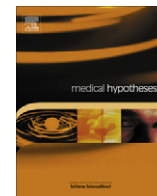


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The world epidemic of sleep disorders is linked to vitamin D deficiency

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ABSTRACT

An observation of sleep improvement with vitamin D supplementation led to a 2 year uncontrolled trial of vitamin D supplementation in 1500 patients with neurologic complaints who also had evidence of abnormal sleep. Most patients had improvement in neurologic symptoms and sleep but only through maintaining a narrow range of 25(OH) vitamin D3 blood levels of 60–80 ng/ml. Comparisons of brain regions associated with sleep–wake regulation and vitamin D target neurons in the diencephalon and several brainstem nuclei suggest direct central effects of vitamin D on sleep. We propose the hypothesis that sleep disorders have become epidemic because of widespread vitamin D deficiency. The therapeutic effects together with the anatomic–functional correspondence warrant further investigation and consideration of vitamin D in the etiology and therapy of sleep disorders.

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Introduction

For the first time in history there are large numbers of humans who spend most of their lives indoors. Multiple social changes, including the use of air conditioning and sunscreen, have produced a world wide epidemic of vitamin D deficiency [1–3]. Vitamin D is now commonly accepted to be, not a vitamin, but a steroid hormone [4,5]. It is the hormonal link that coordinates our metabolism, and the digestive, cardio-vascular, immune, endocrine, and reproductive systems to the sun, and therefore to the presence of food [6].

Over the last 40 years sleep disorders have become epidemic throughout the developed world [7–10]. Though the reasons “why” we sleep are not completely understood, there is a growing understanding of the role that sleep disorders play in the etiology of hypertension, heart disease, stroke, diabetes, depression and chronic pain, all of which have also become epidemic throughout the “developed” world [8–14]. It is our hypothesis that vitamin D plays an important role in the brainstem control of sleep, and thus, the epidemic of vitamin D deficiency is the cause of the current epidemic of sleep disorders. Our hypothesis is supported by the presence of vitamin D receptors in the anterior and posterior hypothalamus, substantia nigra, midbrain central gray, raphe nuclei, and the nucleus reticularis pontis oralis and caudalis. These same areas are considered to play a role in the initiation and maintenance of sleep. The hypothalamus, its associated projections, and the nucleus reticularis pontis appear to coordinate the sleep/wake state and the paralysis of the bulbar and somatic musculature

during sleep. Pacemaker cells of the brainstem appear to play an important role in the timing of sleep. Vitamin D's effects on these brain areas may provide an explanation for seasonal variations in sleep seen in normal humans, as well as suggesting a treatable etiology for the current epidemic of sleep disorders.

Clinical observation suggests that vitamin D may be involved in sleep

The clinical author (SCG) observed that sleep studies performed on patients suffering from daily headache show one of several sleep disorders; obstructive sleep apnea, REM related apnea, absent or reduced REM or slow wave sleep, or insomnia. An uncontrolled trial of continuous positive airway pressure CPAP devices for patients with headache and obstructive sleep apnea was partially successful, but in the fall of 2009 two patients remarked that the serendipitous supplementation of vitamin D, in addition to the use of their CPAP devices had, over a period of weeks, allowed them to wake rested and without headaches. Because the majority of the daily headache sufferers also had vitamin D deficiency the same author went looking for a possible connection between vitamin D and paralysis during sleep. This led to the recognition that several nuclei in the hypothalamus and brainstem that are known to be involved in sleep have high concentrations of vitamin D receptors [15–17]. An uncontrolled clinical trial of vitamin D supplementation in 1500 patients over a 2 year period, maintaining a consistent vitamin D blood level in the range of 60–80 ng/ml over many months, produced normal sleep in most patients regardless of the type of sleep disorder, suggesting that multiple types of sleep disorders might share the same etiology.

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How is sleep “designed” to function?

If one analyzes sleep from the standpoint of being “biologically engineered” for some “purpose” (though not yet fully understood) there are several important observations that might shed light on how sleep could become abnormal. (1) Sleep is completely involuntary. Most humans fall asleep about the same time every night, and at the same time as the other humans around them. (2) Normal humans transition into and out of the same phases of sleep at about the same time as other humans around them. (3) Waking at the end of sleep is also involuntary and occurs at about the same time for most humans. These observations imply that sleep is not induced by a build up of a substance that makes us tired, but is a carefully orchestrated, time-locked event that happens in all humans at the same time. This further implies a central clock which can be affected by the seasonal changes of sunrise and sunset. Historically, normal human sleep (being day hunters that did not see well at night) was from sunset to sunrise. For modern humans, normal hours of sleep in summer are from 9–10 pm to 6–7 am. In winter we go to bed earlier. This also implies that the millions of Americans who cannot sleep are not “doing it wrong”. Something unnatural is occurring in their brain. There is a warning phase; drowsiness, it warns us that sleep is coming so we can get to our bed. Sleep will then occur, in people who have normal brain chemistry, whether they are at the computer, or sitting on the couch, or have gone to bed. Why then, are there millions of people who do not fall or stay asleep normally? There are also several things that the brain does in order to protect this very important 1/3 of every 24 h from potential interruption. We secrete antidiuretic hormone, which limits urine production while we sleep. We also hormonally limit interruptions of hunger and bowel movements. This implies that humans with normal brain chemistry do not have interrupted sleep. We also intersperse light sleep (during which we are not paralyzed), and deep sleep (paralyzed), throughout the night in a very specific and stereotyped manner (presumably to limit the length of time spent paralyzed), remaining in deeper, paralyzed phases of sleep for maximally 1–2 h at a time. Our pharyngeal muscles are “designed” to be so perfectly paralyzed in REM sleep that we can swallow our own saliva, yet not cry out or talk while we are actively dreaming [18].

All “sleep disorders” can be viewed as malfunctions of either the timing or the paralysis of sleep

In order to understand how vitamin D could play a role in normal sleep one must also clarify how multiple “sleep disorders” might be linked to one another. Most authors divide sleep disorders into separate entities; sleep apnea, periodic limb movements of sleep (PLMS), insomnia, sleep walking, sleep talking, bruxism, acting out of dreams, narcolepsy, cataplexy, sleep paralysis, and circadian rhythm disturbances. But, these abnormalities of sleep could also be seen as different facets of the dysfunction of two basic sleep elements: the *timing* and the *paralysis* of sleep. The timing (i.e., is one in the “sleep state” when one is supposed to be, relative to the time of day) is probably run by a combination of brainstem pacemaker cells and several interlinked nuclei of the brainstem/hypothalamic axis. This “timer” function must, itself, be tightly linked to the nucleus (or nuclei) that control paralysis. As inappropriate excitation of that nucleus could result in dangerously abrupt, inappropriate paralysis (i.e. cataplexy), it must be tightly linked to the timer function to be sure that paralysis only occurs while we are asleep.

Therefore, instead of considering each of the “sleep disorders” as independent diseases of differing etiology, they could all be viewed as: (1) disorders of timing: insomnia, circadian rhythm

disorders, decreased REM or slow wave sleep, or (2) disorders of paralysis. Obstructive sleep apnea is not due to a malformed pharynx, or a fat neck. It is more appropriately viewed as an intermittent malfunction of the nucleus reticularis pontis circuits during sleep. The bulbar muscles are briefly too paralyzed and obstruction results. Inappropriate movements during sleep such as talking, chewing or PLMS can be pictured in the same way, but with the muscles not quite paralyzed enough. As many patients manifest both obstructive apnea and PLMS during the same sleep study one might picture these two disorders as the result of an inappropriately “wobbly” paralysis switch resulting in brief periods of “too paralyzed” interspersed with brief periods of “not paralyzed enough” [18].

Brain regions responsible for sleep–wake regulation

Most authors believe that the neural systems that control the opposing states of arousal and sleep are predominantly confined to the brainstem, hypothalamus and the thalamus. Some authors have recently adopted an idea from electronics called a “flip-flop switch”, which refers to the purposeful engineering of a system that guarantees that states A and B can never coexist, (i.e., mutual inhibition) to model a sleep/wake “switch” in the brain [19,20]. It appears that for normal sleep to occur there must always be the combined stimulation of one part of the brainstem during active suppression of another. Tonic activation of the brainstem reticular formation, which includes the locus ceruleus and the raphe nuclei, (which must be deactivated for the development of sleep), plays a large role in keeping the forebrain awake [18]. The hypothalamus is thought to be integrally involved because stimulation of the posterior hypothalamus induces arousal, stimulation of the anterior hypothalamus and the adjacent basal forebrain region causes sleep [18]. The nucleus reticularis pontis oralis/caudalis is thought to control the paralysis that accompanies deep sleep as experimental destruction of this region in cats eliminated the normal paralysis of REM sleep, though the sleep phase proceeded normally [21].

The central circadian clock, which coordinates the light/dark state of the outside world to the internal milieu of the body, is believed to begin in the suprachiasmatic nucleus [22]. This nucleus receives direct input from the retina through the optic nerve. In addition, in the rat direct projections of retinal ganglion cells have been traced to the anterior hypothalamic periventricular region, outside of and dorsal to the suprachiasmatic nucleus. And, in the tree shrew, an endocrine-visceral optic pathway, distinct from the visual optic pathways, has direct projections not only from the retina to the suprachiasmatic nucleus, but also to the anterior hypothalamus, the anterodorsal thalamic nuclei, and the nucleus opticus ventralis of the medulla [23]. Therefore the hormonal systems involved in the sleep/wake cycle can be envisioned as an intricate feedback complex with the hypothalamus receiving cues from the internal and external environment and integrating this information in the medial basal diencephalon [22–24]. Vitamin D target sites in the periventricular brain and brainstem are closely associated with retinal projections of light cues, and therefore to the circadian clock mechanism and the sleep/wake cycle [15,17].

Vitamin D target neurons thought to be involved in sleep regulation

Using radiolabeled 1,25(OH)₂ vitamin D₃ and the sensitive receptor microautoradiography method, vitamin D target neurons (those with nuclear concentrations of the hormone) have been discovered in specific brain and spinal cord locations in multiple animals [15–17,25]. In rats, nuclear uptake and retention of radiolabeled 1,25(OH)₂ vitamin D₃ has been demonstrated in neurons located

in the midbrain central gray, the nucleus raphes dorsalis, and the nucleus reticularis pontis oralis and caudalis [15]. Vitamin D target cells are also present in the basal forebrain, the hypothalamic periventricular region, and preoptic-septal regions. In the thalamus the reticular nucleus is strongly labeled. Target neurons exist in the bed nucleus of the stria terminalis that are linked to the nucleus of the central amygdala and contiguous with labeled neurons in the piriform and entorhinal cortex, as well as the ventral hippocampus [15–17]. In the hamster brain vitamin D target neurons have been noted in the midbrain central gray nucleus of Darkschewitsch, the interstitial nucleus of Cajal, the nucleus tractus optici lateralis and medialis, and the substantia nigra [16]. In human brain, immunohistochemical studies with antibodies to vitamin D receptor proteins have provided evidence for similar target neurons, especially in the substantia nigra [26].

Discussion

Our hypothesis, that there is an anatomic and epidemiological connection between sleep disorders and vitamin D deficiency, makes little sense if vitamin D's actions are thought to be limited to bone and calcium metabolism, a dogma that has predominated for many decades and stifled progress and recognition of vitamin D's full effects [27,28]. However, once the totality of this hormone's actions are understood it seems only logical that the hormone that links us to the sun would also affect sleep, our most circadian of actions.

Vitamin D's role in the sleep–wake cycle should be viewed in the larger context of the steroid hormone anatomic model proposed by Stumpf and Jennes in 1984 called the Allocortex (Limbic Brainstem Core model [29]. In all species, extending back to fish, the steroid hormones control an endocrine-autonomic regulatory system which begins at the level of the cervical spinal cord, extends through the medulla oblongata, pontine and midbrain nuclei to the hypothalamus-preoptic-septal regions [29] (Fig. 1). This integrated, autonomic-endocrine system has been shown to coordinate respiratory, cardio-vascular, reproductive, metabolic, and digestive functions. It appears that sleep is part of this coordinated system as well [30]. Vitamin D, phylogenetically probably one of

the oldest of the steroid hormones, is central to this system, linking the presence of sun to the presence or absence of food, allowing all animals that wander away from the equator to modulate their activity, metabolism, sleep and reproduction to the latitude and seasons. Vitamin D, like other steroid hormones, follows the “Multiple Activation of Heterogeneous Systems” concept, its receptors are found in selective cell populations in many organs, notably in the brain they are in the pituitary, hypothalamus and brainstem [15–17]. They are found in myoendocrine cells of the cardiac atrium [31]. They are widespread throughout the GI tract, from the teeth to the gastric glands and entero-endocrine cells to the pancreatic islet cells [32]. Vitamin D's reproductive function is evidenced by the receptors found in the testicles, epididymis, prostate, mammary gland, ovaries, and fallopian tubes [33].

Like other steroid hormones, Vitamin D is thought to exert its effects in the nucleus of the cell, at the vitamin D receptor, promoting transcription of specific genes. There are also reports of actions unrelated to transcription, possibly mediated by surface membrane receptors, such as Ca⁺⁺ channels, that produce cellular effects in minutes [5]. Surprisingly, doses of 20,000 IU/day promote normal sleep without being sedating, and the effect is apparent within the first day of dosing in patients who have had severe sleep disruption and very low 25(OH) vitamin D3 levels.

Many of the ideas about normal sleep expressed here grew out of watching patients return to normal sleep cycles, over a period of months, with just the return of the 25(OH) vitamin D3 blood level to 60–80 ng/ml. A totally unexpected observation was that the sleep difficulties produced by vitamin D levels below 50 return, in the same form, as the level goes over 80 ng/ml suggesting a narrower range of “normal” vitamin D levels for sleep than those published for bone health. Also, Vitamin D2, ergocalciferol (widely recommended as an “equivalent” therapy for osteoporosis) prevented normal sleep in most patients, suggesting that D2 may be close enough in structure to act as a partial agonist at some locations, an antagonist at others.

Because sleep disorders are known to increase the incidence and severity of hypertension, obesity, diabetes, heart disease, stroke, depression, and chronic pain, the observation of a clinical and anatomic link between sleep and vitamin D not only suggests a new treatment for sleep disorders, it also suggests a need for

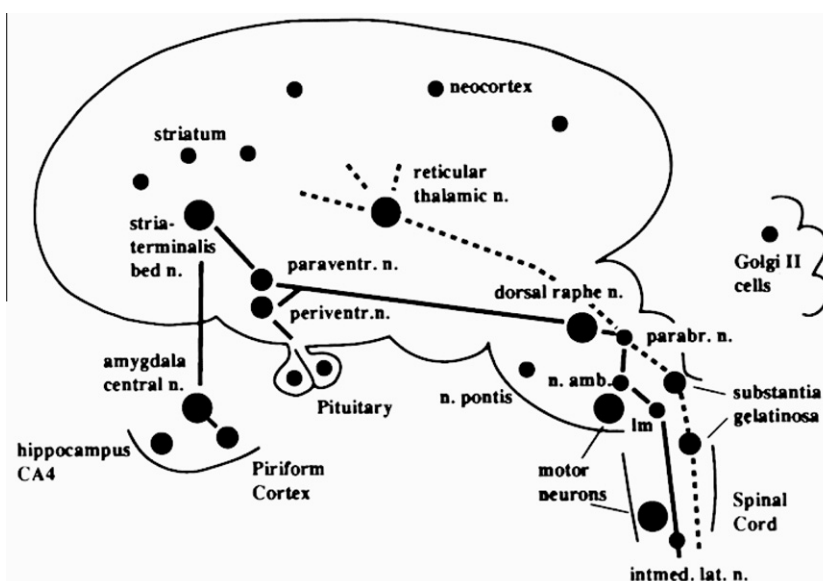


Fig. 1. Major sites of nuclear concentration of ³H-1,25(OH)₂ vitamin D₃ in neurons of brain and spinal cord of rats and mice, indicating neuroendocrine-autonomic (solid line), sensory (dotted line) systems, ventral motor areas, and dispersed cortical target neurons. Size of the black dots corresponds to intensity of nuclear uptake and retention after injection of the radiolabeled hormone. Schematic prepared after results from autoradiograms (from Ref. [34]).

investigation of careful management of vitamin D levels to prevent or improve several medical conditions that have become epidemic in developed countries at the same time. Our clinical observations concerning the narrow range of 25(OH) vitamin D3 blood levels necessary to produce normal sleep and the differing effects of D2 and D3 will need to be confirmed by extended studies, but the present observations suggest that clinical trials using vitamin D will need to closely monitor the subjects' sleep as well as the vitamin D level. Medical conditions that have been shown to be improved by normalizing sleep (as evidenced by the improvement with CPAP devices) will not be successfully treated by controlling the vitamin D dose. As with other hormones such as thyroid, it is the 25(OH) vitamin D blood level, not the dose, that must be stabilized to observe a clinical effect. For vitamin D there is also the unique issue of two sources of D, one given orally the other made on the skin during the summer. Our hypothesis, that vitamin D deficiency may be a primary cause of sleep disorders, should also prompt clinical trials for patients suffering from several sleep disorders that have historically been very difficult to treat; primary insomnia, patients unable to tolerate CPAP, patients inexplicably tired on awakening. A simple, inexpensive way to improve or normalize sleep could have a very large impact on the health of much of the world population.

Conflicts of interest

None declared.

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