Vitamin D in Brain Health

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Contributor: Francesca Uberti

In the present review a novel role of vitamin D has been described during aging condition, focusing on vitamin D mechanism in brain and how it can help slow down diseases related to neuroinflammation and cognitive decline. In particular vitamin D metabolism and the role of vitamin D receptor (VDR) in brain was underlained. Despite the important role of vitamin D in this context, we discussed the potential effects of curcumin on the health of the central nervous system. Finally we focused on possible treatments triggered by vitamin D and curcumin, especially in neuroprotection and maintaining brain health.

Keywords: vitamin D ; neuroinflammation ; Curcumin ; nutraceutical ; neuroprotection ; brain health ; aging

1. Introduction

In the present critical review, alongside the description of the most recent knowledge on the role of the essential micronutrient vitamin D (vitD) in various mechanisms underlying neurodegenerative disorders and other adverse effects, the potential effects of curcumin on the health of the central nervous system (CNS) are discussed, where curcumin is a nutraceutical that is extensively used in herbal medicine. Vitamin D has gained great fame as a nutritionally essential factor since the elucidation of vitamin D's chemical structure revealed that it is a steroid hormone that is able to exert its effects through a specific receptor, which was discovered in the 1960s[1]. Vitamin D can either be ingested or synthesized in the skin[2][3], and to make it biologically active, the prohormone vitamin D is transported through the bloodstream to the liver, where it is metabolized[4]. 25-hydroxyvitamin D (25(OH)D3) is the major circulating metabolite of vitamin D in plasma and is essential for providing an index of a patient's vitamin D nutritional status[5][6]. A successive metabolization of 25(OH)D3 generates the hormonally active form of vitamin D, namely, 1,25-dihydroxyvitamin D3 (1,25(OH)2D3), which is responsible for most of the biological actions of vitamin D[4]. It was assumed that the brain's 1,25(OH)2D3 supply depends on the plasma concentration of 1,25(OH)2D3 (vitD)[7][8][9]. VitD works through two types of receptors: (i) the nuclear vitamin D receptor (VDR) to induce genomic action[9] and (ii) the putative membrane receptor MARRS (membrane-associated, rapid response steroid-binding) to induce non-genomic actions[11].

Maintaining an adequate plasma level of vitamin D can be a problem and vitamin D deficiency is more common than previously thought[12]. Natural food sources of vitamin D are uncommon; therefore, most people rely on skin production following safe exposure to sunlight. Exposure to sunlight is certainly the safest form of vitamin D supply and it could reduce the dependency on supplements[13]; however, many variables influence the amount of UV rays that reach the skin and its effectiveness. These include the time of day, season, latitude, altitude, clothing, use of sunscreen, pigmentation, and age. For this reason, especially in the elderly, exogenous administration through food supplements is necessary[14]. The U.S. National Academy of Science established a recommended daily intake for vitamin D of 15 µg/day (600 units/day) for people under the age of 70 and 20 µg/day (800 units/day) for people over the age of 70[15]. Due to its broad therapeutic index, vitamin D toxicity is extremely rare. However, close attention should be paid to a prolonged excess of vitamin D intake, which could lead to hypercalcemia, hypercalciuria, and hyperphosphatemia, which are considered to be the initial signs of vitamin D intoxication. In particular, the impairment of the calcium/phosphate balance could lead to cardiovascular damage, such as arrhythmia, cardiac arrest, calcification of the vessels, and hypertension[16]. Recently, the localization of vitamin D3 25-hydroxylase and 25-hydroxyvitamin D3-1α-hydroxylase enzymes in the brain was demonstrated, confirming a local bioactivation of the vitamin D3 prohormone and its presence in the cerebrospinal fluid [17][18][19]. Furthermore, the local catabolism performed by vitamin D3 24-hydroxylase was found[20]. The fact that the CNS can locally perform both its activation and inactivation makes vitD a neurosteroid by definition[21]. Among the many functions that have been attributed to vitamin D, some concern the nervous system. A number of pleiotropic functions were recognized, such as maintaining healthy neuronal development, an adequate trophism of the adult brain, and a slow aging process[22]. VDRs are widely distributed throughout the embryonic and adult brain and appear most prominently in the neuroepithelium and proliferating zones in both rats[23][24][25][26][27] and humans[28]. Their presence has also been noted in neurons and glia of the human prefrontal and the cingulate cortices, thalamus, hypothalamus, cerebellum,

substantia nigra, caudate, putamen, amygdala, and hippocampus [28][29]. Since the initial reports of Stumpf et al., on the presence of vitamin-D-specific nuclear binding in the brain and spinal cord[30][31], evidence has accumulated to suggest that both mRNA encoding the VDR and the protein itself are present in the nervous system. Thus, VDR gene expression has been demonstrated in neuronal and glial cells[32][33][34][35][36][37][38]. Expression of the VDR occurs early in the developing rodent brain at embryonic day (E) 11.5 and E12 in the rat dorsal root ganglion, spinal cord, and midbrain. Increasing levels of VDR expression throughout gestation coincides with increasing levels of apoptosis and decreasing levels of mitosis, and appears to be localized to the neuroepithelium and differentiating fields[39][40]. The sites of expression of VDR change during development, leading to the hypothesis that vitD may play a role in brain development[41]. For these reasons, the many functions that vitD exerts on the central nervous system have made it possible to hypothesize its use to counteract the mechanisms that lead to brain aging and neurodegenerative diseases.

2. A New Possible Treatment Approach to Support Brain Health

The data shown so far demonstrate that there are several functions played by vitamin D and curcumin, especially in neuroprotection and maintaining brain health. Furthermore, these substances could play an important role in the early, mild stages of neurodegenerative diseases and in cognitive impairment. Therefore, the question arose about the use of such compounds regarding combined treatment, whether there is a synergistic effect, and whether they are safe to use in such a combination. In a study published in 2015, in which a scopolamine-hydrobromide-induced Alzheimer's disease rat model was used to reduce the effective action at the synapse by antagonizing muscarinic acetylcholine receptor without changing the concentration of acetylcholine to produce a stage of memory impairment, animals were subjected to a drug treatment schedule for 27 days, where there was a scopolamine group, a scopolamine–curcumin group, a scopolamine–vitamin D group, and a scopolamine–donepezil group. All groups underwent behavioral tests, namely, the rectangular maze and locomotor activity tests, followed by histological analysis for cellular degeneration to determine whether there was amelioration in this stage after treatment, and immunoblotting procedures were used to detect the expression of modified microtubule-associated tau protein. Results show that scopolamine treatment has led to a decrease in transfer latency as a result of significant memory loss, which was obvious in behavioral tests, where a large number of degenerated cells was observed in histological imaging along with a significant presence of abnormal tau protein. In contrast, treatment groups had an ameliorated transfer latency regarding locomotion, indicating improved memory, as seen from the behavioral test results, where the histological examination showed equal cell numbers and similar cell morphology compared to the control groups, which proved the presence of memory regions. Furthermore, there was a strong reduction in tau phosphorylation normalized to β-actin. From these results, they concluded the potential of curcumin and vitD to reverse some cognitive and memory impairment within the same AD-induced model[42].

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