Psychopharmacology (1989) 97:285–294

Psychopharmacology

Review

Light, vitamin D and psychiatry

Role of 1,25 dihydroxyvitamin D_3 (soltriol) in etiology and therapy of seasonal affective disorder and other mental processes*

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Abstract. This is a review and a prospectus of effects of vitamin D on the brain. Effects of sunlight and equivalent artificial light on physiological and behavioral processes are probably mediated, in large part, through the skin-vitamin D-endocrine system. Experimental evidence from our laboratory reveals sites of action and concomitant direct effects of $1,25(OH)_2$ vitamin D_3 (soltriol) on brain, spinal cord, pituitary and other endocrine tissues. This appears relevant for the activation and modulation of mental and endocrine processes, particularly related to seasonal and daily biorhythms. Effects of sunlight and corresponding artificial light are likely to be mediated through direct actions of soltriol on brain and endocrine tissues that are independent of its effect on calcium levels. Those direct actions are receptor mediated and appear to be dose related as they depend on intensity of light and length of exposure, considering light (photons) as a drug. A role for soltriol, the steroid hormone of sunlight, in the etiology and helio- or phototherapy of affective disorders with cyclic seasonal onset (seasonal affective disorder) is discussed and the significance of research in the new frontier of vitamin D and brain relationships is noted.

Key words: Vitamin D – Brain – Sunlight – Seasonal affective disorder – Soltriol

Effects of vitamin D on brain functions are sparsely reported in the clinical literature and are generally related to changes in calcium blood levels. Vitamin D is widely believed to be "the calcium homeostatic steroid hormone" and not to act on the brain, but rather to interact peripherally with calcitonin and parathyroid hormone to regulate calcium levels in blood and tissues. Experimental information from our laboratory, however, points to extensive direct effects of $1,25(OH)_2$ vitamin D_3 (soltriol, vitamin D) on nervous tissues, independent of and in addition to its effects on serum calcium levels. A new area in vitamin D research has thus opened, with implications for nosology and therapy of various diseases.

This article provides a brief review on clinical observations possibly related to vitamin D and a discussion of sites and mechanisms of action of soltriol in neural and endocrine tissues pertinent to mental health and general well being. At the basis of the considerations is the concept that the hormone of sunlight, soltriol, is a comprehensive somatotrophic activator and modulator and not only a regulator of systemic and cellular calcium levels. The philosophy underlying the new concept is that the steroid hormone soltriol is the skin-derived endocrine messenger of the zeitgeber sunlight, in order to attune vital functions of the organism to conditions of our solar environment toward optimal adaptation for development, growth, reproduction, and maintenance of life (Stumpf and O'Brien 1987; Stumpf 1988a, b).

In the past, biological effects of light have been ascribed solely to eye-mediated hypothalamic and pineal connections, and the involvement of melatonin as its primary endocrine messenger was believed to be restricted largely to the regulation of reproduction. In view of the new insights gained for actions of vitamin D, it has been proposed that melatonin, similar to soltriol, has comprehensive actions and that two endocrine systems, the eye-diencephalic-pineal system and the skin-vitamin D system, operate in a complementary yang-yin fashion in an "endocrinology of sunlight and darkness" (Stumpf 1988b).

Aspects of biological rhythms that hitherto escaped explanation under consideration of effects of light through the "retino-hypothalamic pathway" and melatonin alone can be expected to be better understood, when effects of soltriol are also considered. It is of interest and characteristic of the zeitgeist that in a recent review on "melatonin and psychiatry" (Miles and Philbrick 1988), vitamin D was not even mentioned. With the information now at hand, it is apparent that antagonistic and complementary actions exist between the pineal-melatonin and skin-vitamin D endocrine systems.

Clinical observations

In current textbooks of psychiatry, vitamin D is either not mentioned or only mentioned in the context of treatment of hypocalcemia. Mental manifestations associated with hypocalcemia may include social withdrawal or frequent irritability. Neurotic symptoms may occur and include: obses-

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* The term "soltriol" is used for the "steroid hormone of sunlight", $1,25(OH)_2$ vitamin D_3, in correspondence to other steroid hormones, such as "estradiol" and "cortisol". "Vitamin D" is a misnomer, related to its historic discovery as an ingestible vital extract, before being recognized as a steroid hormone

sions, phobias, tics, emotional lability, irritability, anxiety, fatigue, depression, and in severe cases, delirium and delusions, intellectual impairment or even mental retardation, often associated with organic syndromes (Kaplan and Sadock 1985). Hypercalcemia related to hyperparathyroidism may be associated with various neurotic symptoms, lack of initiative and spontaneity, depression, sometimes associated with suicidal tendencies, loss of the ability to concentrate, short-term memory deficits; in severe cases, confusion and acute organic psychosis (Kaplan and Sadok 1985). Changes in vitamin D metabolism in vitamin D replete individuals have been accompanied by significant rises in phosphorus and calcium (Mawer et al. 1984). Whether or not, or to which degree symptoms of hyper- and hypocalcemia are related to changes in levels or central effects of soltriol, remains to be clarified.

The syndrome of hypervitaminosis due to vitamin D intoxication in a survey of 111 cases (Chaplin et al. 1951), contains neurological and psychiatric symptoms that include headache, paresthesias, vertigo, variable mental symptoms, depression, mild psychosis, and stupor. Such symptoms usually developed over prolonged treatment for weeks or months with a wide range of doses, and disappeared upon cessation of treatment. In a survey of 21 patients with hypercalcemia due to vitamin D poisoning, episodes of poisoning were accompanied by anorexia, nausea or vomiting, weight-loss and headaches or mental symptoms such as apathy, fatigue, or confusion (Paterson 1980). Several cases of depressive illness in the context of hypervitaminosis D have been reported (Anderson et al. 1968; Keddie 1987). Changes in the electroencephalogram with slowing, diffuse bursts, and evidence of a diffuse cortical disturbance, sometimes associated with convulsions, were noted in several patients with hypervitaminosis D and associated hypercalcemia (Beare and Millar 1951; Lehrer and Levitt 1960). Hypercalcemia due to primary hyperparathyroidism may be associated with neuropsychiatric disorders, including overt psychosis with hallucinations and delusions, apathy, lethargy, depressive states, confusional and amnestic states, psychoneurotic manifestations and other personality changes (review Karpati and Frame 1964; Gatewood et al. 1975). Neuropsychiatric manifestations were found in 14 out of 33 patients and to dominate the clinical picture in 4 of the 14 cases (Karpati and Frame 1964). In a survey of 54 patients with primary hyperparathyroidism, psychiatric disorders were found in more than 50% of patients, correlated to the serum calcium levels (Petersen 1968). The higher the serum calcium, the more severe the mental disturbances, which include slight or severe neurasthenic personality change with lack of initiative, depression, and acute organic psychosis in the most severe cases. These symptoms were wholly reversible when the serum calcium returned to normal.

Conversely, two patients with hypocalcemic psychosis due to uremia and hypoparathyroidism were successfully treated with 1(OH) vitamin D_3 (Gertner et al. 1976). For "profound dementia and convulsions" with a 3-year history and associated with idiopathic hypoparathyroidism, "a virtually complete restoration of mental function was seen" 24 h after oral treatment with 1(OH) vitamin D_3 (Mateo and Gimenez-Roldan 1982). In this latter case, low values of plasma calcium remained for 6 weeks after initiating treatment.

In this context, of interest are changes in $1,25(OH)_2$ vitamin D_3 blood levels observed in experimental animals due to dietary manipulations of calcium. Rats when fed a low calcium diet (0.04% calcium) show an increase in plasma $1,25(OH)_2$ vitamin D_3 from 45 to 165 pg/ml, and when fed a high calcium diet (1.6% calcium), show a decrease in plasma $1,25(OH)_2$ vitamin D_3 levels to 26 pg/ml (Clark et al. 1986a; Bruns et al. 1987). Changes in plasma levels of $1,25(OH)_2$ vitamin D_3 in humans remain to be studied. It is conceivable from the results obtained with rats that in humans changes in blood levels of vitamin D metabolites may be induced by long lasting nutritional, pharmacological or pathological changes in blood levels of calcium and that effects due to secondary elevation or lowering of $1,25(OH)_2$ vitamin D_3 contribute to or predominate over effects from high or low systemic calcium.

Another observation that points to the complex relationships among different systems deserves to be mentioned. Vitamin D deficiency may be associated with long-lasting anticonvulsant therapy with phenobarbital and diphenylhydantoin or congeners. The first observation was reported by Schmid (1967) and confirmed repeatedly that rickets may develop in children (Kruse 1968; Crosley et al. 1975; Winnacker et al. 1977) and osteomalacia in adults (Hahn et al. 1972) undergoing such therapy. Serum levels of vitamin D metabolites and calcium were lowered in about 10–30% of the patients, and the changes in serum levels were paralleled by the degree of radiographic bone calcium loss. These changes returned to normal when vitamin D was added to the anticonvulsant drugs. The vitamin D deficiency is believed to be related to the drug-induced stimulation of the microsomal enzyme system followed by an increased metabolic breakdown of steroid hormones. These clinical reports, however, focused exclusively on bone pathology and no mention was made on changes in sex and adrenal steroid hormone deficiencies, which one would also expect, nor were any other symptoms related to lowered calcium and vitamin D levels reported. Further studies in such patients, therefore, should not be confined to bone-related symptomatology and should include monitoring possible changes in other endocrine systems and in functions of the peripheral and central nervous system, including the mental status.

Altogether, it is evident that associations between vitamin D and psychiatric states are characterized by considerable complexity. This is due to the non-specificity and heterogeneity of psychiatric symptoms as well as to the complicated nature of endocrine regulations and the interactions between different systems. Mental consequences of abnormal vitamin D levels could be related to primary or secondary influences, that is, direct or indirect effects of soltriol, parathyroid hormone, calcitonin, calcium or phoshorus, thyroid hormone, insulin, metabolic activity of liver and kidney, and many others.

Interpretation of the data published in the literature is, therefore, difficult and limited. For instance, while vitamin D intoxication is associated with hypercalcemia, it is not clear whether the clinical symptoms associated with hypercalcemia due to primary hyperparathyroidism are causatively linked to changes in blood calcium levels and related effects on neuronal excitability or to effects on endocrine secretions, contractility, and others. The bias toward calcium-mediated effects and the lack of comparable data on $1,25(OH)_2$ vitamin D_3 blood levels does not permit any conclusions, except that mental symptoms exist under vary-

ing conditions, and these symptoms are similar to those reported as the unspecific endocrine psychosyndrome of Bleuler or the exogenous reaction type of Bonhoeffer. Although direct effects of vitamin D on neural tissues were not considered by the authors of the clinical reports cited above, direct interactions between $1,25(OH)_2$ vitamin D_3 and neural tissue must be expected to exist in brain, spinal cord and spinal ganglia, as well as in certain endocrine organs.

Therapy with light

Seasonal relationships of occurrence of certain affective disorders together with known biological effects of light argue for possible involvement of skin-derived biological transduction of light cues. Such effects of light are suggested by the difficulties in explaining heliotherapeutic effects through involvement of the lateral eyes and pineal alone, and by our experimental findings of soltriol receptors in the central nervous system and in endocrine organs. The biological effects of light have been reviewed repeatedly and extensively (Wurtman et al. 1985), but remained confined to considerations of light input through the lateral eyes. Beyond these reviews and in the present context, the effects of light on the skin are considered (Stumpf 1988c).

The salubrious effects of sunlight in the treatment and prevention of rickets and osteomalacia have been recognized for over 60 years. There are great differences between natural and artificial light (Thorington 1985). However, artificial light that corresponds to the intensity and wavelengths of sunlight can be expected to emulate effects of exposure to sunlight. It is likely that all components of sunlight, including ultraviolet, visible and infra-red, are involved in its full or maximal biological effects. In this treatise, focus is on the short wave lengths which are necessary for the procurement of the prohormone vitamin D_3.

Light therapy appears to be the treatment of choice for patients with seasonal affective disorder (SAD). A fundamental question is whether the artificial sources of light used in phototherapy are capable of producing the wavelengths essential for converting 7-dehydrocholesterol into the secosteroid vitamin D_3. Many translucent materials absorb and diffuse ultraviolet radiation while allowing the passage of longer wave-lengths. The glass bulb in artificial light sources acts similarly to the ozone layer for natural light, limiting the ultraviolet to about 280 nm for fluorescent lamps (Thorington 1985). This lower limit, however, is still sufficient to provide the spectral component needed for the dermal procurement of the soltriol prohormone vitamin D_3. Few experiments address directly the question of vitamin D synthesis by artificial light sources. One study demonstrated a significant rise in calcium absorption in elderly men following daily ultraviolet radiation exposure, attributed to new synthesis of vitamin D (Neer et al. 1971). It is well recognized that the capacity to synthesize vitamin D is reduced with age, even though a relatively low intensity exposure to artificial light can produce physiological levels of the active hormone in the elderly. In another study, vitamin D-deficient subjects showed a marked transient increase in serum 25(OH) vitamin D_3 concentration within 24–48 h of exposure to ultraviolet radiation (Adams et al. 1982). The magnitude of the increase in 25(OH) vitamin D_3 levels depended on the dose of ultraviolet light delivered and on the ability of the individual to synthesize vitamin D at the time of the treatment. In addition, ultraviolet light has also been shown to increase serum $1,25(OH)_2$ vitamin D_3 in vitamin D-replete adults (Mawer et al. 1984). Exposure to a single quantitative dose of UV radiation results in a significant rise in vitamin D and its metabolites attaining a peak in about 48 h (Adams et al. 1982). In the absence of further exposure, the levels of vitamin D and its metabolites fall off, with a half-life of about 48 h, and return to basal levels in about 7 days (Adams et al. 1982). A similar temporal incidence is apparent with relief of symptoms in SAD patients treated with phototherapy. Following exposure to bright light, patients demonstrate relief from SAD symptoms within 2–4 days (Rosenthal et al. 1985). When light treatment is discontinued, relapse of symptoms occurs in an equivalent time period (Rosenthal et al. 1985). If light therapy is maintained the improvement of SAD symptoms remains effective year after year, and can be used prophylactically to prevent seasonal onset of symptoms in the fall (Jacobsen et al. 1987), possibly by replenishing depleted stores of vitamin D precursors. Therefore, when considered together, these data demonstrate that artificial light sources are capable of providing the necessary spectral components for the procurement of the prohormone vitamin D_3, and that relief or prevention of symptoms may result from modulation by vitamin D of neural and behavioral processes.

Latitude is suggested to contribute to the severity of depressive symptoms of SAD (Rosenthal et al. 1984). Exposure of the earth to UV decreases with increased latitude, to a more or lesser extent, depending on the season. Serum levels of 25 hydroxyvitamin D_3 are dependent primarily on the amount of exposure of UV and the interval between exposure (Adams et al. 1982). Unlike 25 hydroxyvitamin D_3, the presence of normal 1,25 dihydroxyvitamin D_3 levels in vitamin D-deficient patients suggests 1,25 dihydroxyvitamin D_3 may not be a reliable measure of a person's vitamin D status (Adams et al. 1982). It may be important, therefore, to measure several vitamin D metabolites, including 25 hydroxy, 1,25 dihydroxy and 24,25 dihydroxyvitamin D_3 before and during treatment to reveal a clearer physiological picture. This information may be useful to determine correlations between severity of symptoms and vitamin D levels which could lead to a possible index for diagnosis as well as a screen for predictability of benefit from phototherapy.

Results from previous experiments suggest that certain factors such as intensity and duration of light must be considered for a beneficial outcome from phototherapy. Some investigators have proposed a phase advance theory (Lewy et al. 1985) which asserts that the appropriate timing of light treatment or interruption of sleep is necessary to realign out of phase circadian rhythms to improve symptoms in patients with chronobiological disturbances. However, time of day (Wehr et al. 1986a, b) and interruption of sleep (Rosenthal et al. 1985) have been shown not to be critical determinants in patients with seasonal depression. These findings have encouraged some researchers to adopt a photon hypothesis which holds that exposure to a critical number of photons is necessary for benefit from phototherapy (Lewy and Sack 1986). This photon counting hypothesis has led these investigators to wonder if perhaps the skin, and not the eyes, mediates the antidepressant effects of phototherapy in SAD. A study addressing this question concludes that the antidepressant effects of phototherapy were greater when light was applied to the eyes than when it

was applied to the skin (Wehr et al. 1987). However, the authors admit that the expectations of the patients nearly always predicted the outcome of the treatment and considering the methodological problems with respect to placebo effect and double blind techniques, the interpretations of this study became difficult.

Bright artificial light, in order to be useful in the treatment of jet lag and entrainment of circadian rhythms, needs to exceed a threshold of 3000 lux and a duration of exposure of 3 h (Wever 1985). Normal artificial illumination (below 1000 lux) has only marginal influence on the circadian system of humans (Wever 1985). Light of the intensity and composition of sunlight provides a biological stimulus of a special quality, which is reflected in the concept of photons as a drug and most likely involves the skin-soltriol endocrine system.

1,25(OH)$_2$ vitamin D$_3$ (soltriol)

New areas of research and understanding of the effects of light in relation to vitamin D have been opened with our discovery of receptors for soltriol in the central nervous system and in endocrine glands. The new concept on soltriol action (Stumpf and O'Brien 1987; Stumpf 1988a, b) is based on evidence mostly from our autoradiographic studies that soltriol nuclear binding exists in brain and spinal cord, anterior and posterior pituitary, skin, pancreatic island B-cells, adrenal medulla, stomach G-cells, thyroid follicular and parafollicular cells, testis Sertoli cells, epididymis, prostate, ovary, oviduct, uterus, placenta, and many other tissues. Many of the new findings have been reviewed (Stumpf 1988a).

Vitamin D$_3$ prohormone is produced in the skin by the short-wave component of sunlight and converted by hydroxylation first in the liver to yield 25 hydroxvitamin D$_3$ and then in the kidney to produce the active hormone 1,25 dihydroxycholecalciferol. Production of vitamin D$_3$ and its precursors is higher during the spring and summer months in latitudes remote from the equator (Loomis 1967; Chesney et al. 1981; Juttmann et al. 1981). However, its synthesis, metabolism, and action, are modulated by many factors that include parathyroid hormone, insulin, sex steroids, soltriol, prolactin, and growth hormone. 25 Hydroxyvitamin D$_3$ appears to provide an endogenous precursor pool for 1,25 dihydroxyvitamin D$_3$. When a vitamin deplete state exists, both 25 hydroxy and 1,25 dihydroxyvitamin D$_3$ levels are low, the 1,25 being the last to reflect this deficit. When the vitamin-deplete individual is exposed to appropriate light, 25 hydroxy and 1,25 dihydroxyvitamin D$_3$ levels rise until a temporary overcompensation of 1,25 dihydroxyvitamin D$_3$ is attained, perhaps resulting from the oversensitized 1-alpha hydroxylase in the kidney due to chronic vitamin D depletion. At this point, 1,25(OH)$_2$ vitamin D$_3$ may feed back to inhibit dermal synthesis of the prohormone and deflect toward synthesis of inert by-products such as lumistrol or tachysterol (Holick 1985) and to increase melanin production in melanocytes. The effect of sunlight on vitamin D$_3$ formation is regulated in the skin, among others, by its melanin content and distribution. Accordingly, pigmented individuals absorb less ultraviolet light and are, therefore, more prone to rickets in equator-distant latitudes, compared to less pigmented individuals (Loomis 1967; Holick 1985). The role of melanin in the regulation of vitamin D$_3$ production can be defined from observations

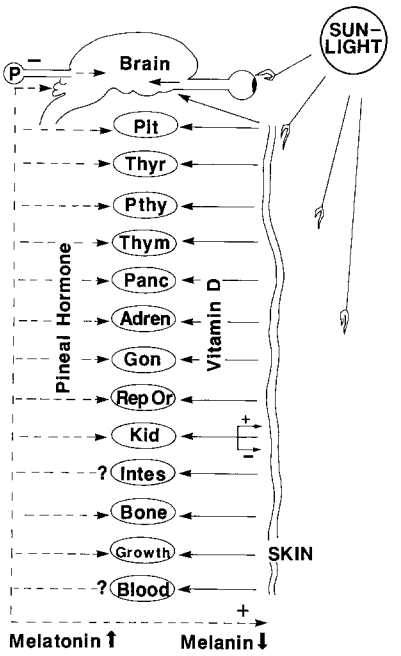

Fig. 1. The complementary skin-soltriol and eye-pineal hormone endocrine systems are activated respectively by the presence or absence of sunlight, and provide for a purposeful adaptation to the solar conditions of our environments, facilitating thus development, procreation, and maintenance of life (Stumpf 1988a)

that the "hormone of sunlight", soltriol, stimulates melanin production, as shown in vitro (Tomita et al. 1986), and that the "hormone of darkness" melatonin lightens melanocytes (Lerner et al. 1958) in a suggested feedback relationship between the two endocrine systems in the related concept of the "endocrinology of sunlight and darkness", in which effects of 1,25(OH)$_2$ vitamin D$_3$ are considered complementary to effects of pineal hormone(s) (Fig. 1).

Evidence from the literature indicates that current concepts of action of both pineal hormone and skin-vitamin D$_3$ are too restrictive. The emphasis on respective regulation of reproduction and calcium homeostasis needs to be revised and broadened. As is now evident for vitamin D$_3$, pineal hormone also affects functions of brain, pituitary, thyroid, adrenal, pancreatic islands, kidney, and many others (reviewed Relkin 1983; Stumpf 1988b). While there is much indirect evidence suggesting interactions between the two hormonal systems, the various mechanisms need to be elucidated.

In light of our present knowledge and new evidence, a role of the skin-vitamin D$_3$ system in the etiology and therapy of SAD is proposed as being mediated through several endocrine systems and nervous circuits that have been identified in our studies as targets for soltriol (Figs. 2 and 3).

Vitamin D and the brain-pituitary-adrenal axis

Adrenal cortical steroids as well as adrenal medullary hormones have all been implicated in stress response and mental processes. Adrenal medullary cells concentrate soltriol in their nuclei (Clark et al. 1986b). This indicates that these cells contain receptors for this hormone. Colocalization of

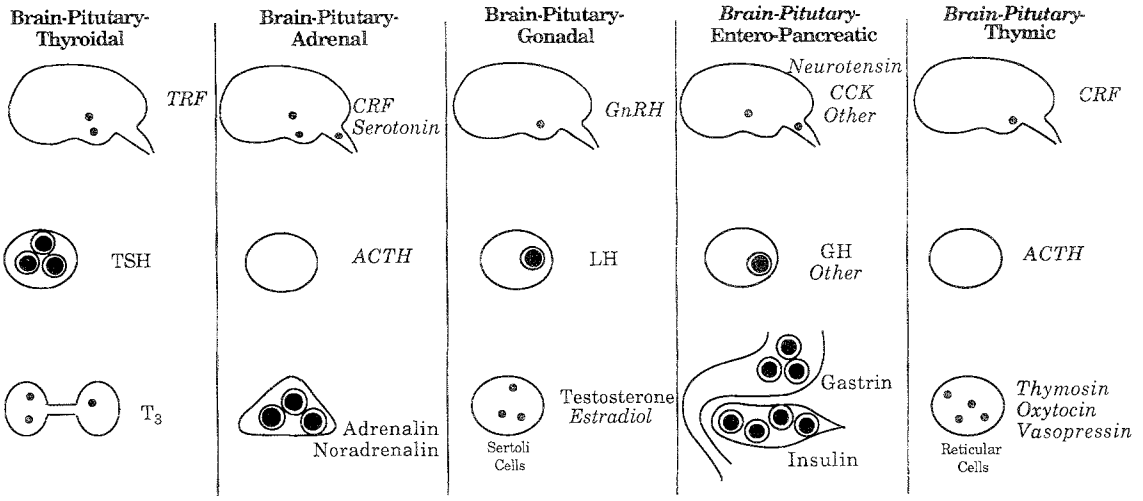

Fig. 2. Evidence indicates or suggests that soltriol regulates or modulates manufacture and secretion of messengers in all major endocrine systems. Colocalization of ^3H 1,25$(OH)_2$ vitamin D_3 and of antibodies to messengers in identical cells has been demonstrated (◉). Other target cells that were found in regions involved in the production of messengers, but not yet colocalized, are also depicted (•). Brain involvement in all systems is suggested but needs to be supported by further evidence (designations in cursive letters). An endocrine system that involves thymus reticular cells (Stumpf and Downs 1987) is not depicted but needs to be considered too

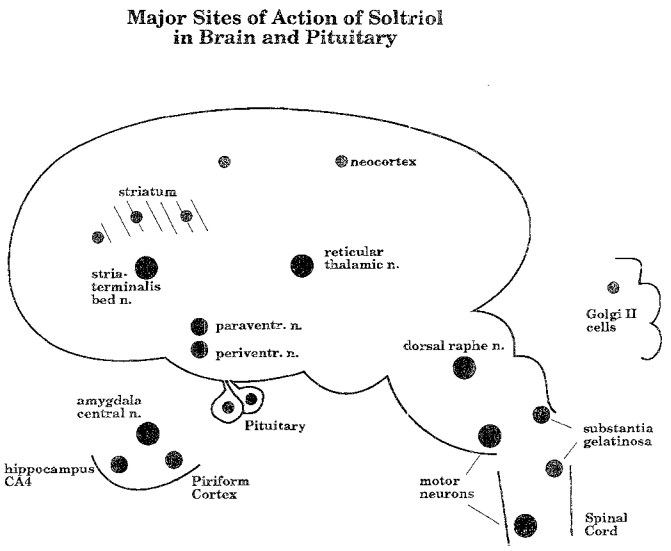

Fig. 3. Major sites of nuclear concentration of ^3H soltriol in neurons of brain and spinal cord, derived from autoradiograms of rats and mice (Stumpf and O'Brien 1987). Size of the black dots corresponds to intensity of nuclear uptake and retention of ^3H soltriol after subcutaneous injection. Both transient activational effects in the adult and permanent organizational affects in the developing brain can be expected to occur and to involve all or certain of these sites in response to exposure to sunlight and related actions of soltriol. The dorsal raphe nucleus, reticular nucleus of the thalamus, paraventricular and periventricular nucleus, central nucleus of the amygdala and bed nucleus of the stria terminalis, as well as ventral motor neurons, are of special interest

radiolabeled soltriol by autoradiography and of antibodies to the enzyme phenylethanoleamine-N-methyltransferase by immunohistochemistry revealed that both epinephrine and norepinephrine cells are targets for soltriol. The binding of tritiated soltriol in the adrenal medulla, while it does not match the distribution of 28k calcium binding protein, is likely to be consistent with a genomic regulation or modulation of the synthesis and secretion of catecholamines and perhaps other adrenal medullary hormones. An induction of adrenal tyrosine hydroxylase activity after 4-day treatment with vitamin D_2 had been observed earlier and related to effects of alteration of serum calcium (Mueller and Peng 1976). From the results of our studies, however, it appears more likely that tyrosine hydroxylase induction was mediated through a direct effect of 1,25$(OH)_2$ vitamin D_3 on adrenal medullary cells.

At the pituitary level, no evidence exists presently for direct effects of soltriol on ACTH secretion, although modulation of ACTH secretion at this level remains a possibility and needs to be studied. Subpopulations of other anterior pituitary cell types, as well as of pituicytes in the posterior pituitary, have been identified as targets for soltriol (Stumpf et al. 1987), suggesting indirect effects on pituitary adrenal regulation.

In the brain, parvocellular neurons in the nucleus paraventricularis, a site known to contain CRF-producing neurons, show nuclear concentration of ^3H 1,25$(OH)_2$ vitamin D_3 (Stumpf and O'Brien 1987). Therefore, CRF synthesis and secretion can be expected to be influenced directly by soltriol blood levels. Additional central effects on neuroendocrine control of adrenal functions are likely and may be mediated through neurons in the dorsal raphe nucleus and various limbic system structures that have been shown to contain receptors for soltriol (Stumpf and O'Brien 1987).

Vitamin D and the brain-pituitary-thyroid axis

Thyroid hormones have wide-spread affects on protein synthesis and energy metabolism with influences on brain functions and behavior, as is evident in hypo- and hyperthyroidism. Extensive cellular distribution of thyroid hormone receptors throughout the brain has been reported (Stumpf and Sar 1975).

1,25$(OH)_2$ Vitamin D_3 has been shown to bind to nucle-

ar receptors in pituitary thyrotropes (Sar et al. 1980), to elevate TSH blood levels in vivo (Sar et al. 1981; Törnquist and Lamberg-Allardt 1985), and to stimulate TSH secretion in vitro (Rose and Holick 1985). In addition, uptake and concentration of $1,25(OH)_2$ vitamin D_3 has been reported to exist in the thyroid in certain follicular and interfollicular cells and in the colloid of large follicles (Stumpf and Downs 1987). The latter indicates direct effects of soltriol on certain elements in the thyroid. In the anterior hypothalamus, nuclear concentration of soltriol in periventricular neurons may involve TRF-producing cells or cells closely associated with them.

Changes of TSH blood levels and of thyroid hormone secretion during changes of the light cycle and parallel changes in the production of $1,25(OH)_2$ vitamin D_3 have been reported (Panda and Turner 1968). This observation and the evidence cited above clearly indicate a modulatory effect of soltriol on thyroid function, mediated probably at all levels of the brain-pituitary-thyroid axis, most clearly demonstrated at the pituitary level. In this context, the role of thyroid activity in temperature regulation and in induction to and arousal from hibernation in certain mammalian species is of interest.

Vitamin D and the brain-pituitary-gonadal axis

Target sites for gonadal steroids are widely distributed throughout the central nervous system and many brain functions are affected in a characteristic fashion by estrogen, progestagen, and androgen. Recent evidence indicates that reproductive organs and certain tissues associated with the regulation of reproduction also contain receptors for soltriol (reviewed by Stumpf 1988a). This suggests that soltriol is a modulator of reproductive functions in the female as well as in the male. Nuclear receptors for $1,25(OH)_2$ vitamin D_3 have been identified in our autoradiographic studies in the male in Sertoli cells in the testis, in epithelial and stromal cells in the epididymis, in the ductus deferens, and in the prostate. In the female evidence for nuclear binding of soltriol exists in the ovary, oviduct, uterus, mammary gland, and placenta. In the anterior pituitary, a subpopulation of gonadotropes has been shown to display nuclear binding of $1,25(OH)_2$ vitamin D_3, and select neurons in the hypothalamic arcuate, ventromedial and periventricular nuclei, as well as in septal and amygdaloid regions, also concentrate the radiolabeled hormone in our autoradiograms (Stumpf et al. 1982; Stumpf and O'Brien 1987). These soltriol target areas are known to be associated with the control of gonadotropin secretion and sex behavior. It has been shown recently that $1,25(OH)_2$ vitamin D_3 elevates serum LH and testosterone (Sonnenberg et al. 1986). On the other hand, sex steroids are known to affect hydroxylation of 1(OH) vitamin D_3 in the kidney (Tanaka et al. 1976) and $1,25(OH)_2$ vitamin D_3 blood levels are elevated during puberty (Aksnes and Aarskog 1982; Clark et al. 1986a). These data together strongly suggest an important role of soltriol in the seasonal regulation of reproductive processes and associated brain functions, and indicate a close interrelationship between the skin-soltriol and gonadal endocrine systems.

Vitamin D and the enteroendocrine-pancreatic system

Mental functions are influenced by metabolic conditions that are linked to the functioning of the intestine and its associated organs. $1,25(OH)_2$ Vitamin D_3 appears to affect several components of the digestive system. This includes the absorptive epithelium of the small and large intestine, the epithelium of the esophagus, pyloric muscle cells, G-cells in the antrum of the stomach, and B-cells in pancreatic islands (reviewed by Stumpf 1988a). $1,25(OH)_2$ Vitamin D_3 stimulates insulin secretion by acting directly on pancreatic island B-cells (Clark et al. 1980, 1981) and probably gastrin secretion by acting directly on stomach G-cells (Stumpf et al. 1988b).

While the role of soltriol in enteroendocrine regulations remains to be further assessed, it appears that regulation of calcium absorption is only one of its actions in the gastrointestinal tract. Effects of soltriol on gastrin and insulin secretion are likely to be of significance not only for nutritional events but may have modulation consequences on systemic and perhaps central endocrine regulations.

Brain-pituitary-thymic axis

Experimental and anecdotal evidence suggest that our behavior and emotional state can influence the immune system. Generally, it is agreed that the hypothalamic-pituitary-adrenal axis participates in some capacity through the biphasic effects of corticosteroids to arouse or pacify the immune response. There is now evidence that suggests the immune system may itself be able to modify behavior through hormone-like thymosins synthesized and secreted by the reticular cells of the thymus. Vitamin D is also known to have a multifaceted involvement in the immune function of monocytes and lymphocytes in humans and animals (Provvedine et al. 1983; Ravid et al. 1984). Results from autoradiographic studies demonstrated binding of soltriol to nuclei of reticular cells in the thymus (Stumpf and Downs 1987). Therefore, vitamin D may participate in behavioral and other changes mediated through the immune system by direct actions on the thymus, direct and indirect actions on the adrenal and concomitant effects on the brain.

It has been reported that vitamin D promotes in vitro the differentiation of monocyte precursors toward macrophages (Amento et al. 1984) and that it is most likely involved in the intrathymic differentiation of T lymphocytes (Tsoukas et al. 1984). Evidence for the actions of thymosins on the CNS was demonstrated when injections of thymosin-B-4 into the cerebral ventricles of rats resulted in the release of luteinizing hormone (Hall et al. 1985). Also, in vitro experiments have shown that adrenocorticotropic hormone and beta-endorphin are released from isolated pituitary cells by thymosin fraction 5 (Smith and Blalock 1981). Furthermore, thymosins and lymphokines reduce hypothalamic norepinephrine levels which results in suppression of CRF (Besedovsky et al. 1983), while lymphokines (interleukin-1) alone induce sleep and hyperthermia when injected into cerebral ventricles (Krueger et al. 1984). These findings reveal an action on the CNS induced by thymosins and lymphokines that is consonant with known defense responses by the body to infection. Soltriol is likely to influence these central processes by modulating CRF or LH release indirectly through actions on thymosin synthesis from thymic reticular cells. The potential importance of bidirectional pathways between neuroendocrine systems and the immune system is emphasized by evidence that emotional states resulting in stress and anxiety are often associated with increased susceptibility to disease.

Soltriol receptors in brain and spinal cord

Traditionally, the brain and pituitary have not been considered to be involved in the actions of vitamin D (Norman 1979). However, evidence could be provided for the presence of receptors for soltriol in both organs (Stumpf et al. 1979, 1982). Continued autoradiographic studies with ^3H 1,25$(OH)_2$ vitamin D_3 in rats and mice revealed an extensive but selective presence of specific binding sites throughout the central nervous system (Stumpf and O'Brien 1987; Stumpf et al. 1988a). Nuclei of certain neurons showed concentration and retention of the hormone in all animals which was strongest in the central nucleus of the amygdala and the lateral portion of the bed nucleus of the stria terminalis. Strong nuclear binding was present also in motor nuclei of cranial nerves and of lamina IX in the spinal cord, in neurons of the reticular nucleus in the thalamus, in the substantia gelatinosa of the trigeminus and the spinal cord, in the piriform cortex, in the dorsal raphe nucleus, the parabrachial nuclei, in different layers of the pallium, in the ventral hippocampus in area CA4, and in other regions (Fig. 3). This wide distribution of nuclear ^3H soltriol argues for strong potential influences of soltriol on neural activities in diverse components of the central nervous system with effects on motor, sensory, endocrine and autonomic systems. The presence of soltriol target neurons in sensory ganglia and in the substantia gelatinosa of the spinal cord and medulla oblongata has been considered to affect sensory perception (Stumpf and O'Brien 1987). It is proposed that these neurons are involved in the perception of temperature, that is, the long wave component of sunlight. Thus, it is conceivable that temperature signals are being modulated when relayed from nerve endings in the skin to the thalamus and the anterior hypothalamus for neuroendocrine feedback.

Allocortical as well as neocortical soltriol target neurons may provide specific substrates toward modulation by vitamin D of various mental processes, including mood, alertness, and affective behavior.

Support for direct effects can be derived from recent experimental observations on increased choline acetyltransferase activity in certain brain nuclei after soltriol treatment (Sonnenberg et al. 1986).

Complementary skin-vitamin D and eye-pineal-hormone endocrine systems

In all of the endocrine systems discussed above, antagonistic or complementary effects for both melatonin and soltriol can be adduced from the literature. Both endocrine systems appear to have comprehensive and wide-spread actions on vital processes (Fig. 2) for adaptation to our solar environment as has been pointed out in the "endocrinology of sunlight and darkness" (Stumpf 1988a, b).

Results from published studies demonstrate that serum concentrations of Ca, P, PTH (Curruthers et al. 1964; Dube et al. 1972; Markowitz et al. 1981) GH, renin, TSH (Krieger 1979; Minors and Waterhouse 1981) testosterone, cortisol (Faiman and Winter 1971), aldosterone (Lightman et al. 1981) and others undergo regular daily fluctuations in humans. Studies in laboratory animals show a diurnal rhythm of plasma levels of 24,25 dihydroxyvitamin D_3 and renal activity of 1-alpha hydroxylase (Norman et al. 1980; Miller and Norman 1982; Wrobel and Ghazarian 1982). These data suggest a daily rhythm could be expected for 1,25 dihydroxyvitamin D_3. However, evidence from studies addressing this question is equivocal and a definite conclusion is not yet available. These findings argue for probable confounding influences of other hormones, rapid deposition of vitamin D in large tissue reserves (Mawer et al. 1972) or effects of nutritional factors on vitamin D metabolism. Carefully controlled experiments are needed to clarify the role of 1,25$(OH)_2$ vitamin D_3 in day-night rhythm in addition to seasonal rhythms. Sex and adrenal steroids are well recognized to mediate not only seasonal or monthly but also daily changes, even though steroidal (genomic) effects are generally understood to be delayed and sustained, compared to the more rapid and transitory effects of amino acid-derived messenger molecules. It is therefore conceivable that soltriol acts both as a seasonal-estival adjuster of biological activities as well as a regulator of certain daily events in tune with our solar environment.

Entrainment of biological rhythms, especially those of longer interval and duration, are likely to be mediated or modulated by soltriol actions on identified brain target regions and circuits. This is another new area of research that has opened up, and it needs to be explored to which degree nuclear regions of the stria terminalis with the nucleus centralis of the amygdala and the bed nucleus of the stria terminalis, the periventricular nucleus of the anterior hypothalamus with its extension of the parvocellular paraventricular nucleus, the reticular nucleus of the thalamus, the dorsal raphe nucleus of the midbrain, and other regions are involved in circuits of neural regulation of biorhythms (Fig. 3) and related neuroendocrine and autonomic processes. This concept is at variance with the currently held belief of a single center as a central clock. Brain regions identified as targets for soltriol together with the identified endocrine target tissues probably are all involved in the multiple manifestations of seasonal biological rhythms, such as changes in productivity and reproduction, motor activity, mood, depression, affective disorder, and suicide rate.

Conclusions

A review of the literature about direct effects of 1,25$(OH)_2$ vitamin D_3 on brain functions provides very limited evidence. Probably this has to do with conceptual restrictions related to the common exclusive or predominant association of vitamin D with calcium and bone mineralization and the traditional exclusion of the brain and pituitary from the regulation of vitamin D-calcium homeostasis, the late identification of the acting metabolite of vitamin D in 1970, and the only recent discoveries of the unexpected wide range of brain and endocrine targets for soltriol.

Soltriol, like other steroid hormones, has target sites in the brain, and therefore can be expected to have both organizational effects on the developing brain to induce permanent changes, as well as activational effects on the mature brain to incur transitory functional changes. Organizational effects of soltriol are likely to include entrainment of certain biorhythms, while activational effects may include: heightened mood and increased alertness; facilitated sensory perception and motor responses; increased libido; and other functions to be determined. Organizational and activational effects of soltriol are perceived as direct and

receptor-mediated actions of the steroid hormone and are not linked to possible changes in calcium levels.

The evidence reviewed indicates that $1,25(OH)_2$ vitamin D_3 can be expected to modulate or regulate many somatic and mental processes. Whether or to which degree such effects are mediated through actions of soltriol on cellular or systemic calcium homeostasis, as may be postulated according to the prevailing concepts of vitamin D action, or through effects on other cell-specific mechanisms, remains to be further studied. While steroid hormone effects on calcium levels are to be expected, the predominant mechanism of action of soltriol is viewed as pertaining to a genomic activation of diverse target cell actions independent of effects on manufacture of calcium binding protein. Effects of soltriol on production of hormones, e.g., TSH, insulin, gastrin, epinephrine, serotonin, on cell proliferation, on neurotrophic and mental processes, on immune response, and on others, may be equally or more important than the established effects on calcium levels.

As is evident from experience with other steroid hormones, the complexity of endocrine regulation must not mislead to an exclusive approach that favors a selective therapy over a comprehensive therapy. In the assessment and therapy of season-related changes, factors pertaining to the whole spectrum of sun radiation, including the visible, the red end (temperature), as well as its blue end, must be considered. In addition, nutritional factors, specific endocrine status, age, and general health, modify, support or diminish effectiveness of vitamin D-linked therapeutic measures. Relationships to pineal hormone(s) levels are postulated to play a role if one accepts the reasoning put forth in the concept of the complementary "endocrinology of sunlight and darkness." Thus, should an antagonist to melatonin be included in a therapeutic regimen to treat Seasonal Affective Disorder? Would soltriol do it alone, if treated at the right dose – or would the other components of the spectrum of sun light, including heat, be necessary for a full effect? Certainly, oral soltriol treatment must be contained and limited to an optimal dose, just as is recognized in the treatment with adrenal steroids or estradiol. It needs to be kept in mind that "vitamin D" is not a vitamin, even though it can be ingested. Is vitamin D the only hormone of sunlight, or are other messengers produced simultaneously upon exposure of the skin? These and other such questions need to be kept in mind.

There is now a need to conduct well controlled experiments, considering vitamin D and calcium content of diet, intensity and duration of artificial and natural lighting, time of day and year, age and sex, blood levels of various vitamin D metabolites, and others. In the past, such experiments posed difficulties in animals under laboratory conditions. They are likely to be more complicated in humans. Unless proper controls and precautions are observed and base line conditions well established, confusion rather than clarification may result.

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Received August 1, 1988 / Final version October 11, 1988