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Hypothesis

Why Vitamin D in Alzheimer's Disease? The Hypothesis

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Abstract. Scientists have worked for over a century to uncover the basis of Alzheimer's disease (AD) with the ultimate goal of discovering a treatment. However, none of the approaches utilized have defined the exact cause of the disease or an ultimate treatment for AD. In this review, we aim to define the role of vitamin D in AD from a novel and fundamental perspective and attempt to answer the following question: Why should we seriously consider "simple" vitamin D as a "fundamental factor" in AD? To answer this question, we explain the protective effects of vitamin D in the central nervous system and how the action of vitamin D and AD-type pathology overlap. Furthermore, we suggest that the role of vitamin D in AD includes not only vitamin D deficiency and vitamin D-related genes but also the disruption of vitamin D metabolism and action. This suggestion is supported by evidence that the disruption of vitamin D pathways mimic amyloid pathology. We define the term "inefficient utilization of vitamin D" as any alteration in vitamin D-related genes, including receptors, the enzymes related to vitamin D metabolism or the transporters of vitamin D, and we discuss the potential correlation of vitamin D status with the vulnerability of neurons to aging and neurodegeneration. Finally, in addition to the current knowledge that defines AD, we suggest that AD could be the result of a long-term hormonal imbalance in which the critical hormone is vitamin D, a secosteroid that has long been misnamed.

Keywords: Alzheimer's disease, amyloid-β, calcium homeostasis, ERp57/1, 25-MARRS, haplotype, hormone imbalance, oxidative stress, VDR, vitamin D, vitamin D deficiency

INTRODUCTION

Scientists have worked to uncover the mechanisms of Alzheimer's disease (AD) for over a century. Even today, we are unable to radically contribute to the understanding of Dr. Alois Alzheimer. Every article begins with the same definition: Alzheimer's disease is a progressive neurodegenerative disorder observed in the elderly. As meticulously reviewed by Dr. J. Hardy, AD research is based on three basic approaches: 1) the neurochemical approach, which tries to understand the mechanisms of neurotransmitter loss in AD; 2) the pathological approach, which tries to understand the pathologic lesions of AD; and 3) the genetic approach, which focuses on a positional cloning strategy in Mendelian forms of AD to find the causative variants in disease etiology [1]. Each of these approaches has contributed enormously to the understanding of brain function, AD pathology, and the genetic risk factors of AD. Despite this progress, the cause of and the ultimate solution to AD remain unknown [1, 2]. To overcome the current barriers in AD research and determine the cause of AD and an ultimate treatment, a novel and fundamental perspective that encompasses all three approaches is needed.

In this review, we aim to define the potential of the vitamin D (cholecalciferol) [3] approach as a novel

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and fundamental perspective in AD pathology, progression, treatment, and prevention. We also attempt to answer the question: Why should we seriously consider "simple" vitamin D as a "fundamental factor" in AD?

BECAUSE VITAMIN D HAS PROTECTIVE EFFECTS IN THE CENTRAL NERVOUS SYSTEM (CNS)

Vitamin D and vitamin D receptors and metabolic enzymes in CNS

One of the most important factors in the development and maintenance of healthy life is vitamin D status [4, 5]. 1,25-dihydroxyvitamin D_3 or 1,25-dihydroxycholecalciferol ($1,25(OH)_2D_3$), the hormonally active form of vitamin D, is a secosteroid hormone that has been accepted as having neurosteroid-like functions. This hormone exerts its effects via its nuclear hormone receptor, the vitamin D receptor (VDR), which regulates most of the genes as VDR/RXR (retinoid X receptor) heterodimers in many organs [6, 7]. RXR is also a receptor for retinoic acid which was recently reported to inhibit amyloid-β (Aβ) fibril formation *in vivo* [8, 9]. There is data about the effect that vitamin D itself may play a role in DNA recognition for gene regulation [10]. Independent from RXR, VDR is also suggested to stimulate intracellular signaling pathways [11]. Although the extra-renal enzymes that bioactivate vitamin D such as 1α-hydroxylase (CYP27B1) expression is a controversial topic [12, 13], the VDR and 1α-hydroxylase are abundantly expressed in almost all regions of the CNS, particularly regions that are affected by neurodegenerative disorders [14–17]. The other proposed receptor of vitamin D, suggested to initiate cellular responses to vitamin D via transcriptional regulation or cell-signaling mechanisms [18], is also suggested to be co-localized with VDR in plasma membrane [19]. This suggested receptor is a multifunctional membrane receptor and thioredoxin-like protein known as a glucose responsive protein, 58 kDa (GRP58), endoplasmic reticulum protein 57/60 kDa (ERp57 or ERp60), and recently as a vitamin D membrane associated, rapid-response, steroid-binding protein (1,25-MARRS). Due to the novelty of ERp57/1,25-MARRS in the vitamin D field, few studies have addressed the ERp57/1,25-MARRS-mediated regulatory mechanisms of vitamin D in the brain, although recent studies have indicated the presence and function of ERp57/1,25-MARRS in cortical neurons [20–22]. The enzyme 1,25-hydroxyvitamin D_3 24-hydroxylase (24(OH)ase) which is cytochrome P450, family 24, subfamily A, polypeptide 1 (CYP24A1), is the major regulator of $1,25(OH)_2D_3$ levels in tissues. This enzyme accelerates the catabolism of $1,25\ (OH)_2D_3$ to $1,24,25(OH)_3D_3$, thus indicates the utilization of vitamin D [23, 24]. The main function of the 24(OH)ase enzyme is the inactivation of vitamin D [23]. As an auto-regulatory mechanism $1,25(OH)_2D_3$ induces the 24(OH)ase enzyme [24]. Our recent studies have demonstrated that 24(OH)ase mRNA is expressed in both hippocampal and cortical neurons [25].

Vitamin D action in CNS

Current studies indicate that vitamin D is not only crucial in bone diseases, such as osteomalacia and osteoporosis, but that its deficiency is also associated with many other disease states, such as cardiovascular disease; cancer; autoimmune disorders, including multiple sclerosis; mood disorders, psychosis, schizophrenia; and neurodegenerative diseases, such as AD and Parkinson's disease (PD) [14, 16, 26–33]. Recent studies have demonstrated the numerous functions of vitamin D in the nervous system, especially in key survival mechanisms, including the regulation of neurotrophic factor production, oxidative stress mechanisms, calcium (Ca^{2+}) homeostasis, and immune system functions [4, 14, 16, 20, 26, 29, 30, 34, 35] (Fig. 1). A recent review by Eyles et al. underlined the basis for the relation of vitamin D deficiency in early life and the psychiatric disorders with developmental background such as autistic spectrum disorder and schizophrenia by indicating the effects of vitamin D deficiency in neuronal differentiation, axonal connectivity, dopamine ontogeny, and brain structure and function [36]. Correspondingly, vitamin D deficiency has been suggested to trigger premature aging [37], enlarge the lateral ventricles, reduce nerve growth factor (NGF) protein levels, reduce the expression of multiple genes involved in neuronal structure, disrupt brain development, and induce changes in the adult brains of animals [4]. Developmental vitamin D deficient adult rats were reported to display an altered behavioral profile in response to dopamine releasing and blocking agents that are reminiscent of that seen in schizophrenia patients and developmental vitamin D deficiency suggested to alter cell proliferation, apoptosis, neurotransmission, and development of dopaminergic neurons across the embryonic brain [38, 39]. Although limited in number, collateral findings in human

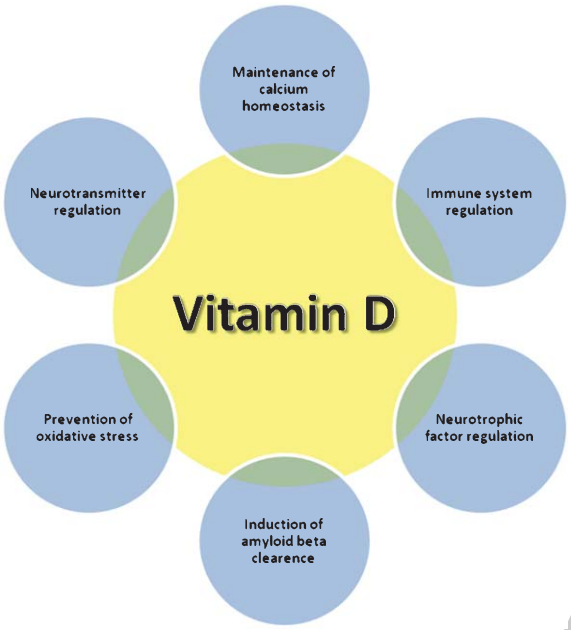

Fig. 1. The basic protective effects of vitamin D in Alzheimer's disease. The suggested protective effects of vitamin D in the Alzheimer's disease were summarized as the regulation of neurotrophic factor production, neurotransmitter levels, oxidative stress mechanisms, calcium (Ca^{2+}) homeostasis and immune system functions, and induction of Aβ clearance [4, 14, 16, 20, 26, 29, 30, 34–36, 52, 103].

studies were also reported. Low levels of plasma 25-dihydroxyvitamin D_3 (25-hydroxycholecalciferol, abbreviated as 25(OH)D) were suggested to be associated with mood disorders, dementia, mild cognitive impairment, PD, AD, and cognitive decline [40–48].

The benefits of vitamin D supplementation in cell cultures, animal models, and human studies

$1,25(OH)_2D_3$ treatment in AD-related cell culture and vitamin D supplementation in animal studies have demonstrated significant benefits. These benefits include the prevention of amyloid-induced cytotoxicity via induction of voltage sensitive calcium channels and inducible nitric oxide synthase (iNOS) [20, 25, 29, 30, 49], the reduction of the number of amyloid plaques and Aβ peptides, the attenuation of inflammation, and the induction of NGF [29, 30, 50]. Furthermore, $1,25(OH)_2D_3$ supplementation in AD-related cell culture and animal studies has been shown to stimulate Aβ phagocytosis, clearance, and brain to blood efflux [51–55]. $1,25(OH)_2D_3$ has been reported to have a potential role in the treatment of CNS injuries [14], and increased consumption of vitamin D and fish oil has been shown to prevent neurodegeneration [53]. $1,25(OH)_2D_3$ was reported to increase neurite outgrowth in embryonic hippocampal neurons [34, 56]. Vitamin D_2 (ergocalciferol) treatment that was initiated immediately after lesioning was suggested to increased axogenesis, axon diameter, and higher functional recovery [57]. Additionally, $1,25(OH)_2D_3$ was suggested to alter cholinergic, dopaminergic, and noradrenergic neurotransmitter systems in CNS [36]. This effect maintained by the regulation of choline acetyl transferase enzyme [58], cholinergic receptors [59], dopamin 1 (DA1) and DA2 receptors [60, 61], and tyrosine hydroxylase enzyme [62, 63]. In addition, ERp57/1,25-MARRS and calreticulin were reported to prevent Aβ aggregation in cerebrospinal fluid [21] and to induce axonal growth and re-growth when stimulated with diosgenin, even under Aβ-induced damaging conditions [22]. Vitamin D binding protein (VDBP), or group specific component globulin (GC-globulin), which is the major transporter of vitamin D, has also been suggested to reduce Aβ-aggregation and prevent Aβ-mediated cell death [64]. Finally, a novel AD treatment protocol, Alzheimer's disease – input of vitamin D with memantine assay (AD-IDEA), by Annweiler and Beauchet, that combines vitamin D and memantine (a commonly used AD drug) demonstrated the benefits of AD-IDEA over memantine alone by increasing the Mini-Mental State Examination (MMSE) scores of patients by an average of 4 points [65].

BECAUSE THE MECHANISMS OF AD-TYPE PATHOLOGY AND VITAMIN D ACTIONS OVERLAP

Neurotrophic factor regulation

After the discovery of selective deficits in cortical markers of cholinergic neurons in AD patients [1, 66, 67], researchers focused on understanding the basis of cholinergic transmission in AD. Scientists utilized cholinesterase inhibitors to increase synaptic acetylcholine levels [1, 49]. Given that cholinesterase inhibitors had an insufficient effect on cognitive decline [68], Tuszynski et al. transplanted NGF-overexpressing cells into the brains of AD patients and managed to reduce the rate of cognitive decline by 36% [69]. Replacement of neurotrophic factors, such as NGF, glia-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), and neurotrophins, and stem cell-related approaches to the treatment of AD are still being investigated [70].

$1,25(OH)_2D_3$ has been reported to have an effect on neurotrophic factor regulation [16]. Vitamin D has been suggested to have protective effects in the nervous system through the regulation of NGF, BDNF, GDNF, and neurotrophins [16, 71–73]. NGF regulation by vitamin D has been demonstrated in several cell types [4, 16, 26, 29, 30, 74–78].

Calcium homeostasis

Almost 25 years ago, the role of Ca^{2+} dysregulation in the aging brain and in AD gave rise to the "Ca^{2+} hypothesis of brain aging and dementia" [79]. Ca^{2+} influx associated with action potentials was reported to induce larger Ca^{2+}-dependent after hyperpolarization and thereby impair short-term synaptic plasticity in brain neurons from aging rodents and rabbits compared to neurons from younger animals [80]. On the other hand, Aβ-induced membrane lipid peroxidation can also impair the function of membrane Na^+/K^+- and Ca^{2+}-ATPases and glucose and glutamate transporters. This impairment results in membrane depolarization and a decrease in cellular ATP levels, which induces the elevation of basal intracellular calcium levels [81–84]. $A\beta_{1\text{-}42}$ and $A\beta_{1\text{-}40}$ were also reported to form calcium-permeable pores and non-selective ion channels in the lipid bilayer of membranes. This event has been suggested to be one of the prime inducers of Aβ-mediated neurotoxicity [85]. In addition to Aβ-induced calcium influx, Ca^{2+} levels have been reported to become elevated with increasing amounts of L-type voltage sensitive calcium channels (LVSCC) in the aging brain and in AD [79]. Cell death observed in the hippocampus was demonstrated to be consistent with the significant increase of LVSCCs in AD brains [86]. Aβ produced by hypoxia has been reported to interact directly with the LVSCC-A1C subunit. This interaction either promotes the trafficking of channels toward or inhibits the retrieval of channels from the plasma membrane. This results in increased Ca^{2+} channel protein at the cell membrane and thus increased Ca^{2+} conductance [87].

The ultraviolet-dependent synthesis of vitamin D has continued for over 750 million years on earth. Although there is not much information about the biological functions of vitamin D in primitive organisms, it has been suggested that in order to evolve, the regulation of calcium metabolism was necessary to produce a skeleton made of calcified bone in vertebrates [43, 88]. Thus, the contribution of vitamin D to the regulation of Ca^{2+} homeostasis in another major organ that uses calcium, the brain, is not surprising. Although the regulation of Ca^{2+} homeostasis by vitamin D in other tissues includes both calcium channels and calcium binding proteins, thus far, only voltage sensitive calcium channels have been reported to be regulated by vitamin D in hippocampal and cortical neurons [20, 25, 29, 30, 49, 89, 90]. In addition, our recent studies indicated that vitamin D prevents the Aβ-induced expression of LVSCC-A1C in cortical and hippocampal neurons [30, 49] and that the disruption of the vitamin D-VDR and the -ERp57/1,25-MARRS pathways results in induction of LVSCC-A1C or -A1D expression regardless of the presence of Aβ [20, 25, 29].

Oxidative stress and immune response

In addition to being a progressive neurodegenerative disorder, AD is considered to be an inflammatory brain disease [91] due to the recruitment of reactive astrocytes and microglia around amyloid plaques, the major pathological hallmark of AD. Elevated levels of cytokines and chemokines around amyloid plaques in AD also contribute to the immune response in AD brains [92–94]. Induced cytokines mark Aβ aggregations as sites of inflammation for the astrocytes and microglia in the affected brains [95, 96]. Moreover, a systemic increase of the pro-inflammatory cytokine, tumor necrosis factor alpha (TNFα), in AD has been reported in various studies [97–100].

Vitamin D is known to be a regulator of many cytokines [22, 101] in multiple types of cells of the immune system and in many diseases, including multiple sclerosis, PD, epilepsy, depression, and schizophrenia. The neuro-immunomodulatory effects of vitamin D have been meticulously reviewed by Fernandes de Abreu et al. [102]. Recent studies by Mizwicki et al. supplied valuable data on the ability of vitamin D to induce cytokines and macrophages to increase the clearance of Aβ in AD patients [52, 103]. Briones and Darwish reported that vitamin D increased clearance of Aβ in aged rats too and the result was correlated with the mitigation of inflammatory state by vitamin D supplementation [54].

iNOS (NOS2) contributes to the synthesis of nitric oxide (NO) and is another major Aβ-induced component that contributes to the immune response. iNOS immunoreactivity was observed in the neurons and astrocytes of AD patients [104, 105]. Aβ-mediated iNOS induction was reported to be caused by an elevation of interleukin 1 beta (IL1β) and TNFα in astrocytes and microglia [106]. iNOS and Aβ were reported to induce the accumulation of each other

[91]. Furthermore, a deficiency in iNOS was shown to significantly suppress Aβ accumulation, reduce phosphorylated tau aggregations, reduce protein tyrosine nitration and protect against gliosis [91].

$1,25(OH)_2D_3$ was tested in various cell lines and animal models to determine its ability to control iNOS-mediated NO production. $1,25(OH)_2D_3$ was shown to attenuate iNOS expression in monocytes, macrophages, and reactive microglia and to reduce the immune response and apoptotic cell death in a rat model of brain inflammation [107, 108]. A recent study by our group suggested that $1,25(OH)_2D_3$ prevents Aβ-induced iNOS expression and that iNOS expression is regulated by the vitamin D-VDR pathway in cortical neurons. Additionally, disruption of this pathway resulted in the induction of iNOS expression regardless of the presence of Aβ [20].

BECAUSE AD PATIENTS ARE SIGNIFICANTLY VITAMIN D DEFICIENT

The efficiency of vitamin D synthesis in the body depends on factors such as pigmentation of the skin, the geographic latitude where an individual lives, the amount of sunlight present, sunlight exposure, and the age of the individual [109]. The primary cause of vitamin D deficiency has been suggested to be geographical conditions, seasons, cultural features, and nutrition. After re-evaluating the data of the 3rd National Health and Nutrition Survey (1988–1994) in the USA, Khazai et al. reported that 61% of the white population and 91% of the African American population have vitamin D deficiency [110]. Similar results were reported in different populations [14]. Although vitamin D deficiency is very common in healthy and young individuals of developed countries, it is particularly prevalent in elderly persons with hip fractures or institutionalized elderly subjects. Studies have reported that 65–74% of inpatients and 87% of patients who have been given medical care have vitamin D deficiency [110].

Significantly low levels of plasma 25(OH)D have been reported in individuals suffering from AD, PD, mood disorders, and cognitive decline [40, 43–46, 48, 111]. A study by Oudshoorn et al. demonstrated that vitamin-D-sufficient patients have significantly higher MMSE scores, compared to vitamin-D insufficient ones [47]. Although longitudinal studies are too few in number to be conclusive, they have indicated that low levels of vitamin D are associated with a substantial cognitive decline in the elderly population [46]. Furthermore, they showed that baseline vitamin D deficiency predicted the onset of non-Alzheimer dementias [41]. Importantly, the association of elevated serum 25(OH)D concentrations with a lower risk of mild cognitive impairment and the association of low 25(OH)D concentrations with mild cognitive impairment status in older, non-demented people with subjective memory complaint in the study of Annweiler et al. indicate that hypovitaminosis D may participate in the dementia process from the prodromal stages [42]. In addition, a systematic review and meta-analysis by Annweiler et al. provided evidence that lower serum 25(OH)D concentrations predict executive dysfunction, especially for mental shifting, information updating, and processing speed [112]. A recent meta-analysis by the same group indicated that AD cases have lower serum 25(OH)D concentrations than aged matched healthy controls [113]. An important recent study by Afzal et al. indicated an association of reduced plasma 25(OH)D with increased risk of the combined end point of AD and vascular dementia in a prospective cohort study that was conducted on 10,186 individuals with 30 years follow-up [114]. Promising studies on the macrophages of AD patients showed that vitamin D strongly stimulated phagocytosis and clearance of Aβ while protecting against apoptosis [51, 52]. Fiala and Mizwicki have suggested that the maintenance of adequate endocrine, paracrine, and/or autocrine production of vitamin D and docosahexaenoic acid (DHA)-derived lipidic modulators by the increased consumption of vitamin D and fish oil could prevent neurodegeneration in some subjects [53]. Finally, the novel AD treatment protocol (AD-IDEA) by Annweiler and Beauchet combined vitamin D and memantine (a commonly used AD drug) and observed improved results compared to memantine alone [115].

Additionally, vitamin D deficiency is also suggested to be associated with cerebrovascular alterations. Buell et al. reported associations between 25(OH)D concentrations and diagnoses of AD and stroke (with and without symptoms of dementia) and specific indicators of vascular pathology on MRI [116]. Recent meta-analysis indicated the inverse relation between serum 25(OH)D levels and risk of stroke [117, 118].

BECAUSE GENETIC STUDIES OF AD IMPLICATE VITAMIN D RELATED GENES AS RISK FACTORS

Additional risk genes for AD on chromosome 12 were recently reported [119–123]. The VDR gene is in

near this region. Our study in 2007 provided the first evidence for a possible genetic association between AD and VDR by indicating that a polymorphism of the VDR gene might increase the risk of AD by 2.3 times [28]. In 2009, according to their genome wide association study conducted on 518 late-onset AD cases that analyzed 555,000 SNPs, Beecham et al. showed that among the number of nearby candidate genes in the 12q13 region, VDR is the most probable risk gene for developing AD [123]. Single nucleotide polymorphisms (SNPs) in the VDR gene might be a cause for some of the alterations in the vitamin D-VDR pathway [28, 124]. These SNPs have been studied in various diseases for a long time [125]. The only SNP that results in the production of an elongated form of VDR (by three additional amino acids) is caused by a SNP in the FokI restriction enzyme in exon 2 of the VDR gene [125]. The SNPs which are recognized by the BsmI, Tru9I, and ApaI restriction enzymes are located in intron 8. The other SNP which is recognized by the TaqI restriction enzyme is located in exon 9. These intronic polymorphisms are believed to have a strong linkage disequilibrium with the polymorphisms in the 3′ untranslated region that are known to be involved in regulating the expression of the VDR gene [125]. Correspondingly, recent studies indicated an association between VDR polymorphisms and cognitive decline [126, 127], AD [28, 124, 128], and PD [129]. Besides, our recent study suggested that "TaubF" haplotype of the VDR gene is a risk factor in AD [124].

Recent studies have also demonstrated that polymorphisms of the low density lipoprotein receptor-related protein 2, also called megalin, a plasma membrane transporter of vitamin D, are associated with AD [130, 131] and cognitive decline [127].

BECAUSE Aβ TARGETS VITAMIN D METABOLISM AND ACTION

The first study that provided an indication of the potential role of vitamin D and its receptor, VDR, in AD was published in 1992 by Sutherland et al. [132]. They reported reduced levels of VDR mRNA in the hippocampal CA1 and CA2 pyramidal cells of AD patients [132]. In 2011, a study by our group demonstrated that Aβ induces neurodegeneration not only by inducing the expression of voltage sensitive calcium channels and altering NGF synthesis but also by significantly suppressing the expression of VDR [30]. This study was the first report that indicated the direct effect of one of the pathological hallmarks of AD on VDR and gave a possible molecular explanation to the findings of Sutherland et al. Our recent findings took this event one step further and indicated that the expression of mRNA for 24(OH)ase, the enzyme that accelerates vitamin D catabolism, is induced by Aβ in hippocampal neurons [49]. This finding suggests that the involvement of vitamin D with AD not only includes vitamin D deficiency and vitamin D-related genes but also the disruption of vitamin D metabolism and action.

On the other hand, VDBP (formerly known as Gc-globulin),the major carrier of vitamin D in the blood and a regulator of vitamin D bioavailability [133], was reported to be elevated in the cerebrospinal fluid (CSF) of AD patients and was even suggested to be a biomarker for AD [134, 135]. In addition, Moon et al. demonstrated the interaction of VDBP with Aβ and suggested that VDBP prevents Aβ accumulation in transgenic mice [64]. From another perspective, the findings of Moon et al. [64] and others who showed increased levels of VDBP in CSF samples of AD patients [135, 136] might also be interpreted as the inability of vitamin D to reach neurons and glial cells in the CNS.

BECAUSE THE DISRUPTION OF VITAMIN D PATHWAYS MIMIC Aβ TOXICITY

The most crucial of our recent studies indicated that the disruption of vitamin D pathways (vitamin D-VDR or vitamin D- ERp57/1,25-MARRS) by post transcriptional gene silencing, regardless of whether it was from the presence of Aβ, resulted in the induction of voltage sensitive calcium channels, A1C, A1D, and iNOS and attenuated NGF. Each of these events has the potential to induce Aβ accumulation and neurodegeneration [20, 25, 29]. These studies showed that VDR siRNA- or Aβ-treated neurons induced very similar amounts of iNOS mRNA (1.6- and 1.3-fold increases, respectively) and LVSCC-A1C mRNA (2.7- and 1.8-fold increases, respectively) compared to untreated neurons [20, 29, 30].

On the other hand, our recent findings demonstrated the presence of VDR and 24(OH)ase mRNA in both hippocampal and cortical neurons [25]. The high expression of the receptor and the enzyme in hippocampal neurons led us to speculate that hippocampal neurons require large amounts of vitamin D; thus, cognitive function requires large amounts of vitamin D [25]. Based on these results, we suggest that the disruption of vitamin D-related mechanisms contributes to cognitive decline. This hypothesis is particularly rel-

evant considering that the hippocampus is one of the earliest affected targets in AD.

Although no studies have been published on the effects of the disruption of vitamin D-related pathways on tau pathology in AD, our unpublished results predict the existence of an effect on tau hyperphosphorylation-related mechanisms.

BECAUSE THE ISSUE IS NOT ONLY VITAMIN D DEFICIENCY BUT ALSO THE INEFFICIENT UTILIZATION OF VITAMIN D

Our studies indicated the presence of another risk factor given that the vitamin D pathway is the target of Aβ-induced toxicity in AD. Briefly, Aβ renders neurons deficient in vitamin D by increasing the degradation of active vitamin D and its receptor, VDR [30, 49]. Aβ may disrupt the utilization of vitamin D in the brain, even if the systemic level of vitamin D is sufficient. In our studies, we have termed this condition "inefficient utilization of vitamin D" [20, 25, 29, 49]. Any alteration in vitamin D related genes, including its receptors (VDR and ERp57/1,25-MARRS), the enzymes that are related to its metabolism and the transporters of vitamin D, may also result in the inefficient utilization of vitamin D; thus, increasing the vulnerability of neurons to aging and neurodegeneration [20, 25, 28–30, 49, 124]. This suggestion is supported by the association of VDR and megalin polymorphisms observed in AD [28, 123, 124, 127, 131] as well as the toxic effects of VDR and ERp57/1,25-MARRS suppression in neurons [20, 25, 29]. Vitamin D deficiency (or hypovitaminosis D) has the potential to result in the accumulation of Aβ through the disruption of calcium homeostasis, an increase in oxidative stress or many other mechanisms that may exacerbate

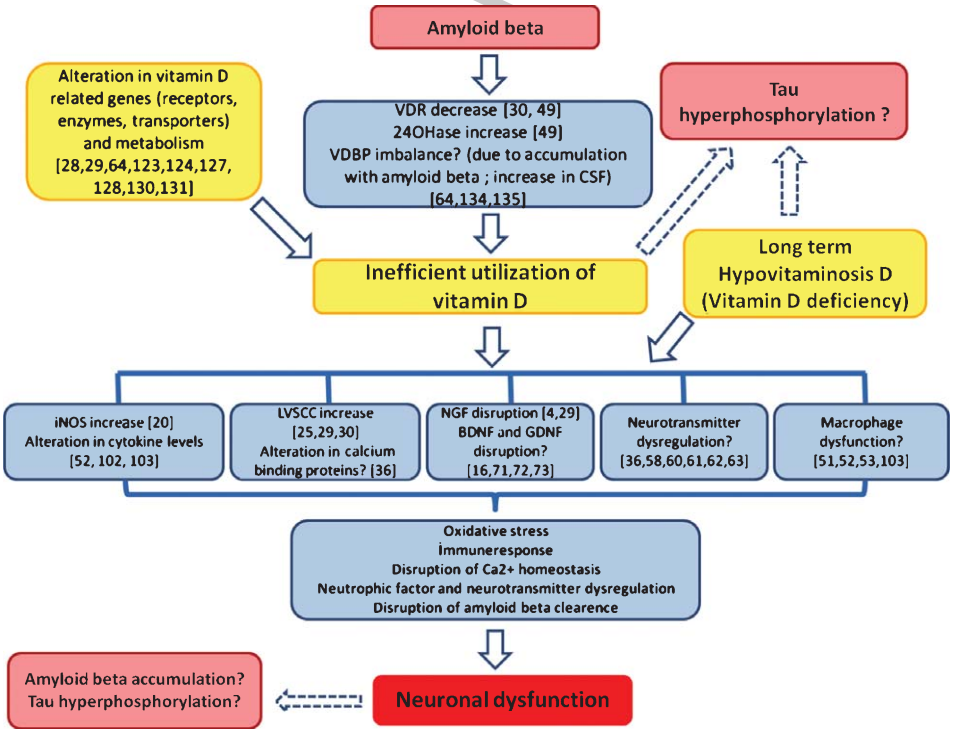

Fig. 2. The hypothesis of inefficient utilization of vitamin D and long-term vitamin D deficiency in Alzheimer's disease (AD). Any alteration in vitamin D related genes, including its receptors, the enzymes that are related to its metabolism and the transporters of vitamin D, may increase the vulnerability of neurons to aging and neurodegeneration. Aβ may disrupt the utilization of vitamin D in the brain, even if the systemic level of vitamin D is sufficient. In our studies, we have termed these conditions "inefficient utilization of vitamin D". Vitamin D deficiency (or hypovitaminosis D) has the potential to result in the accumulation of Aβ through the disruption of calcium homeostasis, an increase in oxidative stress or many other mechanisms that may exacerbate the inefficient utilization of the remaining vitamin D. We suggest that hypovitaminosis D and inefficient utilization of vitamin D are two different conditions, but crosstalk between the two should not be ignored in AD-type pathology. The potential of either long-term hypovitaminosis D or inefficient utilization of vitamin D to be a prime inducer of neurodegeneration in aging and AD should not be underestimated.

the inefficient utilization of the remaining vitamin D. Thus, the question is, "should the inefficient utilization of vitamin D and hypovitaminosis D be evaluated as different mechanisms in AD?" We suggest that hypovitaminosis D and inefficient utilization of vitamin D are two different conditions, but crosstalk between the two should not be ignored in AD-type pathology. Consequently, the potential of either long-term hypovitaminosis D or inefficient utilization of vitamin D to be a prime inducer of neurodegeneration in aging and AD should not be underestimated (Fig. 2).

BECAUSE NEURODEGENERATION IS A LONG-TERM PROCESS, AS ARE VITAMIN D DEFICIENCY AND THE INEFFICIENT UTILIZATION OF VITAMIN D

One of the most significant changes in AD research in last 30 years was catalyzed by the proposal of new criteria and guidelines for AD diagnosis. In contrast to the 1984 criteria, which required memory loss and a decline in thinking abilities severe enough to affect daily life before AD could be diagnosed, the modern criteria for diagnosis included a preclinical or presymptomatic stage. This reflects the current thinking that AD creates changes in the brain as many as 20 years before symptoms occur [2]. Although this radical change in the diagnosis does not establish diagnostic criteria for the clinicians to use now, it states that additional biomarker research is needed before these early stages of AD can be diagnosed [2]. $A\beta_{1\text{-}42}$, total tau, and hyperphosphorylated tau in the CSF are now suggested to be biomarkers of AD which are capable of indicating the presence of the disease [2, 137, 138]. Studies also suggest that VDBP in the CSF could be used as a biomarker for AD [64, 134, 135]. We know that vitamin D deficiency is a problem not only for the elderly but also for younger individuals [110]. Given the fact that vitamin D deficiency and the inefficient utilization of vitamin D might occur concurrently over decades in humans, the amount of vitamin D that the brain needs to maintain its function might differ from the rest of the body; thus, small changes in the brain microenvironment may occur long before the clinical stages of AD are apparent.

CONCLUSION

Similar to many other living organisms on earth, humans have evolved to live in daylight. After the industrial revolution, the daily life of a human dramatically changed, and individuals in developing countries began to spend most of their days in closed quarters, seeing little or no sunlight. Thus, humans who have evolved to use the sun to produce vitamin D, which regulates many mechanisms crucial to life, are now largely deprived of this source. We are well aware that it is not easy for humans to adapt to such an extreme environmental change. However, just as we did in many other aspects of life, we ignored millions of years of evolution and underestimated the consequences of such an extreme change on humans. Recently a systematic review by Rush et al. supported this idea by reporting an inverse association between low vitamin D status and all-cause premature mortality, especially in the elderly [5]. The study by Dr W.B Grant also pointed out the importance and the possible consequences of such changes especially in nutrition [139]. Finally Afzal et al. reported the importance of long-term effect of vitamin D deficiency by indicating an association of reduced plasma vitamin D levels with increased risk of the combined end point of AD and vascular dementia in a prospective cohort study with 30 years follow-up [114]. Thus, the question remains: is this molecule, which is synthesized from the sun, "the source of life", merely a simple vitamin?

Vitamin D is a secosteroid hormone with neurosteroid-like properties. The consequences of long-term deficiency and/or inefficient utilization of vitamin D, especially for the brain environment, should not be underestimated. Accumulating evidence indicates that either hypovitaminosis D or inefficient utilization of vitamin D may cause neurons to be vulnerable to aging and neurodegeneration. AD might be interpreted as a result of a long-term hormonal imbalance in which the hormone is vitamin D, a secosteroid that has long been misnamed.

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