor-mediated signal transmission by rabies virus in persistently infected NG-108-15 mouse neuroblastoma-rat glioma hybrid cells. Proc Natl Acad Sci USA 1984;81:950–4.
[19] Ladogana A, Bouzamondo E, Pocchiari M, Tsiang H. Modification of tritiated γ-amino-*n*-butyric acid transport in rabies virus-infected primary cortical cultures. J Gen Virol 1994;75:623–7.
[20] Glass GE, Childs JE, Korch GW, LeDuc JW. Association of intraspecific wounding with hantaviral infection in wild rats (*Rattus norvegicus*). Epidemiol Infect 1988;101:459–72.
[21] Klein SL, Zink MC, Glass GE. Seoul virus infection increases aggressive behaviour in male Norway rats. Anim Behav (in press).
[22] Moshkin M, Gerlinskaya L, Morozova O, Bakhvalova V, Evsikov V. Behaviour, chemosignals and endocrine functions in male mice infected with tick-borne encephalitis virus. Psychoneuroendocrinology 2002;27:603–8.
[23] Kavaliers M, Colwell DD, Ossenkopp KP, Perrot-Sinal TS. Altered responses to female odors in parasitized male mice: neuromodulatory mechanisms and relations to female choice. Behav Ecol Sociobiol 1997;40:373–84.
[24] Dunlap KD, Schall JJ. Hormonal alterations and reproductive inhibition in male fence lizards (*Sceloporus occidentalis*) infected with the malarial parasite *Plasmodium mexicanum*. Physiol Zool 1995;68: 608–21.
[25] Schall JJ, Dearing MD. Malarial parasitism and male competition for mates in the western fence lizard, *Sceloporus occidentalis*. Oecologia 1987;73:389–92.
[26] Schall JJ, Houle PR. Malarial parasitism and home range and social status of male western fence lizards, *Sceloporus occidentalis*. J Herpetol 1992;26:74–6.
[27] Johnson LL, Boyce MS. Female choice of males with low parasite loads in sage grouse. In: Loye JE, Zuk M, editors. Bird–parasite interactions. Oxford: Oxford Univ. Press; 1991. p. 377–88.
[28] Richner H, Christe P, Oppliger A. Paternal investment affects prevalence of malaria. Proc Natl Acad Sci USA 1995;92:1192–4.
[29] Arnott MA, Cassella JP, Aitken PP, Hay J. Social interactions of mice with congenital *Toxoplasma* infection. Ann Trop Med Parasitol 1990;84:149–56.
[30] Kristensson K, Mhlanga JDM, Bentivoglio M. Parasites and the brain: neuroinvasion, immunopathogenesis and neuronal dysfunction. Curr Top Microbiol Immunol 2002;265:227–57.
[31] Stibbs HH. Changes in brain concentrations of catecholamines and indoleamines in *Toxoplasma gondii* infected mice. Ann Trop Med Parasitol 1985;79:153–7.
[32] Webster JP, Brunton CFA, MacDonald DW. Effect of *Toxoplasma gondii* upon neophobic behaviour in wild brown rats, *Rattus norvegicus*. Parasitology 1994;109:37–43.
[33] Berdoy M, Webster JP, MacDonald DW. The manipulation of rat behaviour by *Toxoplasma gondii*. Mammalia 1995;59:605–13.
[34] Henderson D, Bird DM, Rau ME, Negro JJ. Mate choice in captive American kestrels, *Falco sparverius* parasitized by a nematode, *Trichinella pseudospiralis*. Ethology 1995;101:112–20.
[35] Saumier MD, Rau ME, Bird DM. The effect of *Trichinella pseudospiralis* infection on the reproductive success of captive American kestrels (*Falco sparverius*). Can J Zool 1986;64:2123–5.
[36] Edwards JC. The effects of *Trichinella spiralis* infection on social interactions in mixed groups of infected and uninfected male mice. Anim Behav 1988;36:529–40.
[37] Edwards JC, Barnard CJ. The effects of *Trichinella* infection on intersexual interactions between mice. Anim Behav 1987;35:533–40.
[38] Rau ME. Establishment and maintenance of behavioural dominance in male mice infected with *Trichinella spiralis*. Parasitology 1983;86: 319–22.
[39] Rau ME. Loss of behavioural dominance in male mice infected with *Trichinella spiralis*. Parasitology 1984;88:371–3.
[40] Eymard J, Pittella H. Central nervous system involvement in experimental *Trypanosoma cruzi*. Mem Inst Oswaldo Cruz 1991;86: 141–5.
[41] Schuster JP, Schaub GA. Experimental Chagas disease: the influence of sex and psychoneuroimmunological factors. Parasitol Res 2001;87: 994–1000.
[42] Gill DE, Mock BA. Ecological and evolutionary dynamics of parasites: the case of *Trypanosoma diemyctyli* in the red-spotted newt *Notophthalmus viridescens*. In: Rollinson D, Anderson RM, editors. Ecology and genetics of host–parasite interactions. London: Academic Press; 1985. p. 157–83.
[43] Rätti O, Dufva R, Alatalo RV. Blood parasites and male fitness in the pied flycatcher. Oecologia 1993;96:410–4.
[44] Buchanan KL, Catchpole CK, Lewis JW, Lodge A. Song as an indicator of parasitism in the sedge warbler. Anim Behav 1999;57: 307–14.
[45] Zuk M, Thornhill R, Ligon JD, Johnson K. Parasites and mate choice in red jungle fowl. Am Zool 1990;30:235–44.
[46] Zuk M, Kim T, Robinson SI, Johnsen TS. Parasites influence social rank and morphology, but not mate choice, in female red jungle fowl, *Gallus gallus*. Anim Behav 1998;56:493–9.
[47] Müller G, Ward PI. Parasitism and heterozygosity influence the secondary sexual characters of the European minnow, *Phoxinus phoxinus* (L.) (Cyprinidae). Ethology 1995;100:309–19.
[48] Mulvey M, Aho JM. Parasitism and mate competition: liver flukes in white-tailed deer. Oikos 1993;66:187–92.
[49] Kennedy CEJ, Endler JA, Poynton SL, McMinn H. Parasite load predicts mate choice in guppies. Behav Ecol Sociobiol 1987;21: 291–5.
[50] Freeland WJ. Parasitism and behavioral dominance among male mice. Science 1981;213:461–2.
[51] Kavaliers M, Colwell DD, Choleris E. Analgesic responses of male mice exposed to the odors of parasitized females: effects of male sexual experience and infection status. Behav Neurosci 1998;112: 1001–11.
[52] Willis C, Poulin R. Effects of the tapeworm *Hymenolepis diminuta* on maternal investment in rats. Can J Zool 1999;77:1001–5.
[53] Bakker TCM, Mundwiler B. Pectoral fin size in a fish species with paternal care: a condition-dependent sexual trait revealing infection status. Freshw Biol 1999;41:543–51.
[54] Pfennig KS, Tinsley RC. Different mate preferences by parasitized and unparasitized females potentially reduces sexual selection. J Evol Biol 2002;15:399–406.
[55] Barber I, Ruxton GD. Temporal prey distribution affects competitive ability of parasitized sticklebacks. Anim Behav 1998;56:1477–83.
[56] Isseroff H, Sylvester PW, Held WA. Effects of *Schistosoma mansoni* on androgen regulated gene expression in the mouse. Mol Biochem Parasitol 1986;18:401–12.
[57] Isseroff H, Sylvester PW, Bessette CL, Jones PL, Fisher WG,

Rynkowski TA, et al. Schistosomiasis: role of endogenous opioids in suppression of gonadal steroid secretion. Comp Biochem Physiol 1989;94:41–5.
[58] Larralde C, Morales J, Terrazas I, Govezensky T, Romano MC. Sex hormone changes induced by the parasite lead to feminization of the male host in murine *Taenia crassiceps* cysticercosis. J Steroid Biochem Mol Biol 1995;52:575–80.
[59] Morales J, Larralde C, Arteaga M, Govezensky T, Romano MC, Morali G. Inhibition of sexual behavior in male mice infected with *Taenia crassiceps* cysticerci. J Parasitol 1996;82:689–93.
[60] Lin YC, Rikihisa Y, Kono H, Gu Y. Effects of larval tapeworm (*Taenia taeniaeformis*) infection on reproductive functions in male and female host rats. Exp Parasitol 1990;70:344–52.
[61] Poulin R. Mate choice decisions by parasitized female upland bullies, *Gobiomorphus breviceps*. Proc R Soc Lond B 1994;256:183–7.
[62] Cox DM, Holland CV. The relationship between numbers of larvae recovered from the brain of *Toxocara canis*-infected mice and social behaviour and anxiety in the host. Parasitology 1998;116:579–94.
[63] Holland CV, Cox DM. *Toxocara* in the mouse: a model for parasite-altered host behaviour? J Helminthol 2001;75:125–35.
[64] Bull CM, Burzacott D. The impact of tick load on the fitness of their lizard host. Oecologia 1993;96:415–9.
[65] Christe P, Richner H, Oppliger A. Begging, food provisioning, and nestling competition in great tit broods infested with ectoparasites. Behav Ecol 1996;7:127–31.
[66] Møller AP. Parasite load reduces song output in a passerine bird. Anim Behav 1991;41:723–30.
[67] Combes C. Parasitism: the ecology and evolution of intimate interactions. Chicago: University of Chicago Press; 2001.
[68] Moore J. Parasites and the behavior of animals. Oxford: Oxford Univ. Press; 2002.
[69] Anderson RM, May RM. Coevolution of hosts and parasites. Parasitology 1982;85:411–26.
[70] Kavaliers M, Colwell DD, Choleris E. Parasites and behaviour: an ethopharmacological perspective. Parasitol Today 2000;16:464–8.
[71] Hart BL. Effects of hormones on behavioral defenses against parasites. In: Beckage NE, editor. Parasites and pathogens: effects on host hormones and behavior. New York: Chapman & Hall; 1997. p. 210–30.
[72] Fenner F, Ratcliffe FN. Myxomatosis. Cambridge: Cambridge Univ. Press; 1965.
[73] Francis DP, Essex M, Hardy WD. Excretion of feline leukaemia virus by naturally infected pet cats. Nature 1977;269:252–4.
[74] Able DJ. The contagion indicator hypothesis for parasite-mediated sexual selection. Proc Natl Acad Sci 1996;93:2229–33.
[75] Hamilton WD, Zuk M. Heritable true fitness and bright birds: a role for parasites? Science 1982;218:384–7.
[76] Klein SL. Hormones and mating system affect sex and species differences in immune function among vertebrates. Behav Processes 2000;51:149–66.
[77] Penn D, Potts WK. Chemical signals and parasite-mediated sexual selection. Trends Ecol Evol 1998;13:391–6.
[78] Zuk M. Reproductive strategies and disease susceptibility: an evolutionary viewpoint. Parasitol Today 1990;6:231–3.
[79] Barnard CJ, Behnke JM. From psychoneuroimmunology to ecological immunology: life history strategies and immunity trade-offs. In: Ader R, Felten DL, Cohen N, editors. 3rd ed. Psychoneuroimmunology, vol. 2. California: Academic Press; 2001. p. 35–47.
[80] Klein SL. The effects of hormones on sex differences in infection: from genes to behavior. Neurosci Biobehav Rev 2000;24:627–38.
[81] Hatalski CG, Lipkin WI. Behavioral abnormalities and disease caused by viral infections of the central nervous system. In: Beckage NE, editor. Parasites and pathogens: effects on host hormones and behavior. New York: Chapman & Hall; 1997. p. 201–9.
[82] Johnson RT. The pathogenesis of experimental rabies. In: Nagano Y, Davenport FM, editors. Rabies. Maryland: University Park Press; 1970. p. 59–75.
[83] Nelson RJ, Chiavegatto S. Molecular basis of aggression. Trends Neurosci 2001;24:713–9.
[84] Jackson AC, Reimer DL. Pathogenesis of experimental rabies in mice: an immunohistochemical study. Acta Neuropathol 1989;78:159–65.
[85] Hjelle B, Yates T. Modeling hantavirus maintenance and transmission in rodent communities. Curr Top Microbiol Immunol 2001;256:47–75.
[86] Lee PW, Yanagihara R, Gibbs CJ, Gajdusek DC. Pathogenesis of experimental Hantaan virus infection in laboratory rats. Arch Virol 1986;88:57–66.
[87] Nuzum EO, Rossi CA, Stephenson EH, LeDuc JW. Aerosol transmission of Hantaan and related viruses to laboratory rats. Am J Trop Med Hyg 1988;38:636–40.
[88] Bilbo SD, Klein SL, DeVries AC, Nelson RJ. Lipopolysaccharide facilitates partner preference behavior in female prairie voles. Physiol Behav 1999;68:151–6.
[89] Young LJ, Insel TR. Hormones and parental behavior. In: Becker JB, Breedlove M, Crews D, McCarthy MM, editors. Behavioral endocrinology. Massachusetts: MIT Press; 2002. p. 331–69.
[90] Norgren RB, Lehman MN. Herpes simplex virus as a transneuronal tracer. Neurosci Biobehav Rev 1998;22:695–708.
[91] Bartness TJ, Song CK, Demas GE. CNS efferents to peripheral tissues: implications for biological rhythms. J Biol Rhythms 2001;16:196–204.