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Mini Review

Vitamin D, Cell Signalling Phenotypic Stability and Alzheimer's Disease

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Abstract

Vitamin D deficiency has been linked to many human diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), Multiple Sclerosis (MS), hypertension and cardiovascular disease. A Vitamin D phenotypic stability hypothesis, which is developed in this review, attempts to describe how this vital hormone acts to maintain healthy cellular functions. This role of Vitamin D as a guardian of phenotypic stability seems to depend on its ability to maintain the redox and Ca^{2+} signalling systems. It is argued that its primary action is to maintain the expression of those signalling components responsible for stabilizing the low resting state of these two signalling pathways. This phenotypic stability role is facilitated through the ability of vitamin D to increase the expression of both Nrf2 and the anti-aging protein Klotho, which are also major regulators of Ca^{2+} and redox signalling. A decline in Vitamin D levels will lead to a decline in the stability of this regulatory signalling network and may account for why so many of the major diseases in man, which have been linked to vitamin D deficiency, are associated with a dysregulation in both ROS and Ca^{2+} signalling as is described for Alzheimer's disease (AD).

Keywords: Vitamin D; Calcium; Klotho; Nrf2; Alzheimer's disease

Introduction

Vitamin D deficiency is a major human epidemic [1]. There is increasing evidence for a link between Vitamin D deficiency and many of the major human diseases (Figure 1). While the evidence for such associations is strong, particularly in the case of neural diseases such as Alzheimer's disease, Parkinson's disease and Multiple Sclerosis (MS), there is little information as to why a deficiency in Vitamin D can have such serious consequences. In an attempt to answer this question, I have developed a Vitamin D phenotypic stability hypothesis that sets out to explain why Vitamin D is such an important hormone responsible for maintaining normal cellular functions [2].

Vitamin D - a custodian of phenotypic stability in cell signalling pathways

When cells differentiate during development, they select out those components of their signalling toolkits to assemble specific signalling systems such as the Ca^{2+} and redox signalling systems. For normal cell responses, it is essential that transcription of all the components that make up such Ca^{2+} and redox signalling phenotypes are maintained and it seems that Vitamin D, working together with Nrf2 and Klotho, is the major custodian of such phenotypic stability (Figure 2).

Vitamin D acts by binding to the Vitamin D Receptor (VDR), which interacts with the Retinoid X Receptor (RXR) before binding to the Vitamin D Response Element (VDRE), located on a large number of vitamin D-sensitive target genes. The VDR can also be partially activated by a number of other ligands, which have health benefits such as Lithocholate (LCA), curcumin, omega 3 fatty acids and resveratrol [3]. Vitamin D controls the expression of Nrf2 and the anti-aging protein Klotho, which are also important regulators of multiple cellular signalling systems (Figure 2). Many of the genes that are controlled by the Vitamin D/Klotho/Nrf2 regulatory network function to maintain Ca^{2+} and redox homeostasis. For example, Vitamin D increases the expression of Ca^{2+} pumps, exchangers and buffers to maintain low levels of Ca^{2+}. Similarly, Vitamin D together with Klotho and Nrf2 all increase cellular antioxidants to maintain the normal reducing environment within the cell.

Vitamin D regulation of the epigenetics landscape

In keeping with its proposed role in maintaining phenotypic stability, Vitamin D controls the epigenetic landscape of its multiple gene promoters to maintain the transcription activity of all the genes that operate in its regulatory network (Figure 2). Vitamin D controls both the acetylation and methylation states of its promotor regions.

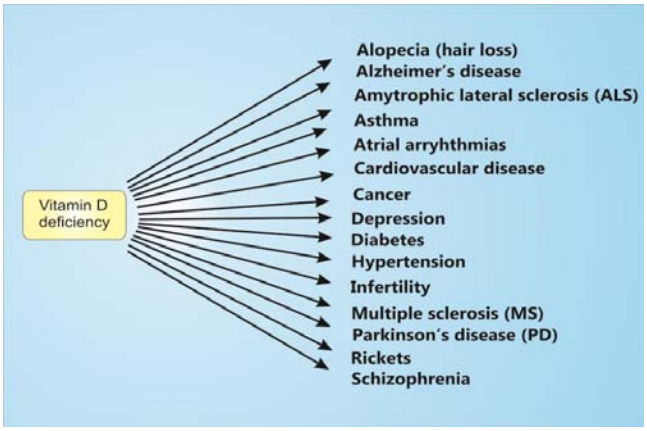

Figure 1: Vitamin D deficiency has been linked to a large number of human diseases.

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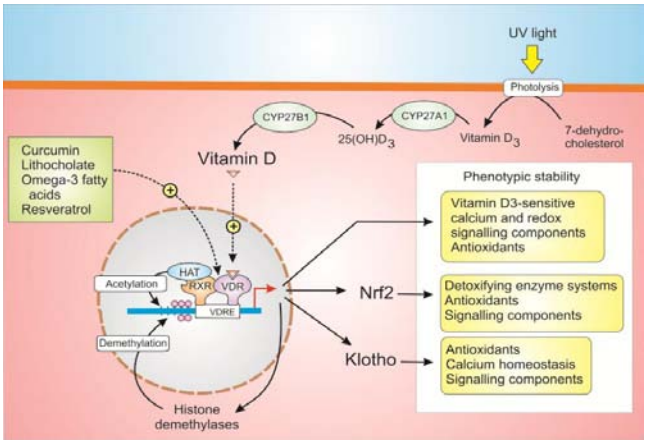

Figure 2: Vitamin D, which is formed through a series of reactions beginning with UV-induced photolysis of 7-dehydrocholesterol to form Vitamin D_3, which then undergoes two hydroxylation reactions to form the active Vitamin D. Vitamin D then acts on the Vitamin D Receptor (VDR) to increase the expression of a large number of genes many of which regulate cell signalling pathways so as to maintain phenotypic stability. Vitamin D also controls the epigenetic landscape of its target genes by regulating both acetylation and methylation.

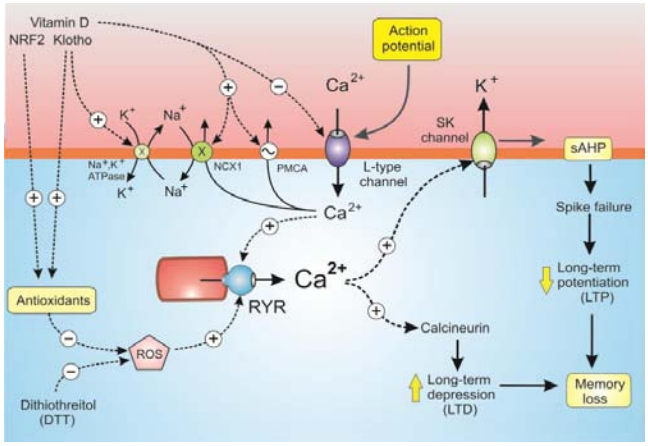

Figure 3: Age-related decline in cognition and its reversal by the Vitamin D/Klotho/NRF2 regulatory network. In aged rats, the neuronal action potentials activate L-type Ca^{2+} channels that provide trigger Ca^{2+} that stimulates ryanodine receptors (RYRs) to generate a large Ca^{2+} signal that results in memory loss through two processes. Firstly, the Ca^{2+} acts on SK channels resulting in a slow After Hyper Polarization (sAHP) that causes spike failure and a decrease in the Long-Term Potentiation (LTP) responsible for memory formation. Secondly, the prolonged elevation in cytosolic Ca^{2+} activates calcineurin that increases Long-Term Depression (LTD) resulting in memory loss. The Vitamin D/Klotho/NRF2 regulatory network acts to suppress the abnormal elevation in Ca^{2+} through a number of mechanisms that act to reduce both Ca^{2+} and Reactive Oxygen Species (ROS) signalling as described in the text.

The VDR complex recruits histone acetylases such as p300/CBP and SRC-1 that acetylate chromatin and it increases the expression of a number of DNA demethylases. This ability of Vitamin D to modulate the epigenetic landscape may contribute to its ability to maintain phenotypic stability and to prevent the onset of multiple diseases [2].

Vitamin D deficiency and age-related decline in human cognition

There is an age-related decline in the ability of human skin to synthesize Vitamin D [4] and this may account for the decline in the level of Vitamin D and Klotho during aging. Vitamin D deficiency may thus contribute to the normal aging process through dysregulation of cell signalling pathways such as those operated by the Ca^{2+} and redox cell signalling pathways. Dysregulation of Ca^{2+} signalling, which is closely linked to mitochondrial dysfunction and ROS formation, has been implicated in aging [5]. Another example of an alteration in Ca^{2+} signalling during aging is the decline in the Ca^{2+} buffer calbindin in neurons [6]. The decline in this buffer may also be linked to a deficiency in Vitamin D, which normally maintains the expression of calbindin. During aging, therefore a decline in Vitamin D may result in an elevation in the Ca^{2+} and redox signalling systems resulting in phenotypic instability and the onset of many age-related human diseases.

There is increasing evidence that a deficiency in Vitamin D can lead to a decline in neurological functions such as cognition and various neurodegenerative diseases [7]. Strong support for such a notion has come from the study of the decline in cognition in aging rats that is driven by a marked increase in the amplitude of the slow After Hyper Polarization (sAHP) that depends on a build-up of Ca^{2+} that activates the SK potassium channel [8] (Figure 3). This Ca^{2+} signal, which depends on the opening of L-type voltage-dependent Ca^{2+} channels that provides trigger Ca^{2+} to activate ryanodine receptors (RYRs), inhibits memory by curtailing the spiking activity necessary for LTP, whereas the increase in Ca^{2+} stimulates calcineurin to induce the Long-Term Depolarization (LTD) that erases memories [9]. The development of this sAHP during aging depends on dysregulation of both Ca^{2+} and ROS signalling that can be directly attributed to Vitamin D deficiency (Figure 3). The increase in ROS signalling sensitizes the RYRs and this can be reversed by treating neurons with Dithiothreitol (DTT) [10].

The Vitamin D/Klotho/Nrf2 regulatory system can prevent the dysregulation of Ca^{2+} and ROS signalling through multiple mechanisms (Figure 2). Vitamin D suppress the expression of the L-type Ca^{2+}channel [11] that initiates the Ca^{2+} signal that induces the sAHP and it also maintains the expression of PMCA and NCX1, which extrude Ca^{2+} from the cell (Figure 3). Klotho acts to stimulate the Na^+/K^+-ATPase responsible for maintaining the Na^+ gradient necessary for Ca^{2+} extrusion by NCX1. Finally, Nrf2 increases the expression of many antioxidants that ensure that ROS levels are kept low, which will prevent the sensitization of the RYRs that are triggering the sAHP and memory erasure.

The central role of vitamin D deficiency in this neuronal dysregulation and cognitive decline can be reversed by treating neurons with Vitamin D that dramatically reduces the sAHP [12]. When tested on aging rats, Vitamin D was found to enhance hippocampal synaptic function and, more significantly, it could prevent the decline in cognition [13]. Such activation of the RYRs by L-type Ca^{2+} channels, which is responsible for this age-related decline in cognition, is a significant feature of Alzheimer's disease (AD) (Figure 4) [14]. Such observations are consistent with the finding that a deficiency in Vitamin D predicts a decline in human cognition that occurs with aging [15-17]. The decline in the level of Klotho during aging, which is probably linked to the decline in Vitamin D,

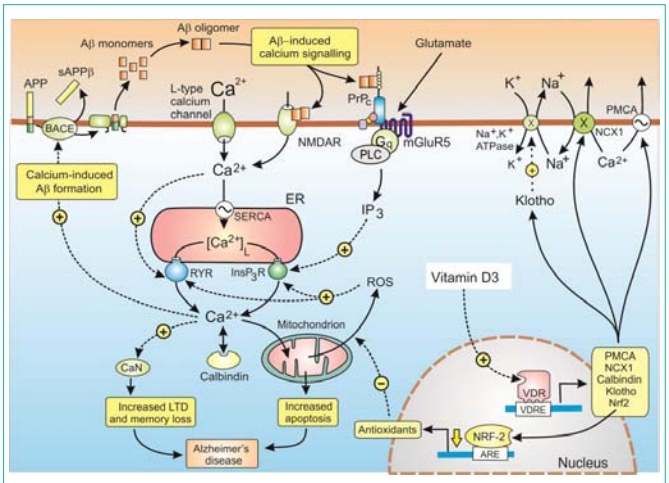

Figure 4: Dysregulation of Ca^{2+} signalling in Alzheimer's disease. Hydrolysis of the Amyloid Precursor Protein (APP) by β-site APP-Cleaving Enzyme (BACE) generates the amyloid β (Aβ) monomers that then form the Aβ oligomers that result in Aβ-induced calcium signalling. One of the main actions of Aβ is to bind to the cellular prion protein (PrP^C) that is coupled to the mGluR5 receptor to generate inositol 1,4,5-trisphosphate ($InsP_3$) to increase the release of Ca^{2+} from the ER. Much of the released Ca^{2+} enters the mitochondria to induce an increase in the formation of Reactive Oxygen Species (ROS), which sets up a positive feedback loop because the ROS acts to sensitize both the $InsP_3Rs$ and the Ryanodine Receptors (RYRs). The increased level of Ca^{2+} then acts on calcineurin (CaN) that enhances memory loss by increasing Long-Term Depression (LTD). Vitamin D counteracts this abnormal elevation of both Ca^{2+} and ROS through a number of mechanisms as described in the text.

may also contribute to the decline in cognition. A single allele of the KL-VS variant of the Klotho gene, which greatly enhances longevity, markedly reduces the age-related decline in human cognition [18].

Despite many attempts to explain aging, there is no consensus as to what the mechanism might be. These studies illustrating how Vitamin D deficiency contributes to the age-related decline in cognition suggests the interesting possibility that Vitamin D might be a key element in determining the rate of the aging process and the onset of age-related diseases such as Alzheimer's disease (AD) as described below (Figure 4).

Vitamin D deficiency and Alzheimer's disease (AD)

Why is it that some individuals develop Alzheimer's disease (AD) as they grow older while others do not? The answer may lie in their relative Vitamin D levels that may determine the rate of aging as proposed above. Those with low Vitamin D levels will experience abnormal elevations in Ca^{2+}, similar to those described in aged rats (as described above), that will trigger calcium-induced Aβ formation [19-22] (Figure 4). Such Ca^{2+}-induced increase in amyloidal formation then initiates a positive feedback loop because it is followed by Aβ-induced Ca^{2+} signalling [2]. Such a scenario may explain the sporadic nature of AD.

The Aβ can activate Ca^{2+} signalling through different mechanisms. It can bind to the cellular prion protein (PrP^C), which is coupled to mGluR5 to increase the formation of $InsP_3$ to release internal Ca^{2+} [23]. Aβ can also activate the NMDARs to increase Ca^{2+} entry. An increase in ROS formation that occurs in AD will also enhance Ca^{2+} signalling by sensitizing both the $InsP_3Rs$ and the RYRs (Figure 4). Such ROS-dependent dysregulation of Ca^{2+} release by neuronal RYRs, which is triggered by entry of Ca^{2+} through the L-type Ca^{2+} channels, is a feature of age-related memory loss as described earlier [24]. Such an interaction between the L-type Ca^{2+} channels and RYRs (Figure 4) is a significant feature of AD [14]. This persistent elevation in the resting level of Ca^{2+} may act to induce Long-Term Depression (LTD) to continuously erase memories shortly after they are formed during the wake period [25,26].

There are an increasing number of studies indicating that a deficiency in Vitamin D may contribute to the onset of AD [27-29]. Since AD seem to be caused by abnormal elevations in Ca^{2+}, the deleterious effect of vitamin D deficiency may be explained by a decrease in its normal role as a custodian of Ca^{2+} and ROS homeostasis. Vitamin D may act to reduce the onset of AD through its ability to stimulate the expression of Ca^{2+} pumps (PMCA and NCX1) and Ca^{2+} buffers such as calbindin and parvalbumin and to reduce the expression of the L-type Ca^{2+} channels. Neuronal levels of calbindin are known to be reduced in AD [6,30]. The level of Nrf2, which is markedly reduced in the brain of patient with AD [31], is increased by Vitamin D. Cognition in AD transgenic mice was markedly improved following vector-mediated expression of Nrf2 in the hippocampus [32]. Nrf2 may act to reduce the symptoms of AD by maintaining the cellular level of the redox buffer GSH, which is a critical factor in preventing AD [33].

In a mouse model of AD, the synaptic and cognitive defects characteristic of AD were improved by increasing the expression of Klotho [34] and this neuroprotective effect may depend on the ability of Klotho to increase antioxidant enzymes [35].

Conclusion

Vitamin D is a major custodian of the phenotypic stability of the Ca^{2+} and redox signalling systems that are central players in many human diseases. Any reduction in Vitamin D levels will result in a decline in the phenotypic stability of these signalling systems resulting in elevated neuronal Ca^{2+} and ROS levels and this could contribute to the age-related decline in cognition and it may also act to trigger the onset of AD. It is proposed that this dysregulation of Ca^{2+} initiates the formation of the pathological Aβ oligomers to trigger the Aβ/Ca^{2+} positive feedback loop (Figure 4) responsible for the onset of AD [2]. Such a scenario is entirely consistent with the fact the Vitamin D deficiency is such a strong risk factor for AD.

It is clear that the medical community should be more aware of the importance of Vitamin D because there is increasing evidence that maintaining normal levels of this critical hormone would markedly reduce the development of AD and many of the other major human diseases.

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