Sleep Medicine 54 (2019) 262–265

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Review Article

The lullaby of the sun: the role of vitamin D in sleep disturbance

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ARTICLE INFO

Article history:
Received 26 August 2018
Accepted 17 October 2018
Available online 24 November 2018

Keywords:
Sleep disturbance
Sleep
Vitamin D
Sun
Vitamin

ABSTRACT

Vitamin D is a pro-hormone belonging to the category of the fat-soluble group of vitamins; it is obtained more from solar exposure and in smaller quantities through feeding. Although vitamin D has traditionally been shown to be involved in calcium homeostasis and bone health, recent studies have found a positive association between vitamin D and sleep. In particular, clinical studies in humans indicate that low levels of vitamin D are correlated with poor quality and short sleep duration. The mechanism by which this association is explained is still unclear. However, vitamin D receptors have been found in the brain regions involved in sleep regulation, and vitamin D appears to be involved in regulating the sleep–wake cycle. The current review summarizes the available evidence regarding the association between vitamin D and sleep, focusing on both clinical and preclinical studies.

1. Introduction

Vitamin D is a pro-hormone belonging to the category of fat-soluble vitamins group; it is synthesized in vivo when solar ultraviolet B (UVB) radiation interacts with the precursor molecule, 7-dehydrocholesterol, in the skin [1–3]. Although endogenous production is estimated to account for 90% of total vitamin D in healthy individuals, a minor source of vitamin D comes from dietary intake and supplementation [1,4]. Vitamin D is subsequently transported in the blood (bound to vitamin D-binding protein) to the liver where it is hydroxylated to 25-hydroxyvitamin D (25-(OH)D) [3]. 25-(OH)D is further converted to the metabolically active form, 1α, 25-dihydroxyvitamin D (1α, 25-(OH)2D), primarily in the kidneys [5].

Calcitriol (1α, 25-(OH) 2D) binds to the vitamin D receptor (VDR), a transcription factor that translocates to the cell nucleus, in which it is heterodimerized with the retinoid X receptor (RXR). Then, the calcitriol-VDR-RXR complex couples to a specific sequence of DNA known as the.

Vitamin D response element (VDRE), which is associated with promoters of several target genes and co-activator molecules [4].

Many conditions interfere with the endogenous synthesis of vitamin D such as low sun exposure [6], use of sunscreen [7], age [1], race/ethnicity and skin color [8], season, altitude, and latitude [9].

Vitamin D deficiency has been historically defined and recently recommended by the Institute of Medicine (IOM) as a 25(OH)D of less than 20 ng/ml. Vitamin D insufficiency has been defined as a 25(OH)D of 21–29 ng/ml [9–15]. While vitamin D has traditionally been shown to be involved in calcium homeostasis [16] and bone health [1], recent evidence suggests extraskeletal effects. An inadequate level of vitamin D has been linked to a number of diseases including metabolic disorders, psychiatric, respiratory and cardiovascular disorders, autoimmune conditions, and cancers as well as osteoporosis and osteomalacia [1,17,18]. The widespread systemic effects of vitamin D have been attributed to the ubiquitous expression of vitamin D receptors in various organ systems [1,19].

Recently there is growing evidence that vitamin D could play a role in sleep regulation. Low vitamin D levels have been reported to be associated with shorter sleep duration in the National Health and Nutrition Examination Survey (NHANES) [20]. Furthermore, it

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https://doi.org/10.1016/j.sleep.2018.10.033
1389-9457/

has been reported that adequate levels of vitamin D are necessary for the maintenance of sleep, reducing the number of nocturnal awakenings [14].

The exact mechanism by which vitamin D regulates sleep is still far from known. Basic studies reported the presence of vitamin D receptor on areas of the brainstem that are known to be pacemaker cells playing an important role in the first stage of sleep and in maintaining sleep. Given the key role of vitamin D in sleep regulation, we aim to review observational studies that report the association between vitamin D status and sleep disturbances (both sleep quality and duration). Moreover, we provide molecular insights to explain this association to better understand if vitamin D supplementation could have a role in the improvement of sleep disturbances.

2. Vitamin D and sleep disturbance: observational studies and clinical trial

Massa et al., [21] found a positive association between low levels of vitamin D and short sleep duration in a cross-sectional study conducted between December 2003 and March 2005 on a large cohort of men aged $\geq$ 65 years. Similar findings were reported by Bertisch et al., [22] who found a modest association between 25(OH)D deficiency and short sleep duration measured in a cross-sectional study conducted between 2000 and 2002 in a large, multiracial/ethnic, community-based cohort. The authors performed a race/ethnicity-specific analysis suggesting that this association persisted in an African Americans subgroup in which 25(OH)D deficiency was associated with a mean reduction of 25 min in average nightly sleep duration. Data from the Korean National Health and Nutrition Examination [_Survey_2013] reported an association between short sleep duration and vitamin D deficiency in Korean women [23].

As a consequence of this background, Wei Huang et al. [24] found an improvement in the sleep duration of about 45 min in a prospective study of a group of patients supplemented with vitamin D (dosage tailored according to the sieric vitamin D of each patient) for three months.

However, vitamin D not only influences sleep duration, but it has been reported to have also an effect on sleep quality. Young Saeng Jung et al., [25] found a significant association between serum vitamin D deficiency and poor sleep quality in a cross-sectional study conducted between January 2015 and December 2015 on a group of workers in the manufacturing industry who worked indoors. Similar results were reported in a cross-sectional study conducted in community-resident men aged $\geq$65 years [21]. The association between low levels of vitamin D and sleep quality has also been confirmed in special categories of patients. An association between low levels of vitamin D and poor sleep quality has been found in hemodialysis patients [26]. Tuck Seng Cheng et al., [27] found that vitamin D deficiency correlated with poor sleep quality in a prospective cohort study conducted between June 2009 and September 2010 in Singapore, in women who were in the first trimester of pregnancy. Another study investigated the association of vitamin D and sleep quality in pregnancy finding no relationship [28]. However, the study performed by Suzan Gunduz et al., was performed in women in the last trimester of pregnancy in which several pregnancy-related factors could contribute to impair sleep quality [28]. Vitamin D supplementation for three months improved sleep quality in a prospective study by Wei Huang et al., [24]. Opposite results were reported by Caitlin Mason et al., [29] who found no association between vitamin D and sleep quality in a double-blind, placebo-controlled randomized clinical trial conducted in Seattle between 2010 and 2012 in overweight or obese postmenopausal women with vitamin D deficiency; which had been supplemented with 2000 IU per day of vitamin D for 12 months. The negative results of this study could be explained by the fact that women enrolled in the study were overweight/obese, and the amount of vitamin D that was used to supplement them could be underestimated for the BMI.

3. Molecular mechanisms: animal and cell studies

The exact mechanism by which vitamin D affects sleep regulation is still unclear, although it has been suggested that some areas of the brainstem, which are involved in sleep regulation, could be the missing link [14]. This hypothesis is supported by evidence of the expression of vitamin D receptors in areas of the brainstem such as the anterior and posterior hypothalamus, substantia nigra, midbrain central grey matter, raphe nuclei, and in the nucleus reticularis pontisoralis and caudalis that are involved in sleep regulation. Indeed, in these areas there are pacemaker cells that play an important role in the first stages of sleep and in maintaining sleep. Using radiolabeled 1,25(OH)2 vitaminD3 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 areas in several animals [30–33]. 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 [30]. 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, as well [30–32]. Target neurons of vitamin D have been found in the bed nucleus of the stria terminals 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 [30–32]. 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 [31]. In the human brain, immunohistochemical studies using antibodies that bind vitamin D receptor proteins have provided evidence for vitamin D target neurons in the substantia nigra [33].

Recent experimental studies [34–36] have suggested that the central circadian clock may also be regulated by vitamin D due to the presence of both 1,25-dihydroxycholecalciferol (VDR) receptor and 1α-hydroxylase (1α-OHase) in human brain [34].

Human behavioral rhythms involve rest and activity cycles such as sleep/wakefulness, which are synchronized by environmental signals, particularly dark/light intervals, across a 24-h period [37]. The synchronization process involves hierarchical mechanisms where the central circadian clock at the hypothalamic suprachiasmatic nucleus (SCN) is entrained to sunlight via the retina and subsequently influences peripheral oscillators through hormonal and neural pathways [38]. Given that sunlight drives both vitamin D synthesis [1] and circadian rhythms [38], it is possible that vitamin D is involved in the transduction of light signals that regulate circadian rhythms [39].

It has been shown that the VDR as well as 25-hydroxylase and 1-hydroxylase, the enzymes controlling vitamin D activation, along with 24-CYP24A1, the enzyme controlling vitamin D degradation, are expressed in the brain [34,40,41]. Thus, the central nervous system (CNS) can synthesize its own vitamin D, which yields auto- or paracrine neurosteroid actions at the local level [34]. Similar to other neuroactive steroids, Vitamin D modulates neuronal excitability by acting on spontaneous regular firing, action potential duration, intrinsic excitability, and sensitivity to neurotransmitters as well as to neurotransmitter receptors such as the GABA receptor and the N-

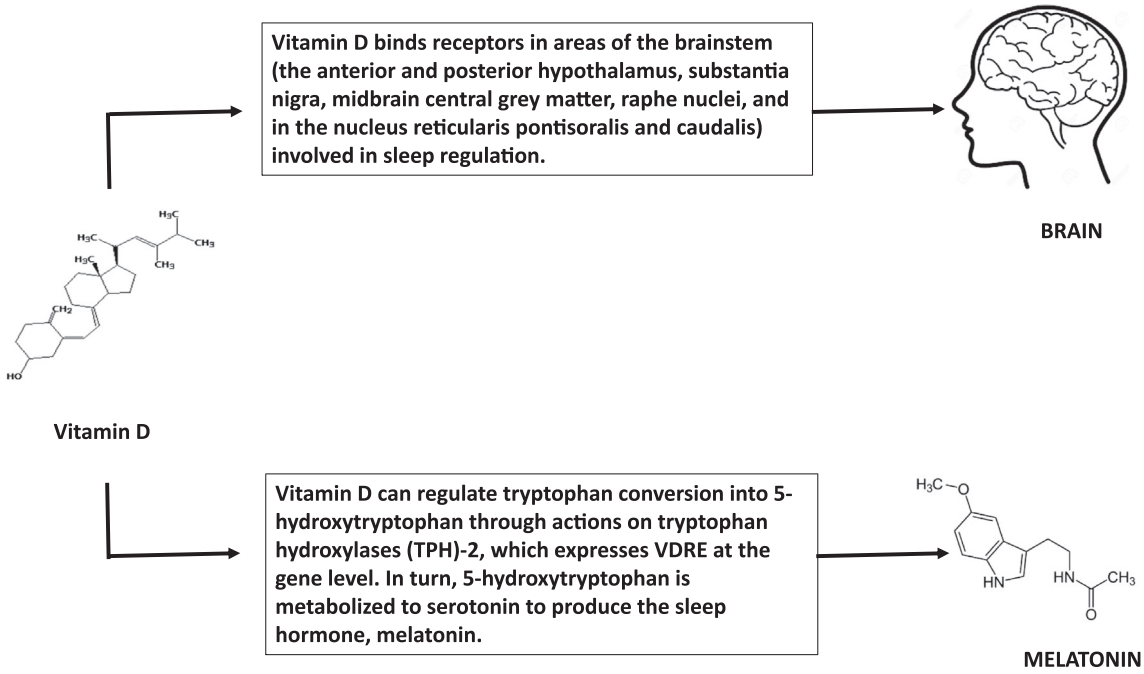

Fig. 1. Mechanism of action of vitamin D on sleep regulation. Vitamin D has been reported to bind in several areas in the brainstem such as the anterior and posterior hypothalamus, substantia nigra, midbrain central grey matter, raphe nuclei, and in the nucleus reticularis pontisoralis and caudalis that have a role in sleep regulation. Furthermore, vitamin D plays a pivotal role in the synthesis of melatonin.

methyl-D-aspartate (NMDA) receptor [42]. In addition, vitamin D upregulates the synthesis of neurotrophins such as neural growth factor (NGF), neurotrophin 3 (NT3), and glial cell line-derived neurotrophic factor (GDNF), whereas neurotrophin 4 (NT4) is downregulated [43]. Therefore, through multiple loops, vitamin D can potentially affect the development, maintenance, and survival of neurons. Moreover, hypothetically, low levels of vitamin D during early life could be relevant for future development of several brain diseases, such as schizophrenia and multiple sclerosis [44]. Whether this link also extends to sleep control is currently unknown.

Nevertheless, previous studies showed VDR expression in both developing [45] and adult rat brain [30]. Receptor sites for vitamin D were found in forebrain nuclei of the Siberian hamster that are known to be affected by neurodegenerative processes such as Alzheimer's disease as well as in adult hamster brain [32]. In the human brain, the VDR distribution has been described as strikingly similar to that detected in rodents [34]. It is found expressed in cortical and subcortical areas involved in sleep control, such as [a] the prefrontal cortex, which mediates normal sleep physiology and sleep-deprivation phenomena during NREM and REM sleep [46]; [b] the cingulate gyrus, which is activated by breathing and blood pressure challenges that are affected by sleep apnea [47]; [c] the hippocampal dentate gyrus, where adult neurogenesis is significant [48] and is influenced by sleep deprivation [49]; [d] in caudate nucleus, which is downregulated in disturbed sleep and insomnia [50]; [e] the lateral geniculate nucleus, a relay center in the thalamus for the visual pathway which plays a major role in ponto-geniculo-occipital waves during REM sleep [51]; [f] substantia nigra, which is claimed to regulate the sleep–wake cycle [52] and is involved in idiopathic rapid-eye-movement sleep behaviour disorder [53]; as well as [g] the anterior hypothalamus, particularly the supraoptic and paraventricular nuclei, which are located in tight contiguity with and receive efferent neural pathways [54] from the ventrolateral preoptic nucleus (VLPO), a hypothalamic site with primary functions in the regulation of NREM and REM sleep [55]. In rat supraoptic and paraventricular neurons, immunostaining for vitamin D binding protein co-localized with Arg-vasopressin [56], which not only regulates fluid balance but also partakes in REM sleep regulation under physiological conditions [57]. Furthermore, there is evidence that vitamin D contributes to regulating the production of melatonin, the pineal hormone controlling human circadian rhythms and sleep. Through actions on tryptophan hydroxylases (TPH)-2, which expresses VDRE at the gene level [58], vitamin D can regulate tryptophan conversion into 5-hydroxytryptophan, which is metabolized to serotonin to produce the sleep hormone, melatonin [59]. It is perhaps worth noting here that, in patients with MS, melatonin has been hypothesized to act as a mediator neuroimmunomodulatory effects of vitamin D [60]. These associations notwithstanding, experimental probing of vitamin D's role in sleep regulation is still scarcely reconnoitered (Fig. 1).

4. Conclusion

Although several findings support the role of vitamin D in Sleep Disturbance, no guidelines are currently available for or against recommending vitamin D supplementation in the prevention or therapy of this disease. Due to the paucity of intervention studies, further clinical trials are needed before evidence-based recommendations can be made to investigate the potential clinical effectiveness of vitamin D supplementation on sleep regulation.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2018.10.033.

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