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Vitamin D and brain health: the need for vitamin D supplementation and sensible sun exposure

In February 2013, Cédric Annweiler invited a number of international experts to form a task force, and they met in Boston in July 2013 to evaluate the evidence regarding the role of vitamin D in the mental health of older adults. The discussions resulted in the task force concluding that vitamin D deficiency is a risk factor for cognitive decline and dementia in older adults [1]. As noted by the task force, vitamin D deficiency is an extremely common problem worldwide for all age groups (from neonates to the elderly) [2]. Evidence suggests that vitamin D deficiency *in utero* as well as throughout life has serious long-lasting consequences for mental health.

In a well-designed rodent model of prenatal vitamin D deficiency, it was found that the vitamin D-deficient pups had brains that were larger and longer with increased ventricular volume and a thinner neocortex than brains from control pups [3]. The changes in brain morphology were due to increases in cellular proliferation as a result of the downregulation of genes controlling apoptosis during gestation and alterations in proapoptotic and cell cycle genes [3, 4]. Thus, vitamin D plays a critical role in brain development.

The task force clearly documented how vitamin D acts not only as a neurosteroid for regulating neuronal differentiation and maturation by regulating the production of neurotrophic factors including nerve growth factor and glial cell line-derived neurotrophic factor, but also serves as a neuroprotective agent by attenuating amyloid-beta accumulation by stimulating the phagocytosis of the amyloid-beta peptide. Alzheimer's disease is associated with inflammatory processes including oxidative damage and elevated levels of nitric oxide. Vitamin D is a potent antioxidant through inhibition of free radical generation by nitric oxide synthase and gamma-glutamyl transpeptidase [5]. In addition, vitamin D appears to a play an important role in vascular health in the brain. Increased stroke severity including greater infarct volumes and greater impairments in poststroke sensorimotor behaviour was observed in vitamin D-deficient adult rodents compared to the vitamin D-sufficient control group [6]. Vitamin D deficiency decreases production in the brain of insulin-like growth factor I, which is a neuroprotectant that limits the infarct size and accelerates neuronal regrowth [6]. Vitamin D also has anti-inflammatory activity and vitamin D deficiency results in a reduction in the levels of a variety of cytokines/chemokines, including IL-1 beta, IL-10 and interferon-gamma, and an increase in IL-6 which is thought to contribute to greater stroke-associated infarct volume [6, 7]. The fact that acute vitamin D repletion had no effect on the consequences of stroke induction in adult rodents [6] clearly demonstrates the importance of maintaining a healthy vitamin D status not only for the elderly but for all adults, young and old alike.

How is it that this calcium-regulating vitamin can have so many potential beneficial effects on the brain? Vitamin D is a hormone that is produced in the skin during sun exposure or obtained from the diet. It is converted sequentially in the liver to 25-hydroxyvitamin D [25(OH)D] (the major circulating form which is used to determine vitamin D status) and then in the kidneys by the 25-hydroxyvitamin D-1 alpha-hydroxylase (also known as CYP27B1) to its active form 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] [8, 9] (Fig. 1). After formation, 1,25$(OH)_2$D enters the circulation and interacts with its nuclear vitamin D receptor (VDR) to regulate serum calcium levels by increasing intestinal calcium absorption and mobilizing calcium stores from the skeleton [8]. Circulating 25(OH)D passes the blood–brain barrier and enters neuronal and glial cells and is converted to 1,25$(OH)_2$D [10, 11]. Then 1,25$(OH)_2$D interacts with the VDR to regulate several thousand genes responsible for up to 80 different metabolic processes including cellular proliferation, differentiation, apoptosis, DNA repair and modulation of both cellular and innate immunity [12]. It is recognized that vitamin D is the calcium-regulating hormone that maintains serum calcium levels in the physiological range and improves bone health. However, in the brain, a high level of calcium leads to neurotoxicity and 1,25$(OH)_2$D downregulates

L-type voltage-gated calcium channels thereby decreasing calcium ion influx [13] (Fig. 1).

Based on this and other findings, the task force unanimously agreed that there was sufficient evidence to suggest that vitamin D deficiency increases the risk of neurocognitive decline, Alzheimer's disease, depression, stroke and dementia. They also concluded that screening for vitamin D status is of little diagnostic value for Alzheimer's disease and related disorders. This is in line with the conclusion of the Institute of Medicine and the Endocrine Society that screening for vitamin D status [i.e. measuring serum 25(OH)D levels] is not warranted in children or adults without additional risk factors for these disorders [14, 15]. Vitamin D deficiency is so common that it would be more cost-effective to supplement not only older adults but all children and adults as vitamin D deficiency has also been associated with increased risk of seasonal affective disorder, autism, multiple sclerosis and Parkinson's disease [1, 16–18] (Fig. 1). To treat vitamin D deficiency, the Endocrine Society recommends 50 000 IU vitamin D_2 or vitamin D_3 once a week for 8 weeks (equivalent to ingesting ~6600 IU daily) to fill the empty vitamin D stores and raise blood levels of 25(OH)D to what is considered to be a healthy range of at least 30 ng mL^{-1} and preferably 40–60 ng mL^{-1} [15]. To maintain vitamin D sufficiency, 50 000 IU vitamin D_2 or vitamin D_3 once every 2 weeks (equivalent to 3300 IU daily) is effective. Obese adults require at least two to three times more vitamin D to both treat and prevent

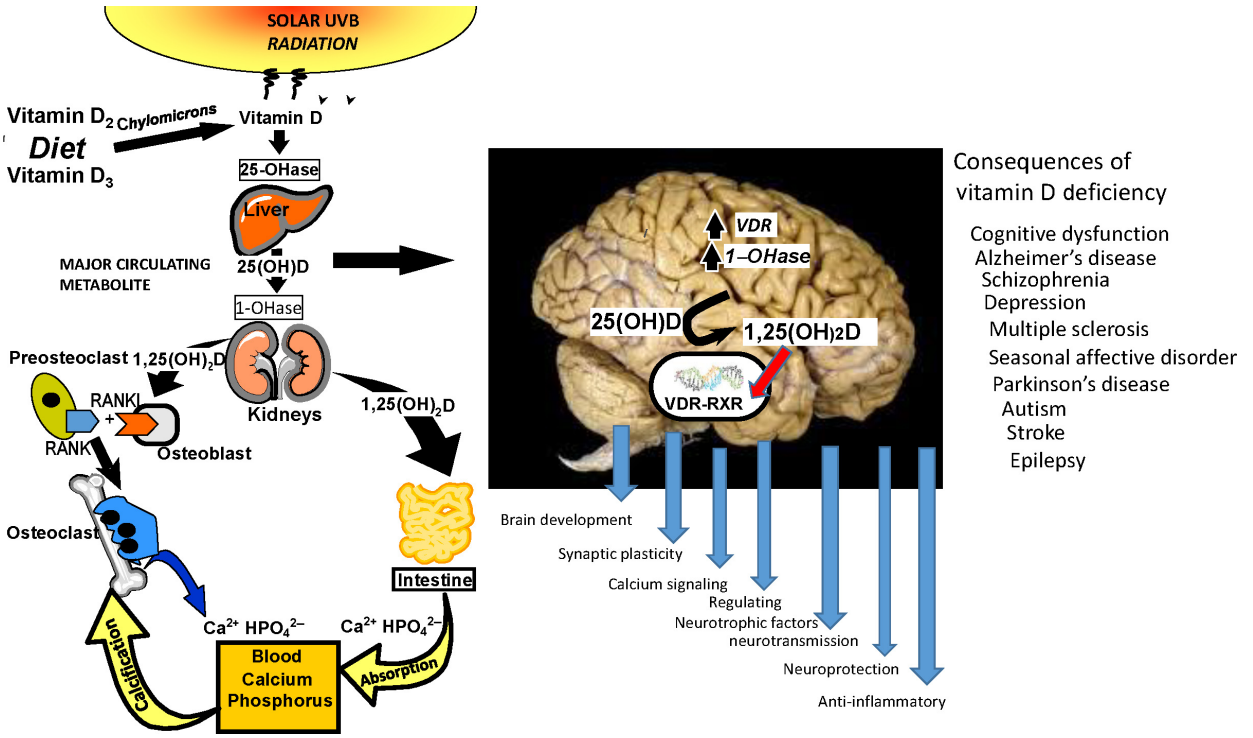

Fig. 1 *Vitamin D produced in the skin from sun exposure or ingested from the diet is converted in the liver by the vitamin D-25-hydroxylase [25-OHase] to 25-hydroxyvitamin D [25(OH)D] and then in the kidneys by the 25-hydroxyvitamin D-1-hydroxylase [1-OHase] to 1,25-dihydroxyvitamin D [1,25(OH)$_2$D]. 1,25(OH)$_2$D interacts with its vitamin D receptor (VDR) retinoic acid X receptor [RXR] in the small intestine to increase in intestinal calcium and phosphate absorption. It interacts with the VDR in osteoblasts inducing signal transduction to increase the number and maturation of osteoclasts. These processes help maintain serum calcium and phosphate in the normal range. In addition, circulating 25(OH)D enters the brain and is converted to 1,25(OH)$_2$D. It interacts with the VDR in neuronal and glial cells resulting in the regulation of a variety of genes and metabolic processes that influences brain development, neurotransmission, neuroprotection amongst other functions. Vitamin D deficiency has been associated with a variety of neurological disorders including neurocognitive dysfunction and Alzheimer's disease. Holick copyright 2014 reproduced with permission.*

vitamin D deficiency due to the sequestration of vitamin D by body fat stores [15]. These recommended regimens for up to 6 years were effective in maintaining blood levels of 25(OH)D in the healthy range of 40–60 ng mL^{-1} without toxicity [19]. Furthermore, sensible sun exposure [i.e. exposure of arms and legs, abdomen and back when appropriate to an amount of sunlight that is about 50% of the time that would cause mild sunburn (one minimal erythemal dose) in the spring, summer and autumn] not only helps supplement the body with its required vitamin D but also has other benefits including inducing the production of beta-endorphin in the skin. This additional benefit may explain why we feel better when outside and exposed to sunlight [20]. Because sun-induced vitamin D synthesis is influenced by latitude, season, time of day, skin pigmentation and ageing, use of the App dminder dminder.info which is free for the iPhone and Android provides useful guidance on how effective the sun is in producing vitamin D and also alerts the user as to when to get out of the sun or to use sun protection to prevent sunburn (i.e. the major cause of skin cancer including melanoma [21]). In addition to all of the neurological health benefits that vitamin D can provide in both the developing and adult brain, including regulating neurotrophic factors, modulating neurotransmission, reducing oxidant activity, maintaining calcium balance and signalling and contributing to synaptic plasticity [3, 22], it also improves muscle function, helps maintain bone health and reduces the risks of infectious diseases, cardiovascular disease, type 2 diabetes, autoimmune diseases and malignant cancers [2, 8, 9, 15]. There is no downside to increasing vitamin D status for all by encouraging vitamin D supplementation and sensible sun exposure.

Conflict of interest statement

No conflict of interest to declare.

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