Vitamin D deficiency and Alzheimer disease: Common links

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Abstract

Vitamin D (VitD) deficiency is a worldwide epidemic with estimates of 1 billion affected. In addition to the classically known roles of VitD in calcium regulation and bone health, recent studies demonstrated VitD to be an essential/vital neurosteroid hormone playing a wide variety of essential protective and regulatory roles in the brain. This paper reviews much of the mounting evidence of the detrimental effects of VitD deficiency on the brain and the association of many of these common links with Alzheimer’s disease (AD). We also discuss the beneficial effects seen from VitD supplementation. Based on this accumulation of studies, we propose that VitD screening should be performed at least in those individuals at risk for VitD deficiency and AD. With appropriate medical counsel, those found to be VitD deficient should be considered for appropriate supplementation.

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1. Introduction

The natural course of brain aging as well as age-related neurodegenerative disorders are thought to be a contributing cause as well as a result of increases in reactive oxygen and reactive nitrogen species (ROS/RNS) in the brain (Butterfield and Lauderback, 2002; Calabrese et al., 2004, 2006b; Poon et al., 2004). These increases in ROS/RNS production occur through growing metabolic inefficiency, breakdown of antioxidant defenses, and free radical damage to metabolic and protective machinery (Anantharaman et al., 2006; Tangpong et al., 2008). Dietary deficiencies can lead to, or at least exacerbate, age-related failure of protective mechanisms (Bourre, 2006; Watson and Preedy, 2013).

Long-known historical functions of Vitamin D (VitD) center on the uptake and use of calcium (Ca\(^{2+}\)) and phosphate (P\(_i\)) primarily for the purposes of bone mineralization, bone resorption, and bone remodeling (DeLuca, 1986). However, it is now recognized that there are many other VitD functions. Mounting evidence supports significant roles for VitD in the brain, and VitD deficiency has been shown to have a long list of neurological consequences. This review provides an overview of the functions of VitD that affect the brain and, more specifically, the effects of VitD insufficiency that may contribute to Alzheimer’s disease (AD).

2. Alzheimer’s disease

2.1. Incidence and overview

AD is a progressive neurodegenerative disorder characterized by a long preclinical stage (PCAD), often progressing into mild cognitive impairment (MCI) and eventual AD (Aluisio et al., 2010a; Mosconi, 2005; Sperling et al., 2011). Currently more than 5 million Americans are estimated to have AD, with 35 million persons worldwide, numbers that are ever-increasing (2014a). Of these, approximately two-thirds are estimated to have AD, with 35 million persons worldwide, numbers that are ever-increasing (2014a). Of these, approximately two-thirds are estimated to have AD, with 35 million persons worldwide, numbers that are ever-increasing (2014a).

2.1.1. Potential for VitD in human therapeutic intervention

The classical primary pathological hallmarks of AD frequently used for diagnosis confirmation are amyloid plaques and NFTs. Amyloid plaques that accumulate outside neurons are made primarily of amyloid beta (A\(_{\beta}\)) peptide, a product of improper cleavage of amyloid precursor protein (APP). NFTs, whose principal component is hyperphosphorylated tau, a microtubule associated protein with a growing number of identified potential functions, build up within neurons. The Alzheimer’s Association also lists oxidative stress, brain inflammation, and cardiovascular disease comorbidity as pathological characteristics of AD. Other pathological substrates include brain atrophy and neurochemical changes (Yaari and Corey-Bloom, 2007). Brain atrophy includes widening sulci, shrinkage of gyri, and loss of synapses, though the specificity of the latter to AD has been questioned (Scheff et al., 2014). Neurochemical changes include well documented decreases in cholinergic activity, as well as changes including glutamate, norepinephrine (NE), and serotonin as well as biomarkers (Rapoport and Nelson, 2011).

Increased A\(_{\beta}\) production and deficits in phagocytosis of A\(_{\beta}\) by the immune system combined with decreased A\(_{\beta}\) degradation and clearance contribute to A\(_{\beta}\) accumulation and soluble A\(_{\beta}\)-induced inflammation in AD (Chagas et al., 2012; Mizwicki et al., 2012, 2013). A\(_{\beta}\) clearance from the brain by innate immune cells helps maintain normal brain function. In addition to A\(_{\beta}\) increases, decreased glucose utilization in the brain is among the earliest known measurable changes that occur during the initiation and progression of AD perhaps even occurring prior to amyloidogenesis possibly decades before onset of clinical symptoms (Pedros et al., 2014; Sperling et al., 2011; Yao et al., 2009). This has led researchers to explore possible connections between AD and diabetes (de la Monte et al., 2006; Steen et al., 2005; Butterfield et al., 2014a).

The Ca\(^{2+}\) hypothesis of AD suggests that A\(_{\beta}\) detrimentally alters neuronal Ca\(^{2+}\) signaling pathways that are involved in cognition (Berridge, 2010; Mattson, 1994). Neurotoxic A\(_{\beta}\) oligomers increase Ca\(^{2+}\) entry into cells and may contribute to the release of Ca\(^{2+}\) from internal endoplasmic reticulum stores (Berridge, 2010, 2011). This dysregulation of Ca\(^{2+}\) is associated with learning and memory deficits like those that occur early in the progression of AD potentially preventing long-term storage of newly acquired memories (Berridge, 2010). As A\(_{\beta}\) accumulates, progressive increases in resting Ca\(^{2+}\) occur, which may mimic a small global elevation of Ca\(^{2+}\) that occurs in slow oscillations in the brain during a phase of memory processing in which memories are erased during sleep and not retained for memory consolidation and storage (Berridge, 2014). A\(_{\beta}\) deregulates this Ca\(^{2+}\) signaling, interfering with memory retention and inducing inflammatory responses in the brain (Berridge, 2014). Long-term dysregulation of Ca\(^{2+}\) levels and signaling can contribute to neurodegeneration seen in later stages of AD (Berridge, 2010, 2011; Camandola and Mattson, 2011; Hensley et al., 1995a; Mark et al., 1995; Mattson, 1994).

Though new evidence exists to suggest other potential functions of tau protein, it is long established that tau within neurons serves to stabilize microtubules for anterograde and retrograde transport along axons providing needed organelles and other factors, including mitochondria to the synapse (Brandt et al., 2005; Ko et al., 2005). Tau function in this capacity is regulated by phosphorylation/dephosphorylation by kinases and phosphatases. Hyperphosphorylation of tau results in the disconnection of tau from microtubules resulting in microtubule disassembly. If sustained, the synapse does not receive needed materials potentially leading to neuronal death. Hyperphosphorylated tau aggregates within the neuron to form NFTs, one of the major pathological hallmarks of AD mentioned (Braak and Braak, 1995).

2.2. AD pathology

The classical primary pathological hallmarks of AD frequently used for diagnosis confirmation are amyloid plaques and NFTs. Amyloid plaques that accumulate outside neurons are made primarily of amyloid beta (A\(_{\beta}\)) peptide, a product of improper cleavage of amyloid precursor protein (APP). NFTs, whose principal component is hyperphosphorylated tau, a microtubule associated protein with a growing number of identified potential functions, build up within neurons. The Alzheimer's...
the impairment of short-term, and progressing to the loss of remote memory. As the disease progresses, memory issues worsen and are accompanied by impairments in executive function, logical reasoning, language, visuospatial function, motor function, behavioral, personality, and psychiatric changes (Yaari and Corey-Bloom, 2007). Less prevalent symptoms include anosmia, sleep disturbances, and seizures. Ability to perform activities of daily living gradually and progressively declines. Depression occurs in up to 50% of individuals with AD (Yaari and Corey-Bloom, 2007; Vos et al., 2015).

2.4. Risk factors

Risk factors for AD include age, gender, family history, genetics, and head trauma, and may include low educational attainment and environmental factors. Advancing age continues to be the biggest single known risk factor for AD with prevalence doubling approximately every five years after age 65 (Yaari and Corey-Bloom, 2007). Gender also contributes to AD risk as approximately two-thirds of diagnosed AD sufferers are women, even after correcting for small differences in overall lifespan (Selkoe, 2001). A family history of AD greatly increases one’s risk of AD especially with diagnosed AD in first-degree relatives (van Duijn et al., 1991), possibly as a combination of genetic and environmental factors. Early onset AD generally occurs during the fifth decade of life, and accounts for fewer than 5% of AD cases. Inheritance of early-onset AD is attributed to mutated genes for presenilin-1 (chromosome 14), presenilin-2 (chromosome 1), and APP (chromosome 21). Down syndrome subjects have a third copy of the gene for APP (chromosome 21) likely accounting for the early appearance of AD pathology in these individuals. Late onset AD accounts for the vast majority of AD cases.

Though no definitive genetic link has been found to cause late-onset AD, susceptibility genes increase the risk of developing AD. For example, an individual’s apolipoprotein E (ApoE) allele status has been shown to greatly affect the risk for AD. The primary role of ApoE is cholesterol transport, regulating lipid transport and injury repair in the brain. Additionally, ApoE plays roles in glucose metabolism, mitochondrial function, neuroinflammation, neuronal signaling, and Aβ processing (Dorey et al., 2014; Liu et al., 2013). Three different alleles of human ApoE exist, ApoE2, ApoE3, and ApoE4, conferring differential risk for AD. ApoE4 is the highest genetic risk factor for late-onset AD. ApoE3 allele confers an intermediate risk, while the ApoE2 allele confers a low risk and is potentially neuroprotective (Corder et al., 1993; Liu et al., 2013; Seripa et al., 2011). These altered risks seem to hold across both genders and all races (Farrer et al., 1997), though the high risk for AD conferred by ApoE4 seems to be even greater in women (Anttila et al., 2002; Mortensen and Hogh, 2001; Payami et al., 1996; Qiu et al., 2004), and evidence exists that ApoE2 may be more neuroprotective in men than in women (Johnson et al., 1998; Qiu et al., 2004).

2.5. Inflammation, apolipoprotein A1, and AD

Apolipoproteins have been shown to be integrally related to Alzheimer’s disease pathology (Liu et al., 2013). In addition to the differential risk for AD afforded by ApoE status, changes to apolipoprotein A1 (ApoA1) in AD contribute to AD progression. Many Aβ-binding proteins including ApoE, ApoJ, and ApoA1 are known to accumulate in amyloid deposits (Moon et al., 2013). Like ApoE, ApoA1 plays major roles in cholesterol transport as well as regulation of inflammation (Aluise et al., 2011; Hyka et al., 2001; Keeney et al., 2013b; Quazi and Molday, 2011; Rader and Daugherty, 2008). Studies have shown decreased levels of ApoA1 in the plasma of AD subjects compared to healthy controls (Kawano et al., 1995; Liu et al., 2006; Merched et al., 2000). Decreased risk of dementia was associated with higher ApoA1 concentrations while lower ApoA1 levels in AD patients correlated with more severe cognitive impairment (Merched et al., 2000; Saczynski et al., 2007). In a mouse model of AD, ApoA1 overexpression protected learning and memory function, while ApoA1 deficiency increased memory deficits (Lewis et al., 2010). Studies have shown that ApoA1 binds to Aβ (Golabek et al., 1995), is present in amyloid plaques (Wnisiewski et al., 1995), and prevents Aβ-induced toxicity in vitro (Koldanova et al., 2001) supporting a protective role of ApoA1 in AD pathology. Carriers of the high AD risk ApoE4 allele have lower levels of ApoA1 (Raygani et al., 2006). ApoA1 oxidation leads to elevation of peripheral levels of the inflammatory cytokine tumor necrosis factor-α (TNF-α) that can cross the blood–brain barrier (BBB) activating microglia and contributing to further inflammatory and oxidative cascades known to lead to neuronal death (Aluise et al., 2011; Liu et al., 2010b; Keeney et al., 2013b; Tangpong et al., 2008; Butterfield, 2014). Decreased plasma levels of ApoA1 are associated with late-onset AD and highly correlated with the severity of disease (Kawano et al., 1995; Merched et al., 2000).

2.6. Oxidative stress in disease progression

As aging progresses, an inevitable general decline in overall health occurs (Harman, 2001; Perluigi et al., 2014; Singh and Newman, 2011). Combinations of the aforementioned AD risk factors and pathological hallmarks prime the brain for the cascade of events providing risks to develop AD. One such neurodegenerative path is oxidative stress (Butterfield et al., 2001; Butterfield and Lauderback, 2002; Butterfield and Stadtman, 1997; Hensley et al., 1995b; Nunomura et al., 2001). Production of dangerous ROS/RNS is a natural and sometimes beneficial outcome of aerobic processes in vivo (Butterfield and Dalle-Donne, 2014; Dasuri et al., 2013; Halliwell, 2011; Sies, 2015; Valko et al., 2007). Metabolic processes in the mitochondria are one source of ROS (Adam-Vizi, 2005; Halliwell and Gutteridge, 1984; Scialo et al., 2013). Antioxidant defenses help to keep ROS/RNS in check under normal physiologic conditions (Halliwell, 2011). Oxidative stress occurs when increases in oxidants and/or decreases in antioxidant defenses create an oxidative imbalance (Butterfield and Lauderback, 2002; Butterfield and Stadtman, 1997; Sies, 1997). Oxidative stress plays a major role in the pathogenesis of AD (Butterfield et al., 2001; Dasuri et al., 2013; Sultana and Butterfield, 2010; Sultana et al., 2013; Swomley et al., 2014).

Mitochondria process oxygen to produce energy at potential self-risk (Adam-Vizi, 2005; Scialo et al., 2013). During aging, progressive oxidative and nitrosative damage to biomolecules in mitochondria lead to increased ROS/RNS production, further compromising antioxidant defenses. Metabolic processes become progressively less efficient posing severe challenges to neuronal survival (Klamt et al., 2002; Schulz et al., 2014; Stadtman and Berlett, 1998; Sultana and Butterfield, 2013). Major forms of oxidative and nitrosative stress include protein oxidation, protein nitration, lipid peroxidation, and oxidative damage to DNA and RNA (Halliwell, 2011; Sanders, 2014; Butterfield et al., 2007, 2010; Butterfield and Lauderback, 2002; Butterfield and Stadtman, 1997; Castegna et al., 2004; Fedirko et al., 2010; Bonda, 2014). Aβ peptide has also been shown to be associated with free radicals capable of beginning a chain reaction of oxidative damage to biomolecules (Hensley et al., 1994; Butterfield et al., 2001; Lauderback et al., 2001; Swomley et al., 2014). Due to factors including, among others, low anti-oxidant defenses, high oxygen consumption, and an abundance of lipid–resident unsaturated acyl chains containing labile allylic hydrogen atoms, the brain is particularly susceptible to oxidative damage (Butterfield and Stadtman, 1997). Aging brain is even more so (Butterfield and Dalle-Donne, 2014; Butterfield and Dalle-Donne, 2014, 2014a, 2014b; Calabrese et al., 2006a; Perluigi et al., 2010).

3. VitD overview

VitD, a steroid hormone (Fig. 1), has long been known to play roles in calcium homeostasis, bone mineralization, immune cell differentiation, and tumor inhibition (Brewer et al., 2006; Deeb et al., 2007; Holick,
Recent studies indicate that long-term Vitamin D deficiency may play an aggressive role in neurodegeneration including that associated with AD (Annweiler et al., 2009; Brewer et al., 2001; Carlberg, 2014b; Dusso and Brown, 1998; Farid et al., 2012; Keeney et al., 2013a). Genome-wide association studies suggest Vitamin D as an important micro-nutrient with a wide variety of functions (Carlberg, 2014a; Carlberg and Molnar, 2012). Gene variants that involve hydroxylation (needed for Vitamin D conversion to the active form) or Vitamin D transport were found to affect Vitamin D status; however, variants involved in cholesterol biosynthesis were also found to substantially increase risk of Vitamin D insufficiency (Wang et al., 2010).

Upon exposure to sunlight (UVB), cholecalciferol (Vitamin D3) is synthesized in the skin from 7-dehydrocholesterol, the immediate biochemical precursor to cholesterol (Deeb et al., 2007). Vitamin D can also be obtained from the diet. Few foods naturally contain Vitamin D. Fatty fish, fish liver oil, beef liver, and egg yolk are among those that do (Holick, 2007). In many developed countries, foods including milk and breakfast cereals are fortified with Vitamin D (Deeb et al., 2007). Vitamin D3, as synthesized, is inactive. Transported through the bloodstream bound to Vitamin D-binding protein (DBP), Vitamin D3 is hydroxylated in the liver to 25-hydroxyvitamin D3 (25-(OH)D3) and further in the kidney to the biologically active calcitriol (1α,25-(OH)2D3) (Fig. 1) (Deeb et al., 2007). Active 1α,25(OH)2D3 is translocated to the nucleus. Most Vitamin D-related signaling occurs via binding of 1α,25(OH)2D3 to its nuclear receptor, the vitamin D receptor (VDR). VDR forms a heterodimer with the retinoid X receptor (RXR), and the VDR-RXR complex binds with the Vitamin D response element (VDRE), thereby modulating transcription (Ramagopalan et al., 2010). VDR-RXR interacts within the promoter regions of target genes on VDRE to regulate transcription (Bosse et al., 2009). 24-Hydroxylation leads to Vitamin D degradation and excretion. Additionally, because cholesterol and Vitamin D are synthesized from the same immediate precursor, statins, which inhibit cholesterol biosynthesis would thereby inhibit Vitamin D biosynthesis, providing another route of Vitamin D deficiency. In the USA, over 30 million individuals are on statin therapy, raising concerns about Vitamin D insufficiency, even in economically developed countries (Robinson and Booth, 2010).

### 3.1. Incidence of Vitamin D deficiency: age, gender, causes

Vitamin D deficiency is widespread with approximately one billion people affected worldwide (Dickens et al., 2011). Vitamin D levels decrease with age: even with regular sun exposure, elderly skin produces on average only 25% of the Vitamin D that young skin produces (Kennel et al., 2010). About 50% of the general adult population is estimated to be Vitamin D deficient across all age groups and ethnicities, and, as noted, a higher percentage of Vitamin D-deficient individuals exists in the elderly.

Approximately 70–90% of AD patients have less than sufficient serum Vitamin D levels (Annweiler and Beauchet, 2011; Bischoff-Ferrari, 2012; Durk et al., 2014; Holick, 2007; Nair and Maseeh, 2012). Vitamin D deficiency is even more common in women (Calabrese et al., 2006b; Looker et al., 2011). In a 7 year follow-up study of elderly women, a higher incidence of AD was found in women with low Vitamin D intake (Annweiler et al., 2012). In addition to being at higher risk of AD, women with low blood levels of Vitamin D have been found to have increased risk of depression (Kerr et al., 2015). The percentage of adults achieving sufficient Vitamin D levels has declined dramatically in recent years from 60% in whites and 10% in African Americans in the early 1990s to half these percentages in the early 2000s (Kennel et al., 2010). Reasons for low Vitamin D in much of the population, especially the elderly, include low sun exposure (indoor, sedentary lifestyle), poor nutrition (lack of access/financial or physical or lack of desire), and genetics (discussed further below) (Binkley et al., 2012). Vitamin D deficiency has been linked to increased overall mortality (Zittermann et al., 2009, 2012); conversely,
VitD supplementation is associated with significantly reduced mortality (Autier and Gandini, 2007).

3.2. VitD binding and transport: VDR and DBP

Most of the biological actions of VitD are mediated by the VDR, its nuclear ligand-induced transcription factor (Carlberg and Molnar, 2006; Dusso and Brown, 1998; Nezbedova and Brtko, 2004). In the absence of vitamin D, only 10–15% of dietary calcium is absorbed. That absorption increases to 30–40% upon interaction of VitD with VDR (Holick, 2007). VDR are present in many areas of the brain, particularly in the hippocampus (2014b; Annweiler et al., 2009). Expression of VDR in the hippocampus and cortex, key areas for cognition, suggest important functions for VitD in the brain. Additionally, Toll-like receptor (TLR) activated macrophages have been found to express both VDR and mitochondrial CP27B, that converts 25(OH)D to the active 1α,25(OH)2D3. The latter can then bind VDR to function as a transcription factor involved in immunity (Adams and Hewison, 2008; Fernandes de Abreu et al., 2009). VDR polymorphisms are known to be associated with altered AD susceptibility (Lee et al., 2014). These polymorphisms may alter the affinity of VDR for VitD, thereby increasing the risk for AD (Gezen-Ak et al., 2007).

By proteomics techniques, DBP, a protein involved in transport of VitD in the bloodstream, was identified as having decreased levels following plasma protein profiling of MCI subjects compared to healthy controls (Muenchhoff et al., 2015). Plasma VitD levels were also reported to be lower in MCI subjects (Olde Rikkert et al., 2014). These results suggest that impairment in VitD transport is present even in the early stages of AD, i.e., prior to development of dementia. A study by Moon et al. found that DBP inhibited Aβ aggregation and prevented Aβ-mediated cell death in cultured hippocampal cells (Moon et al., 2013). Both monomeric and oligomeric Aβ bound to DBP in a dose-dependent manner. Further, following addition of Aβ, DBP treatment resulted in reduced synapse loss in mouse hippocampus and rescued Aβ-induced memory deficits (Moon et al., 2013).

3.3. Effects of VitD on brain structure/function

Young people with poor nutritional status reportedly experienced changes in cognition, behavior, and CNS physiology (Millet et al., 2014). During brain aging, poor nutrition could lead to deleterious consequences or exacerbate existing disease states (Millet et al., 2014). In recent years, VitD has emerged as an important neurosteroid with a wide variety of important functions affecting both the developing and adult brain (Table 1) (Annweiler et al., 2014d; Cui et al., 2015; Eyles et al., 2013; Groves et al., 2014; Kesby et al., 2011; Millet et al., 2014). Cui et al. suggest a two-hit hypothesis for the effects of VitD deficiency on the brain whereby deficient VitD may adversely affect the brain by both genomic and non-genomic means (Cui et al., 2015). VitD has been shown to play key roles in the brain including cell proliferation, cell differentiation, calcium signaling, neurotrophic factor regulation, neurotransmission, and synaptic plasticity (Annweiler, 2014; Brouwer-Brolsma and de Groot, 2015; Groves et al., 2014). Demonstrated physiological benefits of VitD include neurogenesis and synaptogenesis, improved synaptic transmission, improved cognitive performance, elevated Aβ clearance, and neuronal protection (Brouwer-Brolsma and de Groot, 2015). Consequently, low VitD levels are associated with adverse outcomes in the brain as outlined above (Cui et al., 2015).

In a 2012 study, VitD deficiency was found to interrupt neurogenesis and increase apoptotic cells in the dentate gyrus of adult mice. These consequences were ablated by replenishment of VitD (Zhu et al., 2012). A study by Eyles and colleagues showed that the VDR is concentrated in the subventricular zone of the dentate gyrus, and that maternal VitD deficiency alters neurogenesis in the brain of developing rat pups suggesting VitD to be a regulator of cell proliferation in the developing brain (Cui et al., 2007). A more recent study by Keilhoff et al. found that maternal VitD deficiency led to decreased neurogenesis in offspring (Keilhoff et al., 2010). Further, this prenatal restriction of VitD resulted in decreased neurogenesis in the hippocampal dentate gyrus of the offspring even in adulthood (Keilhoff et al., 2010), and the late gestation period may be the key window where maternal VitD deficiency results in disrupted brain function in adult rat offspring (O’Loan et al., 2007). VitD deficiency during brain development has been shown to result in alterations to brain structure, gene expression, and neurochemistry (Cui et al., 2015; Eyles et al., 2013). In addition, several biological pathways important to the brain are adversely and permanently affected by VitD deficiency during brain development (Becker et al., 2005; Burne et al., 2004). These include mitochondrial energy metabolism, redox balance, calcium homeostasis, synaptic plasticity and neurotransmission, cytoskeletal structure and maintenance, and protein post-translational modification (PTM) (Burne et al., 2004).

In addition to neonatal brain changes associated with VitD deficiency as discussed above, adult brain also reportedly adversely responds to low VitD levels, including a variety of neurochemical, cognitive, and structural consequences (Cui et al., 2015). In a 2014 meta-analysis, Annweiler and colleagues concluded that VitD deficiency was associated with decreased brain volume and larger lateral ventricles (Annweiler et al., 2014b). The greater brain atrophy present in subjects with deficient VitD levels was supported by other studies (Hooshmand et al., 2014). Conversely, higher plasma levels of VitD correlate with larger brain volumes (Hooshmand et al., 2014). The Annweiler group and others further demonstrated that low serum VitD levels are associated with increased white matter abnormalities in older adults similar to that seen in AD (Annweiler et al., 2014a, 2015a) especially in elderly women with amnestic MCI or AD (Sakurai et al., 2014).

3.4. VitD treatment and cognition/AD

Adult brain exhibits decreased cholinergic activity, increased calcium-related neurotoxicity, increased glutamate excitotoxicity, and resultant learning and memory deficits (Annweiler and Beauchet, 2012). Although a few inconclusive or conflicting studies exist (Anastasiou et al., 2014; Schneider et al., 2014), mounting evidence suggests a direct correlation of serum VitD levels with cognitive ability (Annweiler and Beauchet, 2011; Brouwer-Brolsma et al., 2013; Schlogl and Holick, 2014). Abnormalities in cholinergic, dopaminergic, and noradrenergic neurotransmitter systems have been implicated in a wide variety of brain disorders. Manipulation of VitD levels through diet or supplementation has been shown to have positive effects on each of these neurotransmitter systems (Eyles et al., 2013). Studies have shown a variety of interactions between VitD and catecholamines including dopamine-induced VDR-mediated signaling as well as VitD2 association with tyrosine hydroxylase (Sanchez et al., 2009; Wang et al., 2001), the rate-limiting enzyme in catecholamine biosynthesis (Daubner et al., 2011). Tyrosine hydroxylase has been shown to be inhibited by nitric oxide (•NO) (Abreu et al., 2000). •NO-related protein nitration in brain is a known downstream consequence of VitD deficiency as well as being present in MCI and AD brain, discussed in a later section (Butterfield et al., 2007; Calabrese et al., 2006c; Keeney et al., 2013a; Sultana et al., 2006). VitD supplementation in rats results in increased choline acetyltransferase activity and the resultant increase in available acetylcholine in brain areas relevant to AD (Sonnenberg et al., 1986). Further, VitD has been shown to play a beneficial regulatory role in cholinergic and dopaminergic receptor gene expression in diabetic rats (Peeyush et al., 2010). VitD administered to newborn rats resulted in increases in both dopamine and norepinephrine in the brainstem in adulthood (Takes et al., 2009). Administration of VitD to adult rats increases dopamine release and storage in the striatum and protects against dopamine and serotonin depletion in response to normally depleting stressors (Cass et al., 2006, 2012). VitD deficiency may exacerbate existing brain disorders and impair the ability to respond to stressors in the brain (Cui et al., 2015; Groves et al., 2014). Annweiler and coworkers demonstrated a potential
### Table 1
AD associated pathological hallmarks, clinical presentations, and risk factors that are influenced by VitD status: selected references.

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<th>Key AD-related topics affected by VitD status</th>
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<th>Primary conclusions of study, impact of VitD</th>
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synergistic effect of memantine (an NMDA receptor antagonist acting on the glutamatergic system currently used as a treatment for AD). Memantine use in combination with VitD decreased cortical axon degeneration in neuronal culture during exposure to lysed blood-induced neurotoxicity (Annweiler et al., 2014c; Charrier et al., 2015). The combination provided a greater protective effect than treatment with either component alone. This combination shows potential promise in protecting neurons during times of stress.

In a rat model of brain aging, older rats exhibited significant decline in learning and memory compared to young rats. VitD treatment ameliorated age-related decline in learning and memory in the older group, while no similar effect of VitD was seen in younger rats (Bromines and Darwish, 2012). In a 6-year follow-up study on human subjects, low initial serum VitD levels were associated with substantial cognitive decline (Floyd, 1999). A 2011 Australian study found that when patients with mild to moderate AD were treated with low dose VitD (1000 IU/day for 8 weeks), cognition and memory improved. No further cognitive or memory improvements were seen following high dose VitD treatment (Stein et al., 2011). Latimer et al. found that middle-aged rats fed a high VitD diet for 5–6 months demonstrated enhanced basal synaptic transmission and significantly outperformed their normal and low VitD-diet counterparts on hippocampal-dependent learning and memory tasks (Latimer et al., 2014). Genes associated with synaptic transmission were upregulated in response to a high VitD diet.

A meta-analysis by Etgen et al. that included nearly 8000 human participants found a strongly significant increased risk of cognitive impairment associated with low VitD status (Etgen et al., 2012). In other studies, lower serum VitD levels also are reported in human subjects with AD versus age-matched controls (Annweiler et al., 2014). These results support the notion of a controlled clinical trial supplementing VitD in MCI patients.

3.5. VitD and inflammation

Serum VitD levels are inversely associated with systemic inflammation (Bella et al., 2013). Low serum VitD is associated with decreased ApoA1 levels (John et al., 2005) that have been associated with an increased inflammatory response mentioned previously. Serum VitD levels are reportedly inversely related to TNF-α levels, and, conversely, levels of TNF-α and other inflammatory markers are reduced upon VitD supplementation (Peterson and Heffernan, 2008; Stubbs et al., 2010). TNF-α is normally found in low levels in healthy brain (Keeney et al., 2013b) having both neuroprotective and neurotoxic roles, the latter involving both necrosis and apoptosis (Badiola et al., 2009; Schneider-Brachet et al., 2004). In other studies, upregulation of inhibitors of apoptosis as well as decreased pro-inflammatory cytokines, including TNF-α, in response to VitD treatment were reported (Fedirko et al., 2009; Hopkins et al., 2011). Calcium and VitD treatment each showed these protective effects; however, no synergistic effect was found. A recent study by Cavalcante et al. demonstrated that VitD insufficient elderly women given high dose VitD supplementation for four weeks showed reduced inflammatory markers (Cavalcante et al., 2015).

Cultured human brain pericytes, cells involved in control and maintenance of the BBB, treated with VitD demonstrated regulatory control of the expression of genes involved in neuroinflammation (Nissou et al., 2014). These cells also responded to exposure to inflammatory cytokines, including TNF-α, by upregulating genes (CYP27B1) involved in VitD metabolism to the active 1α,25(OH)2D3 form (Nissou et al., 2014). An implication of this study is that VitD conceivably may protect the BBB from inflammatory stress.

3.6. VitD and glucose utilization

Type 2 diabetes mellitus (T2DM) is a significant risk factor for AD (Butterfield et al., 2014a; Verdile et al., 2015; Barone and Butterfield, 2015). Though conflicting evidence exists, VitD has been shown to play a regulatory role in some pathways related to T2DM that may also have relevance to AD. VitD is reported to exert a positive influence on glucose homeostasis, a key process that shows detrimental changes early in AD brain, via altering insulin secretion and sensitivity secondary to VitD’s modulation of the inflammatory response (Chagas et al., 2012). In 2015, Berti et al. measured the association of nutrient intake and brain biomarkers of AD and found that VitD was among the nutrients that were positively associated with cerebral glucose metabolism and gray matter volume (less brain atrophy) and negatively associated with markers of fibrillar Aβ (Berti et al., 2015).

3.7. VitD and Aβ

Insoluble Aβ plaques are a pathological hallmark of AD. Together with metabolic deficits, amyloid buildup and deposition is thought to be among the earliest changes in the brain in the progression of AD (Masters and Selkoe, 2011; Aluise et al., 2010a; Butterfield et al., 2001; Sperling et al., 2011; Swomley et al., 2014). However, soluble Aβ oligomers may be the more dangerous form of this damaging peptide (Masters and Selkoe, 2011; Butterfield et al., 2013). Both increased production of Aβ from APP and decreased elimination of Aβ due to defective Aβ phagocytosis, insufficient Aβ transport from brain to blood, and decreased degradation contribute to Aβ accumulation in the brain (Erickson et al., 2012; Mohammad Abdul et al., 2006; Owen et al., 2010; Zhao et al., 2004). Recent evidence demonstrates that low VitD status results in increased Aβ and increased Aβ-related toxicities in the brain, whereas sufficient VitD improves Aβ clearance, decreases Aβ load, and provides protection against Aβ-related cognitive decline (Fig. 2). VitD treatment as well as VDR overexpression have each been shown to suppress APP transcription in cell culture (Wang et al., 2012).

Exposure of hippocampal neurons in culture to Aβ suppressed expression of VDR messenger ribonucleic acid (mRNA) and induced mRNAs for expression of 24-hydroxylase (24(OH)ase) that tags VitD for elimination as well as inducing L-type voltage-sensitive calcium channel A1C (LVSCC-A1C) mRNA (Dursun et al., 2013). Taken together these results suggest that Aβ may disrupt VitD/VDR signaling as well as contribute to the well-known calcium dysregulation and consequent neurodegeneration in AD brain (Garwood et al., 2013).

In a study of mice expressing human APP as a model of AD, acute treatment with VitD reduced soluble Aβ. Long-term VitD treatment of these mice resulted in decreased levels of both soluble and insoluble Aβ in brain, particularly in the hippocampus, leading to improved performance on memory-related tasks (Durk et al., 2014). Higher serum VitD levels correlate with increased Aβ in the CSF suggesting increased clearance from the brain (Hooshmand et al., 2014). VitD supplementation in a rat model of brain aging not only improved learning and memory but increased Aβ clearance and decreased Aβ load in the brain of aged rats (Briones and Darwish, 2014). Aβ treatment suppressed synaptic plasticity in the rat hippocampus and impaired the storage of memories via long-term potentiation (LTP) (Taghzadeh et al., 2014). Dietary VitD supplementation in these animals protected basic synaptic transmission and restored synaptic plasticity in the face of Aβ treatment (Taghzadeh et al., 2014). The effect of VitD on Aβ levels and clearance coupled with the Ca2+ regulatory effects of VitD are consistent with the notion that VitD supplementation may reduce Aβ-induced memory deficits.

In a cross-sectional neuroimaging human pilot study in cognitively normal individuals with known risk factors for AD, higher dietary levels of VitD as well as higher VitD12 and ω-3 polyunsaturated fatty acids, as part of a nutritious diet, were associated with decreased Aβ load assessed by positron emission tomography (PET) in AD relevant brain regions independent of gender, ApoE status, or family history and controlled for age and differences in total caloric intake (Mosconi et al., 2014).
As noted above, Aβ repressed VDR mRNA. VitD activation of VDR-dependent signaling led to recovery of phagocytosis needed to protect the brain from AD-inducing effects of Aβ (Mizwicki et al., 2012). Two types of macrophages are present in AD brain, Type I and Type II. In multiple studies, treatment with VitD strongly stimulated Aβ phagocytosis and clearance, re-balanced inflammation, and protected against apoptosis in both types of macrophages (Fiala, 2010; Masoumi et al., 2009). Some of these effects may be synergistic with curcuminoids (Masoumi et al., 2009). Additionally, VitD supplementation in combination with the anti-inflammatory agent, Resolvin D1, promoted Aβ phagocytosis and reversed Aβ-induced elevation of inflammatory cytokines and chemokines (Mizwicki et al., 2013). The study further concluded that low intake of both VitD and docosahexanoic acid may contribute to AD pathology (Mizwicki et al., 2013).

3.8. VitD and Tau

Studies by Hooshmand et al. and others found no significant differences in levels of Tau protein or Tau phosphorylation based on VitD status (Hooshmand et al., 2014). However, decreased age-related Tau hyperphosphorylation were reported following VitD supplementation (Briones and Darwish, 2014). In this latter study, previous findings of age-related decreases in brain energy metabolism, deleterious changes to the redox state in brain (assessed by levels of ROS, levels of glutathione, and activity of superoxide dismutase), increased Tau hyperphosphorylation, and learning and memory decline were validated (Briones and Darwish, 2014). All of these age-related, detrimental changes to the brain were attenuated by VitD supplementation. Further, the authors showed that VitD restored the activity of protein phosphatase 2A (PP2A), an enzyme that dephosphorylates Tau, and decreased Tau hyperphosphorylation to levels observed in younger control animals (Briones and Darwish, 2014). Consequently, taken together, VitD apparently does not affect levels of Tau, but beneficial effects of VitD appear to be the case with respect to Tau phosphorylation.

3.9. VitD and nitrosative stress

Keeney et al. demonstrated that long term VitD deficiency in aging rats resulted in increased nitrination of brain proteins through a free radical mechanism (Keeney et al., 2013a). The highly reactive superoxide radical anion is produced due to inefficient mitochondrial respiration (Deby and Goutier, 1990; Fridovich, 1986; Halliwell and Gutteridge, 1984). Manganese superoxide dismutase (MnSOD), the primary mitochondria resident superoxide scavenger, has itself been shown to be a target of tyrosine nitration, rendering this enzyme less able to perform its antioxidant duties and exposing other biomolecules to the damaging effects of superoxide (Anantharaman et al., 2006; MacMillan-Crow, 1998; Sompol et al., 2008; Tangpong et al., 2008).

We demonstrated that VitD deficiency in aging brain leads to increased TNF-α-induced activation of nuclear factor κ-light chain enhancer of activated B cells (NF-κB) (Keeney et al., 2013a), increased translocation of NF-κB to the nucleus, and consequent increased levels of inducible nitric oxide synthase (iNOS), a downstream product of the NF-κB transcription pathway, resulting in increased nitration of cortical proteins (Keeney et al., 2013a) via a free radical pathway. NO, a natural free radical, competes with MnSOD to react with superoxide (Amiransour et al., 1999; Ischiropoulos, 2009). Normally, MnSOD efficiently reacts with superoxide converting this free radical to hydrogen peroxide and molecular oxygen. As MnSOD becomes damaged, the resulting elevated superoxide free radical is able to react with NO to form the damaging peroxynitrite (ONOO−). Protein nitration occurs at the 3-position of tyrosine as a result of inefficient mitochondrial respiration (Deby and Goutier, 1990; Fridovich, 1986; Halliwell and Gutteridge, 1984). The highly reactive superoxide radical anion is produced due to inefficient mitochondrial respiration (Deby and Goutier, 1990; Fridovich, 1986; Halliwell and Gutteridge, 1984). Manganese superoxide dismutase (MnSOD), the primary mitochondria resident superoxide scavenger, has itself been shown to be a target of tyrosine nitration, rendering this enzyme less able to perform its antioxidant duties and exposing other biomolecules to the damaging effects of superoxide (Anantharaman et al., 2006; MacMillan-Crow, 1998; Sompol et al., 2008; Tangpong et al., 2008).

As discussed above, vitD decreased TNF-α levels (Diaz et al., 2009; Furman et al., 1996; Giuliani et al., 2007; Keeney et al., 2013a) and downregulated TLR (Sadeghi et al., 2006). VitD suppressed TNF-α-induced activation of NF-κB (Keeney et al., 2013a; Kwon et al., 2010), upregulated the inhibitor of NF-κB (IκB-α), decreased IκB-α phosphorylation, and decreased translocation of NF-κB to the nucleus (Chagas et al., 2012; Keeney et al., 2013a). The VDRE may also inhibit NF-κB–directed expression (Haussler et al., 2008). Taken together, VitD inhibits NF-κB-related protein nitration and production of the inflammatory
cytokine, TNF-α, thereby decreasing many downstream consequences of each (Fig. 4).

3.10. Regulation of redox status and redox signaling

Arguably the primary antioxidant in the brain is glutathione. The thiol group of GSH can react with a variety of ROS to protect the brain and maintain redox balance (Sies, 1997; Halliwell, 2011; Pocernich and Butterfield, 2012). The ratio of reduced glutathione (GSH) to oxidized glutathione (GSSG) gives a measure of the redox status of the brain. A report suggests that higher serum VitD levels are associated with higher plasma GSH and lower GSSG (Alvarez et al., 2014), indicating a favorable redox status to respond to and protect the brain from oxidative stress. Early trials in animal models by Fedirko et al. (2010) suggested that concurrent calcium and VitD supplementation decreased oxidative damage to DNA. Cavalcante et al. (2015) demonstrated that four weeks of high dose VitD supplementation in VitD-insufficient, elderly women resulted in increased antioxidant capacity in these subjects.

VitD may also indirectly regulate cellular redox signaling. Expression of vitamin D upregulating protein 1 (VDUP1), as the name implies, is regulated by VitD. VDUP1 was first known to be a regulator of thioredoxin expression and activity involved in redox regulation, but further studies showed that VDUP1 also plays roles in many cellular processes including cell proliferation, apoptosis, immune regulation, and fatty acid utilization (Chung et al., 2006). In 2006, Nemere et al.
The consensus of the literature is that VitD has a number of important roles in cognition and neurodegenerative diseases, including dementia, especially in the elderly segments of the population. However, currently, due to the association of VitD deficiency with many neurological, neurodegenerative, and non-CNS-related diseases and many areas of uncertainty, VitD status is a crucial but non-specific risk factor for AD (Annweiler et al., 2015b). Cui et al. suggested that specific ‘critical windows’ may exist during which VitD deficiency might result in the most detrimental brain outcomes, and during these times, VitD supplementation might be the most beneficial to prevent long-term damage to the brain (Cui et al., 2015). VitD level appears to be a modifiable risk factor for AD. A potential therapeutic window during which VitD might provide benefit to reduce the risk or delay the onset of AD may be during the pre-clinical and MCI stages in which measurable changes in glucose utilization and $\alpha$-Amylase accumulation already occur (Etgen et al., 2011). The window of opportunity for the benefit of VitD would gradually close as neuronal loss increases. Early in disease progression, changes could still be made to potentially improve outcomes. Accordingly, we suggest that long-term, randomized clinical trials of VitD supplements among large populations of middle-aged adults in several countries should be considered with the end point being the conversion rate to MCI or AD.

4. Conclusions and future directions

More research is needed to deal with existing uncertainties in the roles of VitD in cognition and neurodegenerative diseases, including AD. The consensus of the literature is that VitD has a number of important beneficial effects on the brain, and that VitD deficiency contributes to and has common links with several deleterious consequences to the brain, many of which are strongly associated with AD (Fig. 5). It is our opinion that the current recommendations of daily intake of VitD are too conservative. Higher VitD levels may be essential for healthy brain aging. Further, based on a large number of AD-related issues that have common links with deficient VitD levels as outlined in this review, we opine that VitD should be considered as an adjunct therapy in conjunction with any AD treatment. VitD appears to play both acute and chronic roles in the brain. Critical periods may exist during which VitD deficiency may be the most harmful to the brain during which VitD supplementation might provide the most protective benefit.

As people age, they tend to become more sedentary, often due to physical limitations. As this occurs, older individuals tend to stay inside more, decreasing exposure to the sun. In combination with the declining ability of aging skin to synthesize VitD and the poor dietary status typically experienced in the elderly, VitD levels are often critically low. The widespread use of cholesterol-lowering drugs may also inhibit the ability to synthesize VitD. In our opinion, evidence of the potential contribution of VitD deficiency to neurodegeneration makes testing VitD levels and appropriate VitD supplementation as needed of utmost importance. We strongly urge the development of programs and awareness messages to produce more proactive relationships of patients and their physicians to address the widespread VitD deficiency and the value of supplementation as a part of quality of care/quality of life issues that potentially have a significant possibility to modulate the onset and progression of AD.

References


Fig. 5. Summary of the pathology and clinical presentation of AD where VitD has been shown to play potential beneficial roles. A pictorial representation of identified areas associated with AD where VitD has been shown to play beneficial roles.


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