

THE STEROID HORMONE OF SUNLIGHT SOLTRIOI (VITAMIN D) AS A SEASONAL REGULATOR OF BIOLOGICAL ACTIVITIES AND PHOTOPERIODIC RHYTHMS

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Summary—Neural and systemic somatotrophic effects of the ultraviolet component of sunlight through the skin–vitamin D endocrine system are considered as alternate or additional to the neuroendocrine effects of the visual component of light through the retino–diencephalic input. The extensive distribution of soltrioi nuclear receptor cells, revealed by autoradiography with tritium-labeled 1,25 dihydroxycholecalciferol (vitamin D, soltrioi) and related effects, indicate an involvement of vitamin D–soltrioi in the actinic induction of seasonal biorhythms. This is considered to be independent of the traditionally assigned effects of vitamin D on systemic calcium regulation. Skin–soltrioi mediated seasonal, and to a degree daily, genomic activation involves many target regions in the brain. These include neurons in the central nucleus of the amygdala, in the linked part of the bed nucleus of the stria terminalis, in periventricular hypothalamic neurons, dorsal raphe nucleus, reticular thalamic nucleus and autonomic, endocrine as well as sensory and motor components of the brainstem and spinal cord. Additional to the eye-regulated “suprachiasmatic clock”, existence of a soltrioi–vitamin D regulated neural “timing circuit(s)” is proposed. Both, activational and organizational effects of soltrioi on mature and developing brain regions, respectively are likely to play a role in the regulation of neuronal functions that include the modulation and entrainment of biorhythms. Soltrioi’s central effects correlate with peripheral effects on elements in skin, bone, teeth, kidney, intestine, heart and blood vessels, endocrine organs, and tissues of the immune and reproductive system.

The physical environment of the biosphere is characterized by several major periodicities that derive from the movement of the moon around the earth and the earth around the sun. The ability to contend with a changing environment is requisite for survival. Since the beginning of this planet, life has evolved to cope with and exploit to its advantage pronounced daily and annual cycles of light and temperature. The celestial based predictability of these cycles has presented an opportunity for natural selection

toward seasonally appropriate responses to upcoming opportunities or challenges which has resulted in innate temporal programs transcending both plant and animal kingdoms. The influence of the change in seasons affects all species and is evident by changes in behavior and underlying fluctuations in various physiological, in particular hormonal systems. Thus, the continuity of life and the evolution of species is inextricably bound in various capacities to daily, lunar and annual cycles of solar generated radiation.

Natural selection dictates that the individuals best able to exploit to their advantage the environment will thrive and propagate their gene pool. Accepting parsimony in nature, what then is the utility of a steroid hormone derived from sublight, and why is it derived from the ultraviolet and not from another component of the spectrum? A role for vitamin D (1,25 dihydroxycholecalciferol, soltrioi†) as a transducer of the seasonal environment is proposed based on newly discovered actions and concepts developed for this steroid hormone of sunlight [1, 2].

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†The term “vitamin D” is a misnomer. 1,25(OH)₂ Vitamin D₃ is not a vitamin but a steroid hormone and should be designated as such. Therefore, the term “soltrioi” has been introduced for the steroid hormone of sunlight [1] in analogy to “estradiol” and “cortisol”. Actions of “vitamin D” are not restricted to the regulation of calcium homeostasis, which is but one of the many actions of this hormone. Therefore, the term “calcitriol” would be too narrow and would not designate or signal the main action of this seasonal activator and regulator of growth, maintenance and procreation of life.

For life to adapt and survive in the biosphere, three properties of solar radiation must be considered: wavelength, irradiance, and time variation. Concerning wavelength, the u.v. and visible components of the solar spectrum are conveniently divided into the u.v.B (280–320 nm), u.v.A (320–400 nm), and the visible wavelengths (400–750 nm). Due to physical properties of the ozone layer, specific wavelengths of u.v.B are affected to a greater degree than other spectral components. The most important factor affecting u.v.B spectral irradiance is the incident angle of the sunlight to the earth, also known as the solar angle. The solar angle is a function of the annual cycle of the axis of the earth relative to its revolutionary orbit about the sun. The results of the annual changes are played out on earth in the form of seasons. u.v.B shows an effective cutoff at the earth's surface at about 295 nm [3], due to the absorption of the shorter wavelengths by the ozone layer. u.v.B is also more sensitive to the solar angle because of the greater pathlength required of the direct beam associated with lower sun angles.

When seasonal changes in irradiance are compared by determining the ratios of irradiance between the winter and summer solstice at a corresponding wavelength between 280 and 800 nm, it is realized that the ratios in the visible range and in the u.v.A range remain fairly

constant throughout the year, and indicate little dependence on latitude [4]. In other words, although total irradiance at a particular wavelength increases 100% or more between seasons in the visible and u.v.B. ranges, a relative change between the visible and u.v.A wavelengths from the winter to summer solstice is not apparent. However, the ratio of the visible to the u.v.B wavelengths displays dramatic, but highly predictable seasonal fluctuations (Fig. 1).

LIGHT EFFECTS THROUGH RETINA-DERIVED NEURAL CONNECTIONS TO THE DIENCEPHALON

Circadian periods, and to a degree probably also monthly and seasonal cycles, are now understood to be under the control of the suprachiasmatic nucleus, with or without involvement of the pineal hormone melatonin [6]. The pivotal role of the suprachiasmatic nucleus is supported by accumulated diverse evidence, such as the projection of retinofugal fibers to this nucleus [7], the presence of rhythmic electrical activity [8] and elimination of rhythmicity by ablation or surgical isolation of this nucleus [9–11], and restoration of rhythmicity from suprachiasmatic transplants to the lesioned region [12].

While the significance of the suprachiasmatic region as a pacemaker for circadian period appears to be established, considerable evidence

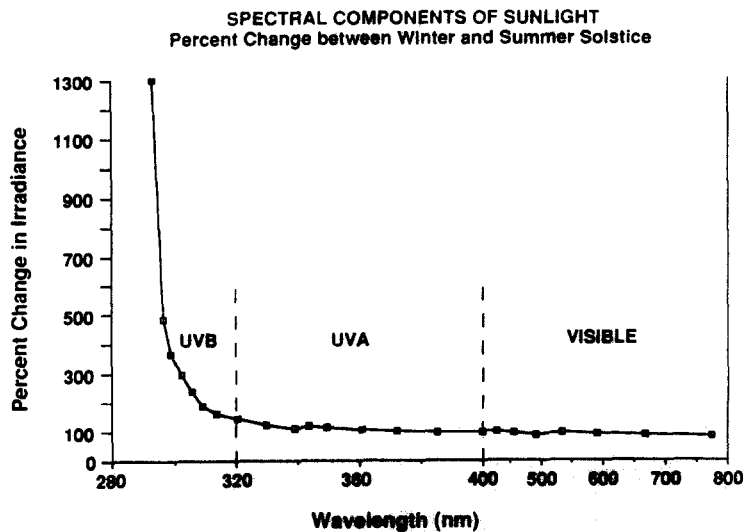


Fig. 1. Percent change, by wavelength, in irradiance ($\mu\text{W}/\text{cm}^2 \text{ nm}$) striking the surface of the earth at Tokyo ($35^\circ 43' \text{ N}$ latitude, 73 m above sea level). The greatest magnitude of change between the summer and winter solstice irradiance is apparent in the u.v.B range. In contrast, the u.v.A and visible wavelengths change relatively little between the seasons. u.v.B radiation shorter than 295 nm is effectively shielded from the surface of the earth due to absorption by atmospheric ozone. Measurements were made on June 22, 1979 at 11:44 a.m. and on December 17, 1979 at 11:42 a.m. with clear conditions on both days (data taken from [5]).

exists for the involvement of other brain regions in the control of light-dark rhythms. When the suprachiasmatic nucleus is bilaterally lesioned, circadian events are reported by some to persist (for review see [13]). Such differences may be related not only to variations in size and precise location of the lesion, but also to the existence of neural circuits instead of a center, that is, the lesioning of one component only. The other brain regions involve predominantly those that are linked to serotonergic, GABAergic, and catecholaminergic messenger systems. Lesions of the ventral noradrenergic bundle that contains fibers from perikarya in the medulla oblongata, disrupt the ACTH circadian rhythm [14]. When the GABA-antagonist picrotoxin was administered, TSH blood level peaks were altered [15], and ACTH diurnal rhythm disturbed [16]. Projections of 5-HT axons from the raphe nuclei into the suprachiasmatic nucleus [17] and reversely from the suprachiasmatic nucleus to the median raphe nucleus, as well as from the retina to the median raphe nucleus [18], suggest either a primary or a secondary modulatory role of the midbrain raphe neurons on functions ascribed to the suprachiasmatic nucleus. Involvement of dorsal raphe neurons and, perhaps, other components of the raphe serotonergic system, have long been invoked to be involved in the induction of sleep. Pharmacological blockade of serotonin synthesis causes insomnia [19] or suppression of circadian changes in plasma levels of corticosterone [20-22], ACTH [23], TSH [24] and LH [25].

Several other photosensitive pathways, in addition to the lateral eyes, have been shown to mediate entrainment of biorhythms. The hypothalamus seems likely to be the site for at least some of the extra-retinal photoreceptors, since the suprachiasmatic nucleus resides there and the diencephalon gives rise to other photoreceptors in the pineal and parietal eye in certain species. In lower vertebrates such as amphibians, reptiles, and fish, the principle cell types of the pineal gland are cells which possess photosensory characteristics [26]. Removal of the pineal and the parietal eye does not prevent entrainment of blinded lizards [27] suggesting another pathway complementing the pineal gland. Wetterberg *et al.* [28] showed that removal of the Haderian gland, a photosensitive gland found behind the eye in higher vertebrates, abolished the response to light in blinded rats. This evidence, collectively, indi-

cates several possible pathways for entrainment of the circadian and seasonal rhythms independent of the retina, implicating a complex circuitry and endocrinology for the control of biorhythms while suggesting the concept of a suprachiasmatic clock may be too narrowly defined.

LIGHT EFFECTS THROUGH SKIN-DERIVED ENDOCRINE ACTIONS OF VITAMIN D-SOLTRIOL ON SYSTEMIC AND NEURAL TARGETS

Vitamin D is unique to the steroid hormone family in that the absorption of u.v. light by the skin is required for the synthesis of its precursor. The synthesis of 1,25-vitamin D₃ begins in the skin with the photochemical transformation of 7-dehydrocholesterol to previtamin D, contingent upon the absorption of u.v. radiation. The optimum wavelengths for the production of previtamin D have been determined to be within the u.v.B range between 295 and 305 nm [3, 29, 30]. Previtamin D is then transported in the blood and hydroxylated in the liver to yield 25-hydroxyvitamin D₃, and again in the kidney by 1- α hydroxylase to provide the active hormone 1,25-dihydroxyvitamin D₃.

Vitamin D status is dependent upon the extent of exposure to sunlight, related to latitude and season of the year. Production of vitamin D and its precursors is relatively high during the spring and summer in latitudes remote from the equator [31, 32]. There is a highly significant positive correlation between summer blood levels of 25(OH)-cholecalciferol and those obtained the following winter [33, 34]. However, synthesis, action and metabolism of the hormone soltriol are influenced by many factors, that include insulin, parathyroid hormone, sex steroids, prolactin and others.

Experimental evidence from our laboratory indicates that soltriol, when circulating in the blood, is acting on a wide but selective range of target tissues. Such tissues include neurons in the brain, spinal cord and spinal ganglia [2, 35], thyrotropes and other cells in the anterior pituitary [36], pituicytes in the posterior pituitary [37], epinephrine and norepinephrine cells in the adrenal medulla [38], B-cells in the pancreatic islets [39], G-cells in the pyloric stomach [40], myoendocrine cells in the heart [41], cells of distal and proximal tubules, the macula densa and podocytes in the kidney [42], certain cells in the thyroid [43], cells in the epidermis and dermis [34, 44], Sertoli cells in

the testis [45], epithelial cells in the prostate and epididymis [46], certain cells in the oviduct and ovary [47], reticular cells in thymus and lymph nodes [48] and others.

These discoveries were followed by ongoing investigations to determine the functional significance of solatriol nuclear binding in the various tissues (for review see [1]), that appears to be independent of the regulation of systemic calcium levels. Effects of solatriol have been reported on secretion of TSH [49, 50], insulin [39, 51], and LH and testosterone [52], cell proliferation, the immune system, blood cell formation, and others (for review see [1, 53, 54]).

Evidence for the presence of *specific receptors in the brain and spinal cord* has been obtained from autoradiographic studies after injection of radiolabeled solatriol into rats and mice and is represented schematically in Fig. 2. Major nuclear target sites include the central nucleus of the amygdala and the bed nucleus of the stria terminalis, the periventricular nucleus and parvocellular paraventricular nucleus in the anterior hypothalamus, the reticular nucleus of the thalamus, area CA4 in the ventral hippo-

campus, the dorsal raphe nucleus, the parabrachial nucleus, the nucleus ambiguus, the dorsal nucleus of the vagus, the substantia gelatinosa and motor nuclei of cranial nerves and spinal cord [2].

From the anatomical distribution of vitamin D targets in the central nervous system, and by analogy with the more extensively studied estradiol distribution and related effects, several functional implications can be expected. Solatriol targets include elements of sensory pathways, the motor system, and the endocrine-autonomic system. Therefore, effects can be expected on autonomic regulation through target neurons in the nucleus ambiguus, dorsal nucleus of the vagus, and the parabrachial nucleus. Sensory components include target neurons in spinal ganglia, the substantia gelatinosa, the parabrachial nucleus, and especially the heavily labeled reticular nucleus in the thalamus. Sensory afferents to the cortex are relayed through the reticular nucleus, which contains neurons immunopositive for GABA [55], suggesting modulatory effects of solatriol on sensory perception mediated by GABA, in addition to effects

Sites of Action of Solatriol (Vitamin D)
in Brain and Pituitary

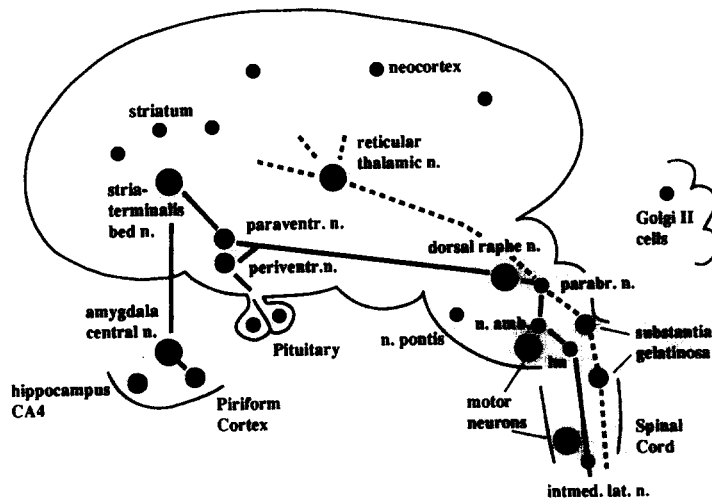


Fig. 2. Sites in the brain that have been identified as nuclear targets for the steroid hormone of sunlight solatriol (vitamin D). Entrainment of biorhythms and other effects may be mediated through interconnected major systems or timing circuits that involve (i) sensory, (ii) motor, (iii) autonomic-neuroendocrine and (iv) mental components. The sensory system (---) includes target neurons in spinal ganglia, substantia gelatinosa, parabrachial nuclei, and reticular thalamic nucleus. The autonomic-neuroendocrine system (—) includes the intermedialateral column, nucleus reticularis lateralis magnocellularis (Im), nucleus ambiguus (n. amb), parabrachial nuclei (n. parabr.), dorsal raphe nucleus, hypothalamic paraventricular and paraventricular parvocellular nuclei, bed nucleus of the stria terminalis, central nucleus of the amygdala and piriform cortex. The motor system includes all of the cranial motor nerve nuclei, motor horn nuclei in the spinal cord, nucleus pontis, and Golgi II cells in the cerebellum. The mental system is likely to be diffuse with input from all of the other systems and to involve solatriol target neurons in allocortex and neocortex, amygdala, striatum and brain stem. Prepared after autoradiograms from rat and mouse brains, following injections of $[^3\text{H}]1,25(\text{OH})_2\text{-cholecalciferol}$ [2, modified after 59].

on peptidergic neurons (substance P, neurotensin) in spinal ganglia and in the substantia gelatinosa. Solatriol target neurons in the anterior hypothalamus suggest regulatory effects on CRF, TRH, somatostatin and vasopressin secretion. In the central nucleus of the amygdala and the related lateral bed nucleus of the stria terminalis, neurotensin and CCK target neurons may be involved. Circannual variations in serum concentrations of pituitary, thyroid, parathyroid, gonadal and adrenal hormones in male laboratory rats [56] may be related to changing blood levels of solatriol. Effects of solatriol on dorsal raphe neurons may be responsible for seasonal changes in serotonin levels reported in human brain regions [57]. Changes of serotonin levels in rat hypothalamus have been observed under conditions of changed solatriol blood levels due to a modification of calcium in the diet (unpublished).

Our data about solatriol nuclear binding and the information on related effects, suggest an extensive regulatory role for many tissues, independent of and in addition to effects on systemic or tissue calcium levels. Results from our studies with combined autoradiography and immunohistochemistry with radiolabeled solatriol and antibodies to 28K calcium binding protein could not demonstrate a congruency between vitamin D nuclear binding and presence of this calcium binding protein, as had been advocated by others and would be expected according to traditional concepts.

The question must now be raised about the nature and degree of tissue-specific effects of solatriol related to the changing blood levels during varying solar exposures. Seasonal fluctuations of 25 (OH)-cholecalciferol and, probably to a lesser degree, of 1,25(OH)₂-cholecalciferol can be postulated to underly photoperiodic changes of, for instance, thyroid function, insulin secretion and glucose metabolism, catecholamine secretion, mood and behavior, growth and cell proliferation/differentiation, mineral turnover, reproductive functions, immune response, motor activity, and most likely others.

The significance must be considered of selective target cell receptor modulation and of changes of specific serum binding proteins for the hormone and its precursors, in addition to changes in hormone blood and tissue levels due to the different skin exposure to u.v. radiation [30], the regulation of related enzymes in the skin, liver, and particularly the 1- α hy-

droxylase in the kidney, as well as interactions with gonadal steroids, adrenal steroids, vitamin A and others.

From the extent of solatriol nuclear binding we proposed that the thyroid regulatory system is most sensitive and responsive among the many targets [1, 50]. If confirmed, this would support our concept of vitamin D as a somatotrophic regulator of growth and maintenance of life, of which the effects on calcium homeostasis are but one component.

CONCLUDING CONSIDERATIONS

Clarification is needed as to what extent changes in seasonal activity are attributable to visual light input to the diencephalon, to extraocular photoreception [58], or to genomic target effects of solatriol that parallel modulations of u.v.-induced blood levels of the hormone or its precursors.

The presence of a circadian clock, regulated by the visible wavelength of light, appears well established in diencephalic areas that involve the suprachiasmatic nucleus, the intermediate geniculate nucleus and the pineal. The study of extraocular photoreception remains a challenge. The available data are controversial [59-62]. Non-nocturnal animals need to be examined in addition to nocturnal rodents that furnish most of the data. In addition to lighting, conditions of diet as to vitamin D and perhaps other seasonal changes or additions, need to be controlled. In view of the discussed data on vitamin D nuclear binding and related effects, it appears justified to advance the concept that an additional photoperiodic timing occurs through the u.v.-mediated genomic solatriol regulation in many brain regions, as well as in endocrine and somatic tissues [63]. The solatriol effects may be considered to be of a more sustained and trophic nature, as is characteristic for other steroids, such as estrogens and androgens. By comparison, more immediate and short-lasting responses may be incurred through the visual light-input to the diencephalon.

Evidence exists to suggest endogenous circadian and circannual regulators, possibly entrained genetically or transduced through the mother during development [60-62]. Clarification of this issue would advance interpretation as to which biological effects are related to which components of sunlight in various species, and to what degree effects of the intermediate visual wavelengths (melatonin), short

u.v. wavelengths (vitamin D), and long wavelengths (temperature) predominate, or complement and support each other [1].

Species differences in habitat-related adaptations are extensive and complicate these studies. However, it can be expected that all components of sunlight work cooperatively toward effective seasonal and diurnal adaptations to assure development, growth, and reproduction for the survival of the species in a constantly changing cosmic-solar environment [1, 2].

Certain regulatory roles can be defined and attributed to the different groups of steroid hormones: seasonal adjustment for the skin-derived soltriol; reproduction for the gonad-derived steroids estradiol, progesterone and testosterone; and metabolic-vascular adjustments related to stress for the adrenal steroids. The effects of the individual steroid hormones are extensive—while specific and selective—and occur at all levels of organization differentially throughout the organism, as it has been outlined for the cardiovascular system [41]. Heterogenous tissues of the organism can thus be regulated genomically and integrated functionally to be prepared for the different requirements for survival.

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