Vitamin D deficiency as a potential risk factor for accelerated aging, impaired hippocampal neurogenesis and cognitive decline: a role for Wnt/β-catenin signaling

Ricardo Gómez-Oliva1,2,*, Noelia Geribaldi-Doldán2,3,*, Samuel Domínguez-García1,2, Lívia Carrascal4, Cristina Verástegui2,3, Pedro Nunez-Abades2,4, Carmen Castro1,2

1Área de Fisiología, Facultad de Medicina, Universidad de Cádiz, Cádiz, Spain
2Instituto de Investigación e Innovación Biomédica de Cádiz, Cádiz, Spain
3Departamento de Anatomía y Embriología Humanas, Facultad de Medicina, Universidad de Cádiz, Cádiz, Spain
4Departamento de Fisiología, Facultad de Farmacia, Universidad de Sevilla, Sevilla, Spain

*Equal contribution

Correspondence to: Carmen Castro, Pedro Nunez-Abades; email: carmen.castro@uca.es, pnunez@us.es

Keywords: vitamin D, neurogenesis, neural stem cells, cognitive performance, Wnt signaling

Received: March 12, 2020   Accepted: June 4, 2020   Published: June 17, 2020

Copyright: Gómez-Oliva et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY 3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

ABSTRACT

Vitamin D is an essential fat-soluble vitamin that participates in several homeostatic functions in mammalian organisms. Lower levels of vitamin D are produced in the older population, vitamin D deficiency being an accelerating factor for the progression of the aging process. In this review, we focus on the effect that vitamin D exerts in the aged brain paying special attention to the neurogenic process. Neurogenesis occurs in the adult brain in neurogenic regions, such as the dentate gyrus of the hippocampus (DG). This region generates new neurons that participate in cognitive tasks. The neurogenic rate in the DG is reduced in the aged brain because of a reduction in the number of neural stem cells (NSC). Homeostatic mechanisms controlled by the Wnt signaling pathway protect this pool of NSC from being depleted. We discuss in here the crosstalk between Wnt signaling and vitamin D, and hypothesize that hypovitaminosis might cause failure in the control of the neurogenic homeostatic mechanisms in the old brain leading to cognitive impairment. Understanding the relationship between vitamin D, neurogenesis and cognitive performance in the aged brain may facilitate prevention of cognitive decline and it can open a door into new therapeutic fields by perspectives in the elderly.

INTRODUCTION

Vitamin D is an essential fat-soluble vitamin that consists of two equally inactive forms, vitamin D2, also called ergocalciferol and vitamin D3 or cholecalciferol. Vitamin D2 can be obtained from vegetable dietary sources and food supplements, whereas vitamin D3 not only can be obtained from dietary sources, but it can also be produced by the human skin after exposure to ultraviolet B radiation in sunlight, with cutaneous production being the main source in the general population. As illustrated in Figure 1, either vitamin D2 or D3 must also be activated by transformations in the liver and kidney. Many variables influence the amount of ultraviolet B radiation from sunlight that reaches the skin and its effectiveness at facilitating the synthesis of vitamin D3. These variables include time of day, season, latitude, altitude, clothing, sunscreen use, pigmentation, and age. The activation of these vitamins into active metabolites occurs in two stages: the first stage is the hydroxylation of carbon 25 of vitamin D2 or D3 catalyzed by 25-hydroxylase leading to calcidiol (also called 25(OH)D or 25-hydroxyvitamin D) in the liver. The second stage is the transformation of 25(OH)D onto calcitriol (also called 1,25(OH)2D3 or 1,25-dihydroxyvitamin D), the most active form of
Vitamin D, catalyzed by 1α-hydroxylase mainly in the kidney. Although, classical function of vitamin D was always limited to calcium and phosphorus homeostasis, the discovery of vitamin D receptor (VDR), present in most tissues and cells in the body, including the brain [1, 2], meant an increase in the number of studies focusing on vitamin D functions. VDR can regulate a large number of genes through 1,25(OH)2D3. The binding of 1,25(OH)2D3 to VDR generates a cytosolic complex that regulates gene transcription and many biological functions (Figure 1). VDR/1,25(OH)2D3 complex can interact with retinoid X receptor (RXR) in the cytosol to form a heterodimeric complex which is recruited to the VDRE (Vitamin D Receptor Element) placed in the promoters of target genes to activate its regulation [3] (Figure 1). The best well known function of 1,25(OH)2D3 is the regulation of calcium homeostasis and bone mineralization. However, ontology analysis describe 11,031 putative VDR target genes identified, 43% of which were involved with metabolism, 19% with cell and tissue morphology, 10% with cell junction and adhesion, 10% with differentiation and development, 9% with angiogenesis, and 5% with epithelial to mesenchymal transition [4]. The number, the location and the VDR expression regulation are determined by cell type [5–7]. These genes are involved in several processes such as cell proliferation, cancer, immune response, glucose homeostasis, cardiovascular homeostasis and activity of the nervous system [8–11].

In the human brain, VDR and vitamin D-metabolizing enzymes are expressed by cerebral structures such as prefrontal cortex, hippocampus, cingulate gyrus, thalamus, hypothalamus, and substantia nigra [12, 13]. In neurons, vitamin D plays different key roles participating in the suppression of oxidative stress, inhibition of inflammation, neuroprotection, down-regulating inflammatory mediators and up-regulating many neurotrophins [13, 14]. Proteomics and gene array analyses show that low levels of vitamin D during gestation influence the regulation of genes involved in nervous system development. These genes play significant roles in the cytoskeletal maintenance, mitochondrial function, synaptic plasticity and cellular proliferation and growth [15]. Regarding neurotrophins, vitamin D exerts neurotrophic support participating in the synthesis of neurotrophic factors. It participates in the synthesis of nerve growth factor (NGF) upregulates, the synthesis of glial cell line-derived neurotrophic factor (GDNF) and neurotrophin 3 (NT-3), and also downregulates levels of neurotrophin 4 (NT-4) [9, 16, 17].

Although there are probably around 50 known metabolites of vitamin D, measurement of serum 25(OH)D is clinically used to define the vitamin D status. The threshold to define adequate stores of 25(OH)D in humans has not been clearly established. Diversity of opinions among researchers has generated different thresholds of vitamin D for human health. Thus, the Institute of Medicine has established the optimal concentration of 25(OH)D serum level being 50 nM (20 ng/mL) for skeletal health [18], insufficiency between 30–50 nM, and deficiency below 30 nM (12 ng/ml), whereas the International Osteoporosis Foundation considers that the adequate values of 25(OH)D for skeletal health are higher than 75 nM (30 ng/mL) [19]. Despite the lack of consensus, it is clear that low levels of vitamin D have detrimental consequences for human health [20].

Though the main source of vitamin D is the sunlight, its deficiency has a high prevalence worldwide and affects half of the world population without excluding those in countries with sun exposure over all the year [21, 22].

**Figure 1. Metabolism of vitamin D.** Vitamin D3 is synthesized in the skin from provitamin D3 (7-dehydrocholesterol) under the influence of UV light. Vitamin D2 (ergocalciferol) is obtained from vegetable dietary sources where it derives from the plant sterol ergosterol. Vitamin D is metabolized first to calcidiol (25(OH)D), and later to the active form calcitriol (1,25(OH)2D3). Interaction of 1,25(OH)2D3 with the vitamin D receptor (VDR), which is an intracellular transcription factor, facilitates its binding to DNA sequences. The binding of the complex VDR/1,25(OH)2D3 to these regulatory sequences (vitamin D response elements (VDREs)) regulate transcription of genes involved in many different cellular homeostatic functions.
thus leading to a great variety of health problems. In addition to the widely studied actions of 1,25(OH)2D3 on intestinal calcium absorption and bone physiology, studies in animal models show that 1,25(OH)2D3 exerts tumor-suppressive actions (anti-angiogenic, anti-invasive, antimetastatic) [23] in several cancers and epidemiological studies report that vitamin D exerts protective effects against several neoplasia, particularly colorectal cancer [24]. Vitamin D deficiency is associated as well with several brain diseases such as schizophrenia, autism spectrum disorders, multiple sclerosis, dementia and Alzheimer’s disease [25–33].

**Vitamin D deficiency and accelerated aging**

Several studies start to consider vitamin D deficiency as a risk factor for accelerated aging [11, 34–36] especially in the elderly [37] since the body reduces its ability to synthesize 1,25(OH)2D3. The skin’s ability to synthesize vitamin D significantly decreases with age, being reduced by more than 50% at 70 years of age compared to 20, whereas other functions such as the intestinal absorption of vitamin D are not affected [38]. Moreover, several studies have reported that hypovitaminosis D is common in aged individuals with previous diseases [39].

Aging is considered to be controlled by multiple genes and environmental factors, and vitamin D is postulated as one of these key factors. Keisala et al. show a direct connection between VDR and aging demonstrating that the phenotype of VDR KO mice includes premature aging and a shorter life span [40]. In addition, VDR KO mice manifest some of the health problems observed during the human aging process such as infertility, muscle atrophy, immune deficiency, osteoporosis and sensitivity to cancer [10, 41, 42]. Additional studies reveal that in addition to a shorter lifespan, VDR mutant mice show other signs of accelerated aging such as skin thickening and wrinkling, alopecia, ectopic calcification, progressive loss of hearing and balance [43, 44]. It is proposed that vitamin D regulates aging by controlling several cell activities such as autophagy, which acts to slow down the aging process by removing dysfunctional mitochondria. Vitamin D also moderates oxidative stress, inflammation, calcium signaling, epigenetics and DNA disorders, including telomere shortening that leads the processes of aging [11, 45–49].

All of this suggests that vitamin D is essential for the maintenance of homeostasis during aging and its deficiency might accelerate its progression. These evidences together with the reduced capacity of human skin to produce vitamin D3 during aging allow to propose a feedback positive loop between vitamin D deficiency and aging: aging provokes more vitamin D deficiency and vitamin D deficiency accelerates the aging process. In the next paragraphs of this review, we will focus on the effect that vitamin D exerts in the aged brain paying special attention to the neurogenic process.

**Hippocampal neurogenesis in the aged brain**

Neurogenesis occurs during development of the central nervous system and remains during the infant and adult stages. New neurons are generated from neural stem cells (NSC) which produce glial cells as well. NSC are ubiquitously distributed along the adult central nervous system [50], however, once the brain has completely developed, neurogenesis predominantly occurs in two specific regions of the adult mammalian brain: the subventricular zone (SVZ) and the dentate gyrus of hippocampus (DG) [51, 52]; nonetheless, there are other minor scattered sites in the brain where neurogenesis occurs such as the hypothalamus or the striatum of several species [53–55]. Within these regions an environment of extracellular signaling molecules creates a neurogenic niche that preserves the necessary conditions to support neurogenesis during a lifetime. Different cell types derived from the NSC progeny can be distinguished within these niches: undifferentiated neural progenitor cells (NPC) produced by activated NSC, and neuronal progenitor cells (neuroblasts) that differentiate into mature neurons. Since the potentiality of NPC is almost identical to that of NSC, they can produce either neuronal progenitors or glial progenitors [56–58] and the fate of NSC may determine the neurogenic capacity of the hippocampus in the long term. NSC activated in the DG undergo a series of asymmetric divisions that produce neurons until they eventually differentiate into astrocytes [59]; thus, the proportion of glial cells produced from NSC over neurons in the DG varies with age and a biased differentiation of NSC towards an astroglial phenotype has been shown in the DG of aged mice, which leads to a depletion of the NSC pool and a reduction of neurogenesis [59, 60]. Extracellular, matrix-bound and membrane-bound signals determine NSC fate toward a neuronal or glial phenotype within the niche [61]. One of these signals is the brain morphogenetic protein (BMP) signaling inhibitor Noggin, which is a key molecule protecting NSC in the aged brain because of its role in the regulation of BMP signaling [60]. Other signaling molecules involved in fate determination are those that initiate the epidermal growth factor receptor (EGFR) or the basic fibroblast growth factor (bFGF) pathways [61–65], which might be stimulated by intracellular signaling molecules such as classical and novel protein kinase C isozymes [66, 67]. Since the year 1965 in which a study about the generation of neurons in the postnatal mammalian brain
was reported, neurogenesis in the adult has been a controversial point [68]. The persistence of hippocampal neurogenesis in the adult mammalian brain has been demonstrated in rodents and other mammalian species, however, a dramatic decline of the rate at which new neurons are generated in older animals has also been observed [51, 69, 70]. Proliferating cells in the subgranular zone (SGZ) of the hippocampus rapidly decline in early childhood [71, 72]. Moreover, the amount of gliogenesis increases whereas that of neurogenesis decreases during aging [70, 73]. Nowadays, the debate continues determining whether human hippocampal neurogenesis remains active during physiological aging. The greatest culmination of this debate has recently come with two very contradictory studies [74, 75]. Both studies were based in the same premise and used a variety of similar antibodies to detect markers of NSC, proliferating cells, migrating neural cells, and various stages of neuronal maturation. One of them concludes that there are undetectable levels of hippocampal neurogenesis in adult brains [74] whereas two other studies conclude that human hippocampal neurogenesis persists throughout adulthood [76] and even in aged adults [75]. Today, the argument that adult neurogenesis persists in the human hippocampus has more adepts, based on BrdU marker and carbon dating but a deeper study on hippocampal adult neurogenesis should be done. Ideally, non-invasive in vivo techniques could be used to detect neurogenesis such as magnetic resonance imaging and positron emission tomography in living humans. This field is under development and there are already some studies describing in vivo imaging of endogenous NPC using these techniques [77].

A key point in the regulation of neurogenesis within neurogenic niches is whether NSC adopt a quiescent state or enter an active state. NSC are exposed to a large variety of signals from the environment, either inhibitory or stimulating, which they integrate resulting in either the maintenance of the quiescent state (qNSC) or the transition into an activated state (aNSC) [78]. These are extracellular matrix, cell-bound or soluble paracrine signals. Interestingly some of these signals regulate stem cells in different tissues in a similar manner; i.e. BMPs promote quiescence whereas activation of the Wnt signaling pathway promotes activity of various types of stem cells [78].

Recent studies demonstrate that the number of hippocampal NSC decreases with age and concomitantly, these cells undergo a transition into a senescent state characterized by a complex morphology. The capacity of these senescent cells to undergo activation is greatly reduced. Thus, NSC remain quiescent for longer periods of time in the DG of aged adults [79, 80]. The quiescence maintenance is probably the major factor contributing to the preservation of the neurogenic rate during aging since it protects NSC reservoir from full depletion. However, a basal activation rate is required for the continuous generation of new neurons. Within this context, the niche plays a major role in reducing qNSC activation in the aged brain. Recent works have demonstrated that inflammatory signals within the aged DG niche may increase quiescence in NSC [79] and have elucidated some of the cellular and molecular mechanisms underlying this phenomenon [80], which include the hypomethylation of genes involved in the Wnt signaling pathway stabilizing the expression profile of some of its components [80].

In general, most studies yield to the aging-induced quiescence conclusion and therefore it seems reasonable to hypothesize that in order to control NSC aging, it is important to regulate the balance between quiescence and activation of NSC by understanding the role of the signals within the niches that can lead NSC to exit quiescence [81]. Interestingly, in addition to the inflammatory signals and cascades that modulate NSC quiescence and activation, the Wnt signaling pathway seems to play a crucial role in regulating the balance quiescence/activation. Several Wnt signaling proteins participate in this process [78, 80].

**Neurogenesis and Wnt signaling**

**Wnt signaling pathways in the central nervous system**

Typically, Wnt proteins play essential roles in different signaling pathways in cellular proliferation, differentiation and cell migration during central nervous system development but recently, studies have shown that Wnt signaling is not only implicated in embryonic development but also in the adult state. Wnt ligands are constitutively expressed in the adult brain and have a role at least in the maintenance of adult brain neurogenesis [82, 83]. The active role of Wnt during brain development is regulating neurogenesis and synaptogenesis of the neural tube [84]. Therefore, constitutive expression of Wnt ligands in the hippocampus of the adult brain might suggest an important role for Wnt in the maintenance and protection of adult hippocampal neurogenesis during adulthood. Moreover, it has been suggested that its deregulation is crucial in neurogenesis during aging [85] and in several neurological disorders such as Alzheimer’s disease, Parkinson’s disease or Schizophrenia [86].

The importance of Wnt signaling can be inferred from the conservation of this pathway in the different organisms across evolution including humans. There are three Wnt stimulated pathways very well characterized:
the canonical β-catenin dependent Wnt pathway, the noncanonical β-catenin independent pathways: planar cell polarity pathway (PCP) and calcium pathway (CaP). These pathways are activated by the binding of a Wnt ligand (Wnt 1-19) to a Frizzled (Fzd) receptor and the LDL-Receptor-related protein coreceptor (LRP5/6) resulting in the activation of Disheveled (DVL) protein which initiate different signaling cascades [87–89].

In the Wnt canonical pathway, Fzd and DVL activation avoid the degradation of β-catenin (Figure 2). In the absence of Wnt, β-catenin is continuously degraded by a protein complex composed of the scaffold proteins Axin and adenomatous polyposis coli (APC), and the kinases casein kinase 1 (CK1) and glycogen synthase kinase 3 beta (GSK3β). CK1 and GSK3β sequentially phosphorylate β-catenin, resulting in β-catenin being recognized and ubiquitinated by the β-Trcp ubiquitin ligase, followed by proteasomal degradation. Binding of Wnt to a Fzd receptor complex induces the binding of Dvl to Fzd and the recruitment of Axin to the membrane, which impairs the destruction complex through the inactivation of GSK3β, promotes the release of β-catenin, and its accumulation in cytoplasm and nuclei leading to β-catenin-activated gene expression [90–92]. Inhibitors of this pathway are the Dickkopf proteins 1-4 (DKK 1-4) and the secreted frizzled related proteins 1-5 (SFRP 1-5) [88]. This branch of the Wnt signaling pathway plays key roles in regulating cell fate, proliferation and survival [93]. The noncanonical pathways PCP and CaP are activated by Wnt4, Wnt5a and Wnt11. These pathways control gene expression through different mechanisms involving RhoA/Rock kinases or the calmodulin kinase CamKII respectively [94]. This branch is more associated with differentiation, cell polarity and migration [93].

**Figure 2. Activation of the Wnt canonical pathway induces β-catenin-regulated gene expression.** Left panel: binding of Wnt to a Frizzled receptor (Fzd) allows its association to Dishevelled proteins (DVL) sequestering Axin and avoiding the formation of the complex composed of Axin, the adenomatous polyposis coli (APC), the kinases casein kinase 1 (CK1) and glycogen synthase kinase 3 beta (GSK3β), which phosphorylates β-catenin, resulting in β-catenin being ubiquitinated by the β-Trcp ubiquitin ligase, followed by proteasomal degradation. Right panel: in the absence of Wnt β-catenin is degraded, whereas Wnt-mediated activation of Fzd induces expression of genes regulated by β-catenin [92].
Wnt and adult neurogenesis

In multiple mammalian tissues canonical Wnt signals within the niche act as self-renewal short range signals for stem cells tissues [89]. There is also increased evidence about Wnt involvement in adult neurogenesis. It has been demonstrated that adult hippocampal progenitor cells express different Wnt ligands which can regulate adult hippocampal neurogenesis acting on both canonical and non-canonical signaling pathways. Recent studies indicate that two major branches of the Wnt signaling pathway, the Wnt/β-Catenin and Wnt/PCP pathways, play essential roles in various steps of adult neurogenesis [86]. However, at least 19 Wnt proteins and 10 Fzd receptors have been found [95]. This diversity of signals and receptors complicate the comprehension of the impact of their different roles in mammals.

The overexpression of Wnt ligands that activate the canonical Wnt β-catenin pathway such as Wnt3 increases neurogenesis of adult hippocampal progenitor cells in vitro and in vivo, suggesting that Wnt signaling enhances proliferation of neural stem cells derived from adult CNS [96, 97]. In agreement with this, Wnt3 signaling inhibition blocks neurogenesis in the DG and decreases long-term retention of episodic memory in adult rats [98]. Accordingly, the deletion of Wnt7a reduced drastically the numbers of newborn neurons in the DG of adult mouse brains preventing NPC proliferation and differentiation through the canonical Wnt/β-catenin pathway [99]. In addition, the implication of Wnt pathway is not only revealed by Wnt ligands but also by their Fzd receptors. Fzd1 knockdown reduces the generation of newborn neurons in the DG and changes the migration of neurons [100]. Another Wnt canonical signaling regulator that participates in adult neurogenesis is GSK3β. Overexpression of this kinase inhibits neurogenesis in the adult DG whereas its inhibition facilitates NSC proliferation and neuronal differentiation (reviewed in Marchetti et al. 2020 [86]). Finally, Wnt-signaling must be finely tuned via Wnt-antagonists such as some Dkk (DKK) proteins. Dkk1 is a potent inhibitor of SVZ- and SGZ-neurogenesis [83].

An additional role for non-canonical Wnt signaling pathway has also been reported. Wnt5a knockdown in the mouse DG impaired neuronal differentiation of progenitor cells and reduced dendritic development of adult-born neurons. In cultured adult hippocampal progenitors, knockdown of noncanonical Wnt5a reduced neuronal differentiation and morphological development of adult neurons, whereas treatment with Wnt5a had the opposite effect. Arredondo et al. determined that Wnt5a signals through CaMKII induce neurogenesis and promotes dendritic development of newborn neurons through activating Wnt/JNK and Wnt/CaMKII signaling suggesting that Wnt5a act as a niche factor in the adult hippocampus that promotes neuronal differentiation and development [101].

Altogether these evidences support the relevance of Wnt signaling pathway on adult neurogenesis. However, the understanding of the complex regulation of Wnt signaling in neurogenesis in the adult brain remains unclear.

Wnt and the aged brain

It has been proposed that neurogenesis could be finely regulated by the expression of specific Wnt receptors in different cell types in young adults and this regulation is altered in the aged brain [102]. In the young adult, hippocampal astrocytes express Wnt3, which stimulates the canonical β-catenin pathway in neuroblasts promoting proliferation and differentiation via paracrine signaling [97]. Autocrine Wnt signals in NSC and NPC within the DG maintain their proliferative activity [103, 104] via the β-catenin pathway. Furthermore, mature granule neurons in the DG express the Wnt inhibitor sFRP3. The expression of this inhibitor can be greatly reduced depending on neuronal activity leading to proliferation of NPC and maturation of newly generate neurons [105]. Non canonical PCP Wnt signaling also plays an important role in neurogenesis in the young adult by inducing neuroblast differentiation and migration [106]. Wnt activity is different in the aged DG compared to the young adult. A reduction in canonical Wnt activity has been described in the hippocampus of aged animals. Wnt3 expression of hippocampal astrocytes and the number of Wnt3-secreting astrocytes is reduced during aging [107]. Decreased Wnt levels together with an elevated expression of Wnt antagonists, such as DKK1, could partially explain the decline in neurogenesis found in aged adults [107–109]. Loss of the Wnt antagonist DKK1 in aged KO mice results in a restoration of the decline in neurogenesis found in non-mutant aged mice. [109]

An attenuation of Wnt signaling has also been found in the SVZ. Zhu et al. detected decreased canonical Wnt activity in the SVZ of old mice compared to younger mice that could be responsible for the reduced adult neurogenesis in rodents [110]. A negative regulator of Wnt is the p38 mitogen-activated kinase (p38 MAPK), which inactivates GSK3β leading to the attenuation of Wnt signaling. Kase et al. have identified p38 MAPK as a key factor in the proliferation of NPC in adult neurogenic niches. p38 expression in adult NSC/NPC is downregulated during aging. Deletion of p38α in NSC/NPC specifically reduces the proliferation of NPC but not stem cells. Overexpression of p38α in NSC/NPC
in the aged mouse SVZ restores NPC proliferation and neurogenesis and prevents age-dependent SVZ atrophy [111].

An effect of Wnt on the transition from qNSC to aNSC that is altered in the aged brain has also been proposed. However, this subject is still an open question. Some evidences point out at a role for canonical Wnt signaling in promoting activation of NSC in the SVZ and DG. Wnt signals produced by astrocytes and NSC induce proliferation and self-renewal of NSC in both niches [97, 99]. Also, elimination of sfrp3 expressed in hippocampal granule neurons results in aberrant NSC activation. Accordingly, sfrp3 gradients regulate qNSC activation regionally. A similar effect is observed upon elimination of DKK1, a Wnt inhibitor expressed by NPC within the hippocampus [105, 109, 112]. In addition, some studies suggest that non-canonical Wnt signaling maintains quiescence of SVZ NSC by facilitating anchoring of NSC within the niche in a mechanism mediated by Rho GTPase Cdc42 [113]. All these suggests that activation requires a switch from non-canonical to canonical Wnt signaling [78]. Wnt signaling molecules have been found to be altered in the pathogenesis of aging. In fact, p38-MAPK is necessary for suppressing the expression of sfrp3 and other Wnt antagonists like DKK1, which inhibit the proliferation of NPCs, and therefore, an age-related reduction in p38 leads to decreased adult neurogenesis via downregulation of Wnt signaling [111].

Studies using mathematical models show that in mice in which the Wnt antagonist DKK1 has been deleted, NSC spend longer periods of time in quiescence but they are more likely to be activated than depleted via their differentiation towards astroglial cells [114]. The study concludes that, high NSC-Wnt activity leads to longer time in quiescence while enhancing the probability of activation.

**Crosstalk between Wnt signaling and vitamin D**

The activation of VDR depends on the presence of 1,25(OH)2D3 which triggers the direct regulation of genes with VDRE (as illustrated in Figure 3). But in some cases, 1,25(OH)2D3 can also indirectly regulate

![Figure 3](image-url)

**Figure 3. Vitamin D interferes with β-catenin induced gene expression via different pathways in different cell types.** Left panel: in cancer cells vitamin D impairs the Wnt/β-catenin signaling pathway. One of these mechanisms relays on the association of the complex VDR/1,25(OH)2D3 to β-catenin to induce VDR-regulated gene expression avoiding β-catenin dependent gene expression. Right panel: in some other non-cancer cell types vitamin D exerts an activating effect of the Wnt signaling pathway by upregulating the expression of the Fzd co-activator Lrp5 or by repressing the expression of the Wnt inhibitors DKK1 y Sfrp2 [116, 171].
genes that do not contain VDRE in their promoters because 1,25(OH)\textsubscript{2}D\textsubscript{3}/VDR can also regulate other pathways through β-catenin which is required for gene expression in response to Wnt signaling (Figure 3). The relationship of this crosstalk is complex and not fully understood in all tissues and cells. The crosstalk between 1,25(OH)\textsubscript{2}D\textsubscript{3} and Wnt/β-catenin pathway has been reported in cancer cells, for example in vitro functional validation studies on melanoma and colon cancer cells showed that elevated 1,25(OH)\textsubscript{2}D\textsubscript{3}/VDR signaling inhibit Wnt/β-catenin signaling genes [24, 115, 116]. Besides, interactions between vitamin D and Wnt/β-catenin pathway has also been reported in different cellular contexts such as colon cancer cells [117], in which 1,25(OH)\textsubscript{2}D\textsubscript{3} acts upregulating the extracellular Wnt inhibitor DKK1 antagonizing of Wnt/β-catenin pathway [118], promoting VDR/β-catenin interactions [119], thus reducing the β-catenin-dependent gene expression or facilitating the sequestration of β-catenin by E-cadherin at plasma membrane adherents junction [117, 119, 120]. Similar mechanisms have been described in other cell types [121, 122].

The 1,25(OH)\textsubscript{2}D\textsubscript{3}-induced repression of β-catenin is not the only mechanism of action of 1,25(OH)\textsubscript{2}D\textsubscript{3} in the Wnt signaling pathway (Figure 3, left). Interestingly, an upregulation of the Wnt/β-catenin pathway by VDR has been described in osteoblasts and keratinocytes in which 1,25(OH)\textsubscript{2}D\textsubscript{3} effects are similar to those of Wnt: 1,25(OH)\textsubscript{2}D\textsubscript{3} induces the expression of the Wnt coreceptor Lrp5 in mouse osteoblast [123] while represses Wnt inhibitors Dkk-1 and Sfrp2 in mesenchymal stem cells (Figure 3, right). In skin, deficiency of VDR produces hair loss and a gradual decrease in epidermal stem cells, while the transcriptional effects of β-catenin are impaired thus normal postnatal hair cycling is only possible with combined action of these two pathways [124]. VDR acts as a Wnt effector and β-catenin as a co-activator to induce transcription of genes involved in the hair follicle differentiation [125]. Theses evidences show that Wnt/β-catenin and 1,25(OH)\textsubscript{2}D\textsubscript{3} can work together or are linked to regulate their target genes. The mechanism of action diverges depending on the biological system. While vitamin D can act as an antagonist of the Wnt/β-catenin pathway in some cancer cells, it can also act as co-activator of Wnt/β-catenin pathway in other physiological cell types.

Considering the cross talk between vitamin D and Wnt pathway and the considerable number of reports demonstrating a role for Wnt signaling in the regulation of neurogenesis, it would be reasonable to hypothesize that vitamin D may play a role in adult neurogenesis affecting brain tasks associated with neurogenesis such as cognitive performance.

**Axis vitamin D deficiency, cognitive decline and neurogenesis in the aged brain**

Nowadays, it is well established that hippocampal neurogenesis is involved in learning and memory; studies where hippocampal neurogenesis was ablated in rodents have shown diminished performance in tests that require memory such as the Morris water maze, spatial and object recognition and pattern separation [99, 126, 127]. Furthermore, adult hippocampal neurogenesis has been linked to cognitive abilities both in rodents and in non-human primates [128]. In the human hippocampus, neurogenesis is still a controversial subject. Recent study suggests that hippocampal neurogenesis declines at young ages to disappear in the adult [74] and a similar decline has also been observed in the hippocampus of other large brain species [129]. However, several evidences show that new neurons can be generated daily throughout the lifespan [75, 76] suggesting a possible functional role for hippocampal neurogenesis in human cognitive capacity [70, 74]. Some studies define potential cognitive functions of new neurons of the hippocampal formation including the ability to discriminate among similar experiences. In fact, neurogenesis functions in fear conditioning are especially striking in discriminative paradigms, where shock is associated with only one of two similar-appearing situations. Consistent with a discrimination function, adult mice where hippocampal neurogenesis is ablated or deficient are frequently capable of initial learning in spatial tasks but have difficulty performing a spatial reversal or discriminating nearby locations or cues [126]. Another potential cognitive function of hippocampal neurons is incorporating time into episodic memories and enabling forgetting of old memories. Increasing neurogenesis after the formation of a memory was enough to induce forgetting in adult mice. Accordingly, during infancy, when hippocampal neurogenesis levels are high and freshly generated, memories tend to be rapidly forgotten (infantile amnesia), decreasing neurogenesis after memory formation mitigated forgetting [130]. Hippocampus-dependent cognitive abilities decline with age in human at the same time that adult hippocampal neurogenesis [51, 131, 132]. Most of these studies use rodent models and they suggest a similar scenario may occur in humans although recent data suggest that maybe age-related decline is not so pronounced in humans [70]. Furthermore, cognitive functions can be regulated by certain positive and negative modulators of hippocampal neurogenesis. Inflammatory signals negatively affect neurogenesis and therefore, considering that chronic neuroinflammation is a common feature of normal aging, hippocampal neurogenesis and cognitive processes would be negatively affected across the lifespan [133–135]. On the contrary exercise training
and environmental enrichment have been suggested as positive factors since it has been demonstrated that both situations stimulate hippocampal neurogenesis [136–138] and improve cognitive function [139–141]. Besides, recent evidences demonstrated that exercise program can be intergenerationally inherited. Among others, these inherited effects include: improving the performance of non-spatial and spatial cognitive tasks, increasing the number of specific cell populations of adult hippocampal neurogenesis and producing changes in hippocampal gene expression [142].

Vitamin D deficiency is a risk factor for accelerated aging and cognitive decline [11, 34–36]. In addition, several studies suggest that low levels of vitamin D are associated with a substantial cognitive decline in the elderly [143, 144]. Aging processes in vitamin D deficient subjects could also promote the beginning of many age-related disorders such as a decline in cognition, depression, osteoporosis, hypertension and cardiovascular disease, diabetes, cancer, muscle weakness, and Alzheimer’s disease [145–151]. In light of these findings some authors propose to use 25(OH)D sufficiency as a biomarker of delayed aging [152] and some others propose vitamin D supplementation as a possible therapeutic agent for the treatment of age-related disorders such as cognitive decline [153]. Recent findings suggest vitamin D deficiency as a risk for cognitive decline in elderly people. Low vitamin D levels (<25 nmol/L) have been associated with a cognitive decline in aged individuals studied over a 6-year period [154]. Similarly, in a different study, low 25(OH)D levels (<35 nmol/L) were associated with poorer performance on cognitive test in older European men [155]. In addition, other studies show that 25(OH)D (<50 nmol/L) is strongly associated with executive functioning and the attention processing speed but no association between 25(OH)D and memory were found [156]. Whereas another clinical study with 1604 elderly men found no significant association between low vitamin D levels (<50 nmol/L) and cognitive decline after adjusting for co-variates [157]. In agreement with this latter study, Lee et al. did not find a direct correlation between vitamin D deficiency and cognitive impairment although they did not discard that vitamin D could be an important covariable factor [158].

Thus, the emerging evidences that suggest associations between lower serum vitamin D concentrations and poor cognitive performance have recently increased. Occasionally, vitamin D levels could be normal but insufficient to accomplish its function. This is the case of impaired VDR function. It is known that VDR gene polymorphisms decrease the VDR affinity for vitamin D but in contrast to vitamin D deficiency studies, little is known about the influence of VDR genes on cognition. Evidences point to the VDR gene variants being linked to changes in cognitive performance in old adults [159, 160]. A clinical study with 563 85-year-old participants showed cognitive differences depending on polymorphisms in the VDR gene [161]. VDR polymorphisms influence susceptibility for cognitive decline in average, 67.4 years old patients with Parkinson’s disease. Particularly, the functional VDR polymorphism Fokl, is associated with cognitive decline in patients with Parkinson’s disease, which worsen with each additional copy of the allele [162]. VDR is expressed in human brain [163] covering a large area including the hippocampus [164] which is partially involved in cognitive abilities and is particularly affected by neurodegenerative disorders.

Besides the link between vitamin D effectivity (vitamin D deficiency or VDR polymorphism) and cognitive decline the mechanism underlying is poorly understood. 1,25(OH)2D3 exerts a direct effect on NSC proliferation, survival, and neuron/oligodendrocyte differentiation participating in the process of remyelination [31–33]. Other studies using different models of knockout mice show an effect of vitamin D deficiency on adult hippocampal neurogenesis. 1α-hydroxylase knockout mice, which lacks the ability to produce the active form of vitamin D (1,25(OH)2D3) [165] and BALB/c mice fed a vitamin D deficient diet [166] show an increase in neuroblast proliferation in the hippocampal DG, but a decrease in the survival of adult hippocampal neurons. Moreover, it has also been observed alterations in neuronal differentiation not only in VDR deficient mice [167] but also in a mice model of Parkinson’s disease in which MPTP downregulates VDR expression [168]. An effect of vitamin D in neuronal differentiation of dopamine systems during development has been described [169]. Accordingly, nutritional supplementation with vitamin D in a mouse model of Alzheimer’s disease improves cognition concomitantly enhancing neurogenesis [170]. Also, it facilitates differentiation and neurite outgrowth of HN9.10e embryonic hippocampal cells [168].

Altogether these findings suggest a role for vitamin D in preserving cognitive function in older adults and indicate that vitamin D is not only related with aging but also with cognitive performance. Hence, it seems reasonable to hypothesize that the cellular mechanisms underlying the effects of vitamin D on cognitive performance in the elderly might be mediated by its capacity to stimulate neurogenesis. They also highlight a role for canonical Wnt signaling cascade as the molecular mechanisms triggering these effects. Considering the role that canonical Wnt signaling plays in stimulating neurogenesis in the aged brain and in maintaining the
balance between aNSC/qNSC avoiding depletion, it may be possible that a deficiency in vitamin D results in Wnt signaling imbalance, impairing the gradual activation of NSC required to maintain a neurogenic rate. However, more studies are required to demonstrate this hypothesis. Only a few human trials have been performed to analyze the benefits of vitamin D supplementation in cognitive performance. However, evidences suggest a beneficial role for vitamin D in brain physiology by the promotion of neurotransmission, neurogenesis, synaptogenesis, amyloid clearance and the prevention of neuronal death [153].

**CONCLUSIONS**

In conclusion, vitamin D has been shown to exert an important role in neurogenesis and neuronal survival. In hippocampal progenitor cells, vitamin D may potentially act as a co-activator of Wnt/β-catenin pathway to preserve neurogenesis in the aged brain. Thus, the decrease of vitamin D during the senescence processes could have a role in the upregulation of Wnt antagonistic signals responsible of the decrease in neurogenesis that may precede the decline in cognitive performance (summarized in Figure 4), and more

---

**Figure 4. Hypothetical role of vitamin D in facilitating the activation of quiescent neural stem cells (qNSC) in the aged brain and its consequences in cognitive impairment.** The effects of vitamin D on cognitive decline might be mediated by its capacity to stimulate neurogenesis in the old neurogenic niche. Several factors such as inflammation, and Wnt signaling inhibition facilitate the state of quiescence in NSC diminishing the neurogenic rate [78, 80]. High NSC-Wnt activity leads to longer time in quiescence while enhancing the probability of activation [114]. Vitamin D may activate canonical Wnt signaling through the repression of Wnt inhibitors such as DKK1 and prolonging the time NSC spend in quiescence, increasing their probability to be activated and avoiding being depleted via their differentiation towards astroglial cells [114]. It may be possible that a deficiency in vitamin D results in Wnt signaling imbalance, impairing the gradual activation of NSC required to maintain a neurogenic rate. Thus, hypovitaminosis D might impair these mechanisms leading to a reduction in neurogenesis resulting in cognitive decline.
studies are required to fully understand the relationship between vitamin D, neurogenesis and cognitive performance in the elderly.

**CONFLICTS OF INTEREST**

The authors declare that there are no conflicts of interest.

**FUNDING**

This work was supported by the Spanish Ministerio de Ciencia, Innovación y Universidades (grant number RTI2018-099908-B-C21), and co-financed by the 2014-2020 ERDF Operational Programme and by the Department of Economy, Knowledge, Business and University of the Regional Government of Andalusia. Project reference: FEDER-UCA18-10664.

**REFERENCES**

1. Nowak R, Szota J, Mazurek U. Vitamin D receptor gene (VDR) transcripts in bone, cartilage, muscles and blood and microarray analysis of vitamin D responsive genes expression in paravertebral muscles of juvenile and adolescent idiopathic scoliosis patients. BMC Musculoskelet Disord. 2012; 13:259. https://doi.org/10.1186/1471-2474-13-259 PMID: 23259508

2. Cui X, Pelekanos M, Liu PY, Burne TH, McGrath JJ, Eyles DW. The vitamin D receptor in dopamine neurons; its presence in human substantia nigra and its ontogenesis in rat midbrain. Neuroscience. 2013; 236:77–87. https://doi.org/10.1016/j.neuroscience.2013.01.035 PMID: 23352937

3. Umar M, Sastry KS, Chouchane AI. Role of vitamin D beyond the skeletal function: a review of the molecular and clinical studies. Int J Mol Sci. 2018; 19:1618. https://doi.org/10.3390/ijms19061618 PMID: 29849001

4. Saccone D, Asani F, Bornman L. Regulation of the vitamin D receptor gene by environment, genetics and epigenetics. Gene. 2015; 561:171–80. https://doi.org/10.1016/j.gene.2015.02.024 PMID: 25682935

5. Nagpal S, Na S, Rathnachalam R. Noncalcemic actions of vitamin D receptor ligands. Endocr Rev. 2005; 26:662–87. https://doi.org/10.1210/er.2004-0002 PMID: 15798098

6. Picciano MF. Vitamin D Status and Health. Critical Reviews in Food Science and Nutrition. 2010; 50:24–5. https://doi.org/10.1080/10408398.2010.526858

7. Hossein-nezhad A, Spira A, Holick MF. Influence of vitamin D status and vitamin D3 supplementation on genome wide expression of white blood cells: a randomized double-blind clinical trial. PLoS One. 2013; 8:e58725. https://doi.org/10.1371/journal.pone.0058725 PMID: 23527013

8. García E, Wion-Barbot N, Montero-Menei CN, Berger F, Wion D. New clues about vitamin D functions in the nervous system. Trends Endocrinol Metab. 2002; 13:100–05. https://doi.org/10.1016/s1043-2760(01)00547-1 PMID: 11893522

9. Brown J, Bianco JI, McGrath JJ, Eyles DW. 1,25-dihydroxyvitamin D3 induces nerve growth factor, promotes neurite outgrowth and inhibits mitosis in embryonic rat hippocampal neurons. Neurosci Lett. 2003; 343:139–43. https://doi.org/10.1016/s0304-3940(03)00303-3 PMID: 12759183

10. Bouillon R, Carmeliet G, Verlinden L, van Etten E, Verslype A, Luderer HF, Lieben L, Mathieu C, Demay M. Vitamin D and human health: lessons from vitamin D receptor null mice. Endocr Rev. 2008; 29:726–76. https://doi.org/10.1210/er.2008-0004 PMID: 18694980

11. Berridge MJ. Vitamin D deficiency accelerates ageing and age-related diseases: a novel hypothesis. J Physiol. 2017; 595:6825–36. https://doi.org/10.1113/JP274887 PMID: 28949008

12. Cui X, Pertile R, Eyles DW. The vitamin D receptor (VDR) binds to the nuclear matrix via its hinge domain: a potential mechanism for the reduction in VDR mediated transcription in mitotic cells. Mol Cell Endocrinol. 2018; 472:18–25. https://doi.org/10.1016/j.mce.2017.11.015 PMID: 29183808

13. Cui X, Gooch H, Petty A, McGrath JJ, Eyles DW. Vitamin D and the brain: genomic and non-genomic actions. Mol Cell Endocrinol. 2017; 453:131–43. https://doi.org/10.1016/j.mce.2017.05.035 PMID: 28579120

14. Lang F, Ma K, Leibrock CB. 1,25(OH)2D3 in brain function and neuropsychiatric disease. Neurosignals. 2019; 27:40–49. https://doi.org/10.1371/journal.pone.0058725 PMID: 23527013

15. Eyles D, Almeras L, Benech P, Patatian A, Mackay-Sim A, McGrath J, Féron F. Developmental vitamin D deficiency alters the expression of genes encoding mitochondrial, cytoskeletal and synaptic proteins in
the adult rat brain. J Steroid Biochem Mol Biol. 2007; 103:538–45.
https://doi.org/10.1016/j.jsbmb.2006.12.096
PMID:17293106

16. Naveilhan P, Neveu I, Wion D, Brachet P. 1,25-dihydroxyvitamin D3, an inducer of glial cell line-derived neurotrophic factor. Neuroreport. 1996; 7:2171–75.
https://doi.org/10.1097/00001756-199609020-00023
PMID:8930983

17. Neveu I, Naveilhan P, Baudet C, Brachet P, Mettsis M. 1,25-dihydroxyvitamin D3 regulates NT-3, NT-4 but not BDNF mRNA in astrocytes. Neuroreport. 1994; 6:124–26.
https://doi.org/10.1097/00001756-199412300-00032
PMID:7703399

18. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, Durazo-Arvizu RA, Gallagher JC, Gallo RL, Jones G, Kovacs CS, Mayne ST, Rosen CJ, Shapses SA. The 2011 report on dietary reference intakes for calcium and vitamin D from the institute of medicine: what clinicians need to know. J Clin Endocrinol Metab. 2011; 96:53–58.
https://doi.org/10.1210/jc.2010-2704
PMID:21118827

19. Dawson-Hughes B, Mithal A, Bonjour JP, Boonen S, Burckhardt P, Fuleihan GE, Josse RG, Lips P, Morales-Torres J, Yoshimura N. IOF position statement: vitamin D recommendations for older adults. Osteoporos Int. 2010; 21:1151–54.
https://doi.org/10.1007/s00198-010-1285-3
PMID:20422154

20. Bikle DD. Vitamin D: newer concepts of its metabolism and function at the basic and clinical level. J Endocr Soc. 2020; 4:bvz038.
https://doi.org/10.1210/jendso/bvz038
PMID:32051922

21. van Schoor NM, Lips P. Worldwide vitamin D status. Best Pract Res Clin Endocrinol Metab. 2011; 25:671–80.
https://doi.org/10.1016/j.beem.2011.06.007
PMID:21872807

22. Palacios C, Gonzalez L. Is vitamin D deficiency a major global public health problem? J Steroid Biochem Mol Biol. 2014; 144:138–45.
https://doi.org/10.1016/j.jsbmb.2013.11.003
PMID:24239505

23. Leyssens C, Verlinden L, Verstuyf A. Antineoplastic effects of 1,25(OH)2D3 and its analogs in breast, prostate and colorectal cancer. Endocr Relat Cancer. 2013; 20:R31–47.
https://doi.org/10.1530/ERC-12-0381
PMID:23319494

24. Ferrer-Mayorga G, Larriba MJ, Crespo P, Muñoz A. Mechanisms of action of vitamin D in colon cancer. J Steroid Biochem Mol Biol. 2019; 185:1–6.
https://doi.org/10.1016/j.jsbmb.2018.07.002
PMID:29981368

25. Chiang M, Natarajan R, Fan X. Vitamin D in schizophrenia: a clinical review. Evid Based Ment Health. 2016; 19:6–9.
https://doi.org/10.11136/eb-2015-102117
PMID:26767392

26. Fernel E, Bejerot S, Westerlund J, Miniscalco C, Simila H, Eyles D, Gillberg C, Humble MB. Autism spectrum disorder and low vitamin D at birth: a sibling control study. Mol Autism. 2015; 6:3.
https://doi.org/10.1007/s00394-015-0970-6
PMID:25874075

27. Brouwer-Brolsma EM, Dhonukshe-Rutten RA, van Wijngaarden JP, van der Zwaluw NL, Sohl E, In’t Veld PH, van Dijk SC, Swart KM, Enneman AW, Ham AC, van Schoor NM, van der Velde N, Uitterlinden AG, et al. Low vitamin D status is associated with more depressive symptoms in dutch older adults. Eur J Nutr. 2016; 55:1525–34.
https://doi.org/10.1007/s00394-015-0970-6
PMID:26141257

28. Eskandari G, Ghajarzadeh M, Yekaninejad MS, Sahraian MA, Ghorj J, Rajaei F, Norouzi-Javidan A, Faridar A, Azimi A. Comparison of serum vitamin D level in multiple sclerosis patients, their siblings, and healthy controls. Iran J Neurol. 2015; 14:81–85.
PMID:26056552

29. Afzal S, Bojesen SE, Nordestgaard BG. Reduced 25-hydroxyvitamin D and risk of alzheimer’s disease and vascular dementia. Alzheimers Dement. 2014; 10:296–302.
https://doi.org/10.1016/j.jalz.2013.05.1765
PMID:23871764

30. Peitl V, Silić A, Orlović I, Vidrih B, Crnković D, Karlović D. Vitamin D and neurotrophin levels and their impact on the symptoms of schizophrenia. Neuropsychobiology. 2020; 79:179–85.
https://doi.org/10.1159/000504577
PMID:31812959

31. Shirazi HA, Rasouli J, Ciric B, Rostami A, Zhang GX. 1,25-dihydroxyvitamin D3 enhances neural stem cell proliferation and oligodendrocyte differentiation. Exp Mol Pathol. 2015; 98:240–45.
https://doi.org/10.1016/j.yexmp.2015.02.004
PMID:25681066

32. Shirazi HA, Rasouli J, Ciric B, Wei D, Rostami A, Zhang GX. 1,25-dihydroxyvitamin D3 suppressed experimental autoimmune encephalomyelitis through both
8. Panin D, Sergienko V, Karlinsky D, Marinova-Kovacheva L, Barkovsky I. Vitamin D and aging: neurobiological mechanisms of longevity and aging. Cell. 2016; 166:822–39.

9. Planelles I, Chong S, Ouyang M, Huch C, Martin-Cabello B, Eisenberg-Manes C, et al. Nutritional and biological hallmarks of ageing. Br J Surg. 2018; 105:1548–62.

10. Pusa T, Mäkitie M, Eronen A, Tassabehji M, Länsiö N. Effect of vitamin D supplementation on bone formation and microstructure in older women: a randomized controlled trial. Calcif Tissue Int. 2018; 102:299-306.

11. Quach HL, Riggs BL, Melton LJ 3rd. Bone formation rate and bone mineral density in an elderly population. J Bone Miner Res. 2002; 17:599-605.

12. Radtke A, Wunderlin M, Pfaffenrath V, Schilling B, Grehl T. Age-related decrease in the expression of the osteocalcin gene is associated with osteosclerosis in the human spine. Osteoporos Int. 2001; 12:391-399.

13. Recker RR, Orwoll ES, Odenwald SH, Haussler MR, Barlow CE, Cauley JA, et al. Effect of vitamin D3 and calcium supplementation on bone density and bone turnover in healthy elderly women: a 2-year randomized controlled trial. J Clin Endocrinol Metab. 2002; 87:3640-3647.

14. Recker RR, Orwoll ES, Odenwald SH, Haussler MR, Barlow CE, Cauley JA, et al. Effect of vitamin D3 and calcium supplementation on bone density and bone turnover in healthy elderly women: a 2-year randomized controlled trial. J Clin Endocrinol Metab. 2002; 87:3640-3647.

15. Recker RR, Orwoll ES, Odenwald SH, Haussler MR, Barlow CE, Cauley JA, et al. Effect of vitamin D3 and calcium supplementation on bone density and bone turnover in healthy elderly women: a 2-year randomized controlled trial. J Clin Endocrinol Metab. 2002; 87:3640-3647.

16. Recker RR, Orwoll ES, Odenwald SH, Haussler MR, Barlow CE, Cauley JA, et al. Effect of vitamin D3 and calcium supplementation on bone density and bone turnover in healthy elderly women: a 2-year randomized controlled trial. J Clin Endocrinol Metab. 2002; 87:3640-3647.

17. Recker RR, Orwoll ES, Odenwald SH, Haussler MR, Barlow CE, Cauley JA, et al. Effect of vitamin D3 and calcium supplementation on bone density and bone turnover in healthy elderly women: a 2-year randomized controlled trial. J Clin Endocrinol Metab. 2002; 87:3640-3647.
50. Magavi SS, Leavitt BR, Macklis JD. Induction of neurogenesis in the neocortex of adult mice. Nature. 2000; 405:951–55. https://doi.org/10.1038/35016083 PMID: 10879536

51. Kuhn HG, Dickinson-Anson H, Gage FH. Neurogenesis in the dentate gyrus of the adult rat: age-related decrease of neuronal progenitor proliferation. J Neurosci. 1996; 16:2027–33. https://doi.org/10.1523/JNEUROSCI.16-06-02027.1996 PMID: 8604047

52. Doetsch F, García-Verdugo JM, Alvarez-Buylla A. Cellular composition and three-dimensional organization of the subventricular germinal zone in the adult mammalian brain. J Neurosci. 1997; 17:5046–61. https://doi.org/10.1523/JNEUROSCI.17-13-05046.1997 PMID: 9185542

53. Ernst A, Alkass K, Bernard S, Salehpour M, Perl S, Tisdale J, Possnert G, Druid H, Frisén J. Neurogenesis in the striatum of the adult human brain. Cell. 2014; 156:1072–83. https://doi.org/10.1016/j.cell.2014.01.044 PMID: 24561062

54. Luzzati F, Nato G, Oboti L, Vigna E, Rolando C, Armentano M, Bonfanti L, Fasolo A, Peretto P. Quiescent neuronal progenitors are activated in the juvenile Guinea pig lateral striatum and give rise to transient neurons. Development. 2014; 141:4065–75. https://doi.org/10.1242/dev.107987 PMID: 25336736

55. Dayer AG, Cleaver KM, Abouantoun T, Cameron HA. New GABAergic interneurons in the adult neocortex and striatum are generated from different precursors. J Cell Biol. 2005; 168:415–27. https://doi.org/10.1083/jcb.200407053 PMID: 15684031

56. Reynolds BA, Weiss S. Generation of neurons and astrocytes from isolated cells of the adult mammalian central nervous system. Science. 1992; 255:1707–10. https://doi.org/10.1126/science.1553558 PMID: 1553558

57. Doetsch F, Caillé I, Lim DA, García-Verdugo JM, Alvarez-Buylla A. Subventricular zone astrocytes are neural stem cells in the adult mammalian brain. Cell. 1999; 97:703–16. https://doi.org/10.1016/s0092-8674(00)80783-7 PMID: 10380923

58. Torroglosa A, Murillo-Carretero M, Romero-Grimaldi C, Matarredona ER, Campos-Caro A, Estrada C. Nitric oxide decreases subventricular zone stem cell proliferation by inhibition of epidermal growth factor receptor and phosphoinositide-3-kinase/Akt pathway. Stem Cells. 2007; 25:88–97. https://doi.org/10.1634/stemcells.2006-0131 PMID: 16960136

59. Encinas JM, Michurina TV, Peunova N, Park JH, Tordo J, Peterson DA, Fishell G, Koulakov A, Enikolopov G. Division-coupled astrocytic differentiation and age-related depletion of neural stem cells in the adult hippocampus. Cell Stem Cell. 2011; 8:566–79. https://doi.org/10.1016/j.stem.2011.03.010 PMID: 21549330

60. Díaz-Moreno M, Armenteros T, Gradari S, Hortigüela R, García-Corzo L, Fontán-Lozano Á, Trejo JL, Mira H. Noggin rescues age-related stem cell loss in the brain of senescent mice with neurodegenerative pathology. Proc Natl Acad Sci USA. 2018; 115:11625–30. https://doi.org/10.1073/pnas.1813205115 PMID: 30352848

61. Codega P, Silva-Vargas V, Paul A, Maldonado-Soto AR, Deleo AM, Pastrana E, Doetsch F. Prospective identification and purification of quiescent adult neural stem cells from their in vivo niche. Neuron. 2014; 82:545–59. https://doi.org/10.1016/j.neuron.2014.02.039 PMID: 24811379

62. Kuhn HG, Winkler J, Kempermann G, Thal LJ, Gage FH. Epidermal growth factor and fibroblast growth factor-2 have different effects on neural progenitors in the adult rat brain. J Neurosci. 1997; 17:5820–29. https://doi.org/10.1523/JNEUROSCI.17-15-05820.1997 PMID: 9221780

63. Gonzalez-Perez O, Romero-Rodriguez R, Soriano-Navarro M, Garcia-Verdugo JM, Alvarez-Buylla A. Epidermal growth factor induces the progeny of subventricular zone type B cells to migrate and differentiate into oligodendrocytes. Stem Cells. 2009; 27:2032–43. https://doi.org/10.1002/stem.119 PMID: 19544429

64. Rabaneda LG, Geribaldi-Doldán N, Murillo-Carretero M, Carrasco M, Martinez-Salas JM, Verástegui C, Castro C. Altered regulation of the Spry2/Dyrk1A/PP2A triad by homocysteine impairs neural progenitor cell proliferation. Biochim Biophys Acta. 2016; 1863:3015–26. https://doi.org/10.1016/j.bbamcr.2016.09.018 PMID: 27686255

65. Carrasco M, Rabaneda LG, Murillo-Carretero M, Ortega-Martínez S, Martínez-Chantar ML, Woodhoo A, Luka Z, Wagner C, Lu SC, Mato JM, Micó JA, Castro C. Glycine n-methyltransferase expression in the hippocampus and its role in neurogenesis
and cognitive performance. Hippocampus. 2014; 24:840–52.  
https://doi.org/10.1002/hipo.22274 PMID:24687756

66. Geribaldi-Doldán N, Gómez-Oliva R, Domínguez-García S, Nunez-Abades P, Castro C. Protein kinase C: targets to regenerate brain injuries? Front Cell Dev Biol. 2019; 7:39.  
https://doi.org/10.3389/fcell.2019.00039 PMID:30949480

67. Domínguez-García S, Geribaldi-Doldán N, Gómez-Oliva R, Ruiz FA, Carrascal L, Bolívar J, Verástegui C, Garcia-Alloza M, Macías-Sánchez AJ, Hernández-Galán R, Nunez-Abades P, Castro C. A novel PKC activating molecule promotes neuroblast differentiation and delivery of newborn neurons in brain injuries. Cell Death Dis. 2020; 11:262.  
https://doi.org/10.1038/s41419-020-2453-9 PMID:32321920

68. Altman J, Das GD. Autoradiographic and histological evidence of postnatal hippocampal neurogenesis in rats. J Comp Neurol. 1965; 124:319–35.  
https://doi.org/10.1002/cne.901240303 PMID:5861717

69. Amrein I, Isler K, Lipp HP. Comparing adult hippocampal neurogenesis in mammalian species and orders: influence of chronological age and life history stage. Eur J Neurosci. 2011; 34:978–87.  
https://doi.org/10.1111/j.1460-9558.2011.07804.x PMID:21929629

70. Spalding KL, Bergmann Q, Alkass K, Bernard S, Salehpour M, Huttner HB, Boström E, Westerlund I, Vial C, Buchholz BA, Possnert G, Mash DC, Druid H, Frisén J. Dynamics of hippocampal neurogenesis in adult humans. Cell. 2013; 153:1219–24.  
https://doi.org/10.1016/j.cell.2013.05.002 PMID:23746839

71. Knoth R, Singec I, Ditter M, Pantazis G, Capetian P, Meyer RP, Horvat V, Volk B, Kempermann G. Murine features of neurogenesis in the human hippocampus across the lifespan from 0 to 100 years. PLoS One. 2010; 5:e8809.  
https://doi.org/10.1371/journal.pone.0008809 PMID:20126454

72. Dennis CV, Suh LS, Rodriguez ML, Kril JJ, Sutherland GT. Human adult neurogenesis across the ages: an immunohistochemical study. Neuropathol Appl Neurobiol. 2016; 42:621–38.  
https://doi.org/10.10111/nan.12337 PMID:27424496

73. Kempermann G, Kuhn HG, Gage FH. Experience-induced neurogenesis in the senescent dentate gyrus. J Neurosci. 1998; 18:3206–12.  
https://doi.org/10.1523/JNEUROSCI.18-09-03206.1998 PMID:9547229

74. Sorrells SF, Paredes MF, Cebrian-Silla A, Sandoval K, Qi D, Kelley KW, James D, Mayer S, Chang J, Auguste Ki, Chang EF, Gutierrez AJ, Kriegstein AR, et al. Human hippocampal neurogenesis drops sharply in children to undetectable levels in adults. Nature. 2018; 555:377–381.  
https://doi.org/10.1038/nature25975 PMID:29513649

75. Moreno-Jiménez EP, Flor-García M, Terreros-Roncal J, Rábano A, Cafiñi F, Pallas-Bazarrn A, Ávila J, Llorens-Martín M. Adult hippocampal neurogenesis is abundant in neurologically healthy subjects and drops sharply in patients with alzheimer’s disease. Nat Med. 2019; 25:554–60.  
https://doi.org/10.1038/s41591-019-0375-9 PMID:30911133

76. Tobin MK, Musaraca K, Disouky A, Shetti A, Bheri A, Honer WG, Kim N, Dawe RJ, Bennett DA, Arfanakis K, Lazarov O. Human hippocampal neurogenesis persists in aged adults and alzheimer’s disease patients. Cell Stem Cell. 2019; 24:974–82.e3.  
https://doi.org/10.1016/j.stem.2019.05.003 PMID:31130513

77. Granot D, Scheinost D, Markakis EA, Papademetris X, Shapiro EM. Serial monitoring of endogenous neuroblast migration by cellular MRI. Neuroimage. 2011; 57:817–24.  
https://doi.org/10.1016/j.neuroimage.2011.04.063 PMID:21571076

78. Urbán N, Blomfield IM, Guillemot F. Quiescence of adult mammalian neural stem cells: a highly regulated rest. Neuron. 2019; 104:834–48.  
https://doi.org/10.1016/j.neuron.2019.09.026 PMID:31805262

79. Martín-Suárez S, Valero J, Muro-García T, Encinas JM. Phenotypical and functional heterogeneity of neural stem cells in the aged hippocampus. Aging Cell. 2019; 18:e12958.  
https://doi.org/10.1111/acel.12958 PMID:30989815

80. Schouten M, Bielefeld P, Garcia-Corzo L, Passchier EM, Gradari S, Jungenitz T, Pons-Espinal M, Gebara E, Martín-Suárez S, Lucassen PJ, De Vries HE, Trejo JL, Schwarzacher SW, et al. Circadian glucocorticoid oscillations preserve a population of adult hippocampal neural stem cells in the aging brain. Mol Psychiatry. 2019. [Epub ahead of print].  
https://doi.org/10.1038/s41380-019-0440-2 PMID:31222184

81. Morrow CS, Moore DL. Stem cell aging? blame it on the niche. Cell Stem Cell. 2019; 24:353–54.
82. Oliva CA, Vargas JY, Inestrosa NC. Wnts in adult brain: from synaptic plasticity to cognitive deficiencies. Front Cell Neurosci. 2013; 7:224. https://doi.org/10.3389/fncel.2013.00224 PMID:24348327

83. Varela-Nallar L, Inestrosa NC. Wnt signaling in the regulation of adult hippocampal neurogenesis. Front Cell Neurosci. 2013; 7:100. https://doi.org/10.3389/fncel.2013.00100 PMID:23805076

84. Hur EM, Zhou FQ. GSK3 signalling in neural development. Nat Rev Neurosci. 2010; 11:539–51. https://doi.org/10.1038/nrn2870 PMID:20648061

85. Kalamakis G, Brüne D, Ravichandran S, Bolz J, Fan W, Ziebell F, Steihl T, Catalá-Martinez F, Kupke J, Zhao S, Llorens-Bobadilla E, Bauer K, Limpert S, et al. Quiescence modulates stem cell maintenance and regenerative capacity in the aging brain. Cell. 2019; 176:1407–19.e14. https://doi.org/10.1016/j.cell.2019.01.040 PMID:30827680

86. Marchetti B, Tirolo C, L’Episcopo F, Caniglia S, Testa N, Smith JA, Pluchino S, Serapide MF. Parkinson’s disease, aging and adult neurogenesis: Wnt/β-catenin signalling as the key to unlock the mystery of endogenous brain repair. Aging Cell. 2020; 19:e13101. https://doi.org/10.1111/acel.13101 PMID:32050297

87. Willert K, Nusse R. Wnt proteins. Cold Spring Harb Perspect Biol. 2012; 4:a007864. https://doi.org/10.1101/cshperspect.a007864 PMID:22952392

88. Sastre-Perona A, Santistebean P. Role of the Wnt pathway in thyroid cancer. Front Endocrinol (Lausanne). 2012; 3:31. https://doi.org/10.3389/fendo.2012.00031 PMID:22645520

89. Clevers H, Loh KM, Nusse R. Stem cell signaling. An integral program for tissue renewal and regeneration: Wnt signaling and stem cell control. Science. 2014; 346:1248012. https://doi.org/10.1126/science.1248012 PMID:25278615

90. Papkoff J, Rubinfeld B, Schryver B, Polakis P. Wnt-1 regulates free pools of catenins and stabilizes APC-catenin complexes. Mol Cell Biol. 1996; 16:2128–34. https://doi.org/10.1128/mcb.16.5.2128 PMID:8628279

91. Rubinfeld B, Albert I, Porfiri E, Fiol C, Munemitsu S, Polakis P. Binding of GSK3beta to the APC-beta-catenin complex and regulation of complex assembly. Science. 1996; 272:1023–26. https://doi.org/10.1126/science.272.5264.1023 PMID:8638126

92. Logan CY, Nusse R. The Wnt signaling pathway in development and disease. Annu Rev Cell Dev Biol. 2004; 20:781–810. https://doi.org/10.1146/annurev.cellbio.20.010403.113126 PMID:15473860

93. Nusse R, Clevers H. Wnt/β-catenin signaling, disease, and emerging therapeutic modalities. Cell. 2017; 169:985–99. https://doi.org/10.1016/j.cell.2017.05.016 PMID:28575679

94. Gao B. Wnt regulation of planar cell polarity (PCP). Curr Top Dev Biol. 2012; 101:263–95. https://doi.org/10.1016/B978-0-12-394592-1.00008-9 PMID:23140633

95. Miller JR. The Wnts. Genome Biol. 2002; 3:REVIEWS3001. https://doi.org/10.1186/gb-2001-3-1-reviews3001 PMID:11806834

96. Zhou CJ, Zhao C, Pleasure SJ. Wnt signaling mutants have decreased dentate granule cell production and radial glial scaffolding abnormalities. J Neurosci. 2004; 24:121–26. https://doi.org/10.1523/JNEUROSCI.437-13.2004 PMID:14715945

97. Lie DC, Colamarino SA, Song HJ, Désiré L, Mira H, Consiglio A, Lein ES, Jessberger S, Lansford H, Dearie AR, Gage FH. Wnt signalling regulates adult hippocampal neurogenesis. Nature. 2005; 437:1370–75. https://doi.org/10.1038/nature04108 PMID:16251967

98. Jessberger S, Clark RE, Broadbent NJ, Clemenson GD Jr, Consiglio A, Lie DC, Squire LR, Gage FH. Dentate gyrus-specific knockdown of adult neurogenesis impairs spatial and object recognition memory in adult rats. Learn Mem. 2009; 16:147–54. https://doi.org/10.1101/lm.1172609 PMID:19181621

99. Qu Q, Sun G, Murai K, Ye P, Li W, Asuelime G, Cheung YT, Shi Y. Wnt7a regulates multiple steps of neurogenesis. Mol Cell Biol. 2013; 33:2551–59. https://doi.org/10.1128/MCB.00325-13 PMID:23629626

100. Mardones MD, Andaur GA, Varas-Godoy M, Henriquez JF, Salech F, Behrens MI, Couve A, Inestrosa NC, Varela-Nallar L. Frizzled-1 receptor regulates adult hippocampal neurogenesis. Mol Brain. 2016; 9:29.
101. Arredondo SB, Guerrero FG, Herrera-Soto A, Jensen-Flores J, Bustamante DB, Øфиate-Ponce A, Henny P, Varas-Godoy M, Inestroza NC, Varela-Nallar L. Wnt5a promotes differentiation and development of adult-born neurons in the hippocampus by noncanonical Wnt signaling. Stem Cells. 2020; 38:422–36. https://doi.org/10.1002/stem.3121 PMID:31721364

102. Choe Y, Pleasure SJ, Mira H. Control of adult neurogenesis by short-range morphogen-signaling molecules. Cold Spring Harb Perspect Biol. 2015; 8:a018887. https://doi.org/10.1101/cshperspect.a018887 PMID:26637286

103. Wexler EM, Paucer A, Kornblum HI, Palmer TD, Geschwind DH. Endogenous Wnt signaling maintains neural progenitor cell potency. Stem Cells. 2009; 27:1130–41. https://doi.org/10.1002/stem.36 PMID:19418460

104. Qu Q, Sun G, Li W, Yang S, Ye P, Zhao C, Yu RT, Gage FH, Evans RM, Shi Y. Orphan nuclear receptor TLX activates Wnt/beta-catenin signalling to stimulate neural stem cell proliferation and self-renewal. Nat Cell Biol. 2010; 12:31–40. https://doi.org/10.1038/ncb2001 PMID:20010817

105. Jang MH, Bonaguidi MA, Kitabatake Y, Sun J, Song J, Kang E, Jun H, Zhong C, Su Y, Guo JU, Wang MX, Sailor KA, Kim JY, et al. Secreted frizzled-related protein 3 regulates activity-dependent adult hippocampal neurogenesis. Cell Stem Cell. 2013; 12:215–23. https://doi.org/10.1016/j.stem.2012.11.021 PMID:23395446

106. Schafer ST, Han J, Pena M, von Bohlen Und Halbach O, Peters J, Gage FH. The Wnt adaptor protein ATP6AP2 regulates multiple stages of adult hippocampal neurogenesis. J Neurosci. 2015; 35:4983–98. https://doi.org/10.1523/JNEUROSCI.1410-14.2015 PMID:25810528

107. Okamoto M, Inoue K, Iwamura H, Terashima K, Soya H, Asashima M, Kwabara T. Reduction in paracrine Wnt3 factors during aging causes impaired adult neurogenesis. FASEB J. 2011; 25:3570–82. https://doi.org/10.1096/fj.11-184697 PMID:21746862

108. Miranda CJ, Braun L, Jiang Y, Hester ME, Zhang L, Riolo M, Wang H, Rao M, Altura RA, Kaspar BK. Aging brain microenvironment decreases hippocampal neurogenesis through Wnt-mediated survivin signaling. Aging Cell. 2012; 11:542–52. https://doi.org/10.1111/j.1474-9726.2012.00816.x PMID:22404871

109. Seib DR, Corsini NS, Ellwanger K, Plaa C, Mateos A, Pitzer C, Niehrs C, Celikel T, Martin-Villalba A. Loss of dickkopf-1 restores neurogenesis in old age and counteracts cognitive decline. Cell Stem Cell. 2013; 12:204–14. https://doi.org/10.1016/j.stem.2012.11.010 PMID:23395445

110. Zhu Y, Demidov ON, Goh AM, Virshup DM, Lane DP, Bulavin DV. Phosphatase WIP1 regulates adult neurogenesis and Wnt signaling during aging. J Clin Invest. 2014; 124:3263–73. https://doi.org/10.1172/JCI73015 PMID:24911145

111. Kase Y, Otsu K, Shimazaki T, Okano H. Involvement of p38 in age-related decline in adult neurogenesis via modulation of Wnt signaling. Stem Cell Reports. 2019; 12:1313–28. https://doi.org/10.1016/j.stemcr.2019.04.010 PMID:31080114

112. Sun J, Bonaguidi MA, Jun H, Guo JU, Sun GJ, Will B, Yang Z, Jang MH, Song H, Ming GL, Christian KM. A septo-temporal molecular gradient of sfrp3 in the dentate gyrus differentially regulates quiescent adult hippocampal neural stem cell activation. Mol Brain. 2015; 8:52. https://doi.org/10.1186/s13041-015-0143-9 PMID:26337530

113. Chavali M, Klingener M, Kokkosis AG, Garkun Y, Felong S, Maffei A, Aguirre A. Non-canonical Wnt signaling regulates neural stem cell quiescence during homeostasis and after demyelination. Nat Commun. 2018; 9:36. https://doi.org/10.1038/s41467-017-02440-0 PMID:29296000

114. Ziebell F, Dehler S, Martin-Villalba A, Marciniak-Czochra A. Revealing age-related changes of adult hippocampal neurogenesis using mathematical models. Development. 2018; 145:dev153544. https://doi.org/10.1242/dev.153544 PMID:29229768

115. Muralidhar S, Filia A, Nsengimana J, Poźniak J, O’Shea SJ, Diaz JM, Harland M, Randerson-Moor JA, Reichrath J, Laye JP, van der Weyden L, Adams DJ, Bishop DT, Newton-Bishop J. Vitamin D-VDR signaling inhibits Wnt/b-catenin-mediated melanoma progression and promotes antitumor immunity. Cancer Res. 2019; 79:5986–98. https://doi.org/10.1158/0008-5472.CAN-18-3927 PMID:31690667

116. Larriba MJ, González-Sancho JM, Barbáchano A, Niell N, Ferrer-Mayorga G, Muñoz A. Vitamin D is a
multilevel repressor of Wnt/b-catenin signaling in cancer cells. Cancers (Basel). 2013; 5:1242–60. https://doi.org/10.3390/cancers5041242 PMID:24202444

117. Larriba MJ, Ordóñez-Morán P, Chicote I, Martín-Fernández G, Puig I, Muñoz A, Pálmer HG. Vitamin D receptor deficiency enhances Wnt/β-catenin signaling and tumor burden in colon cancer. PLoS One. 2011; 6:e23524. https://doi.org/10.1371/journal.pone.0023524 PMID:21858154

118. Aguilera O, Peña C, García JM, Larriba MJ, Ordóñez-Morán P, Navarro D, Barbáchano A, López de Silanes I, Ballestar E, Fraga MF, Esteller M, Gamallo C, Bonilla F, et al. The Wnt antagonist DICKOPF-1 gene is induced by 1alpha,25-dihydroxyvitamin D3 associated to the differentiation of human colon cancer cells. Carcinogenesis. 2007; 28:1877–84. https://doi.org/10.1093/carcin/bgm094 PMID:17449905

119. Pálmer HG, González-Sancho JM, Espada J, Berciano MT, Puig I, Baulida J, Quintanilla M, Cano A, de Herreros AG, Lafarga M, Muñoz A. Vitamin D(3) promotes the differentiation of colon carcinoma cells by the induction of e-cadherin and the inhibition of beta-catenin signaling. J Cell Biol. 2001; 154:369–87. https://doi.org/10.1083/jcb.200102028 PMID:11470825

120. Larriba MJ, Valle N, Pálmer HG, Ordóñez-Morán P, Alvarez-Diaz S, Becker KF, Gamallo C, de Herreros AG, González-Sancho JM, Muñoz A. The inhibition of Wnt/beta-catenin signalling by 1alpha,25-dihydroxvitamin D3 is abrogated by Snail1 in human colon cancer cells. Endocr Relat Cancer. 2007; 14:141–51. https://doi.org/10.1677/ERC-06-0028 PMID:17395983

121. He W, Kang YS, Dai C, Liu Y. Blockade of Wnt/β-catenin signaling by paricalcitol ameliorates proteinuria and kidney injury. J Am Soc Nephrol. 2011; 22:90–103. https://doi.org/10.1681/ASN.2009121236 PMID:21030600

122. Martínez-Moreno JM, Muñoz-Castañeda JR, Herencia C, Oca AM, Estepa JC, Canalejo R, Rodríguez-Ortiz ME, Perez-Martínez P, Aguilera-Tejero E, Canalejo A, Rodríguez M, Almadén Y. In vascular smooth muscle cells paricalcitol prevents phosphate-induced Wnt/β-catenin activation. Am J Physiol Renal Physiol. 2012; 303:F1136–44. https://doi.org/10.1152/ajprenal.00684.2011 PMID:22874762

123. Fretz JA, Zella LA, Kim S, Shevde NK, Pike JW. 1,25-dihydroxyvitamin D3 induces expression of the Wnt signaling co-regulator LRP5 via regulatory elements located significantly downstream of the gene’s transcriptional start site. J Steroid Biochem Mol Biol. 2007; 103:440–45. https://doi.org/10.1016/j.jsbmb.2006.11.018 PMID:17229572

124. Cianferotti L, Demay MB. VDR-mediated inhibition of DKK1 and SFRP2 suppresses adipogenic differentiation of murine bone marrow stromal cells. J Cell Biochem. 2007; 101:80–88. https://doi.org/10.1002/jcb.21151 PMID:17212358

125. Pálmer HG, Anjos-Afonso F, Carmeliet G, Takeda H, Watt FM. The vitamin D receptor is a Wnt effector that controls hair follicle differentiation and specifies tumor type in adult epidermis. PLoS One. 2008; 3:e1483. https://doi.org/10.1371/journal.pone.0001483 PMID:18213391

126. Clelland CD, Choi M, Romberg C, Clemenson GD Jr, Fragnieri A, Tyers P, Jessberger S, Saksida LM, Barker RA, Gage FH, Bussey TJ. A functional role for adult hippocampal neurogenesis in spatial pattern separation. Science. 2009; 325:210–13. https://doi.org/10.1126/science.1173215 PMID:19590004

127. Snyder JS, Hong NS, McDonald RJ, Wojtowicz JM. A role for adult neurogenesis in spatial long-term memory. Neuroscience. 2005; 130:843–52. https://doi.org/10.1016/j.neuroscience.2004.10.009 PMID:15652983

128. Aizawa K, Ageyama N, Yokoyama C, Hisatsune T. Age-dependent alteration in hippocampal neurogenesis correlates with learning performance of macaque monkeys. Exp Anim. 2009; 58:403–07. https://doi.org/10.1538/expanim.58.403 PMID:19654438

129. Parolisi R, Cozzi B, Bonfanti L. Humans and dolphins: decline and fall of adult neurogenesis. Front Neurosci. 2018; 12:497. https://doi.org/10.3389/fnins.2018.00497 PMID:30079011

130. Akers KG, Martinez-Canabal A, Restivo L, Yiu AP, De Cristofaro A, Hsiang HL, Wheeler AL, Gusjkolen A, Niibori Y, Shoji H, Ohira K, Richards BA, Miyakawa T, et al. Hippocampal neurogenesis regulates forgetting during adulthood and infancy. Science. 2014; 344:598–602. https://doi.org/10.1126/science.1248903 PMID:24812394
131. Yassa MA, Mattfeld AT, Stark SM, Stark CE. Age-related memory deficits linked to circuit-specific disruptions in the hippocampus. Proc Natl Acad Sci USA. 2011; 108:8873–78. https://doi.org/10.1073/pnas.1101567108 PMID:21555581

132. Yassa MA, Lacy JW, Stark SM, Albert MS, Gallagher M, Stark CE. Pattern separation deficits associated with increased hippocampal CA3 and dentate gyrus activity in nondemented older adults. Hippocampus. 2011; 21:968–79. https://doi.org/10.1002/hipo.20808 PMID:20865732

133. Yirmiya R, Goshen I. Immune modulation of learning, memory, neural plasticity and neurogenesis. Brain Behav Immun. 2011; 25:181–213. https://doi.org/10.1016/j.bbi.2010.10.015 PMID:20970492

134. Kohman RA, Rhodes JS. Neurogenesis, inflammation and behavior. Brain Behav Immun. 2013; 27:22–32. https://doi.org/10.1016/j.bbi.2012.09.003 PMID:22985677

135. Green HF, Nolan YM. Inflammation and the developing brain: consequences for hippocampal neurogenesis and behavior. Neurosci Biobehav Rev. 2014; 40:20–34. https://doi.org/10.1016/j.neubiorev.2014.01.004 PMID:24462889

136. Kempermann G, Kuhn HG, Gage FH. More hippocampal neurons in adult mice living in an enriched environment. Nature. 1997; 386:493–95. https://doi.org/10.1038/386493a0 PMID:9087407

137. Kempermann G, Gage FH. Experience-dependent regulation of adult hippocampal neurogenesis: effects of long-term stimulation and stimulus withdrawal. Hippocampus. 1999; 9:321–32. https://doi.org/10.1002/(SICI)1098-1063(1999)9:3<321::AID-HIPO11>3.0.CO;2-C PMID:10401646

138. van Praag H, Kempermann G, Gage FH. Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. Nat Neurosci. 1999; 2:266–70. https://doi.org/10.1038/6368 PMID:10195220

139. Chandler K, Dosso H, Simard S, Siddiqi S, Rudyk C, Salmaso N. Differential effects of short-term environmental enrichment in juvenile and adult mice. Neuroscience. 2020; 429:23–32. https://doi.org/10.1016/j.neuroscience.2019.12.028 PMID:31917341

140. Cooper C, Moon HY, van Praag H. On the run for hippocampal plasticity. Cold Spring Harb Perspect Med. 2018; 8:a029736. https://doi.org/10.1101/cshperspect.a029736 PMID:28495803

141. Komitova M, Mattsson B, Johansson BB, Eriksson PS. Enriched environment increases neural stem/progenitor cell proliferation and neurogenesis in the subventricular zone of stroke-lesioned adult rats. Stroke. 2005; 36:1278–82. https://doi.org/10.1161/01.STR.0000166197.94147.59 PMID:15879324

142. McGreevy KR, Tezanos P, Ferreiro-Villar I, Pallé A, Moreno-Serrano M, Esteve-Codina A, Lamas-Toranzo I, Bermejo-Álvarez P, Fernández-Punzano J, Martin-Montalvo A, Montalbán R, Ferrón SR, Radford EJ, et al. Intergenerational transmission of the positive effects of physical exercise on brain and cognition. Proc Natl Acad Sci USA. 2019; 116:10103–12. https://doi.org/10.1073/pnas.1816781116 PMID:31010925

143. Llewellyn DJ, Lang IA, Langa KM, Melzer D. Vitamin D and cognitive impairment in the elderly U.S. Population. J Gerontol A Biol Sci Med Sci. 2011; 66:59–65. https://doi.org/10.1093/gerona/glq185 PMID:21041201

144. Soni M, Kos K, Lang IA, Jones K, Melzer D, Llewellyn DJ. Vitamin D and cognitive function. Scand J Clin Lab Invest Suppl. 2012; 243:79–82. https://doi.org/10.3109/00365513.2012.681969 PMID:22536767

145. Annweiler C, Schott AM, Berrut G, Chauviré V, Le Gall DJ. Vitamin D and cognitive function. Scand J Clin Lab Invest. 2010; 121:425–30. https://doi.org/10.1097/01.STR.0000166197.94157.22 PMID:20628264

146. Pittas AG, Dawson-Hughes B. Vitamin D and diabetes. J Steroid Biochem Mol Biol. 2010; 121:425–30. https://doi.org/10.3109/00365513.2012.681969 PMID:22536767

147. Meehan M, Penckofer S. The role of vitamin D in the aging adult. J Aging Gerontol. 2014; 2:60–71. https://doi.org/10.1161/00031857.94157.22 PMID:20628264

148. Berridge MJ. Vitamin D cell signalling in health and disease. Biochem Biophys Res Commun. 2015; 460:53–71. https://doi.org/10.1016/j.bbrc.2015.01.008 PMID:25998734
149. Costantino S, Paneni F, Cosentino F. Ageing, metabolism and cardiovascular disease. J Physiol. 2016; 594:2061–73. https://doi.org/10.1113/JP270538 PMID:26391109

150. Dawson-Hughes B. Vitamin D and muscle function. J Steroid Biochem Mol Biol. 2017; 173:313–16. https://doi.org/10.1016/j.jsbmb.2017.03.018 PMID:28341251

151. Wang H, Chen W, Li D, Yin X, Zhang X, Olsen N, Zheng SG. Vitamin D and chronic diseases. Aging Dis. 2017; 8:346–53. https://doi.org/10.14336/AD.2016.1021 PMID:28580189

152. Milman S, Schulder-Katz M, Deluty J, Zimmerman ME, Crandall JP, Barzilai N, Melamed ML, Atzmon G. Individuals with exceptional longevity manifest a delayed association between vitamin D insufficiency and cognitive impairment. J Am Geriatr Soc. 2014; 62:153–58. https://doi.org/10.1111/jgs.12601

153. Brouwer-Brolsma EM, de Groot LC. Vitamin D and cognition in older adults: an update of recent findings. Curr Opin Clin Nutr Metab Care. 2015; 18:11–16. https://doi.org/10.1097/MCO.0000000000000114 PMID:25225898

154. Llewellyn DJ, Lang IA, Langa KM, Muniz-Terrera G, Phillips CL, Cherubini A, Ferrucci L, Melzer D. Vitamin D and risk of cognitive decline in elderly persons. Arch Intern Med. 2010; 170:1135–41. https://doi.org/10.1001/archinternmed.2010.173 PMID:20625021

155. Lee DM, Tajar A, Ulubaev A, Pendleton N, O’Neill TW, O’Connor DB, Bartfai G, Boonen S, Bouillon R, Casanueva FF, Finn JD, Forti G, Giwercman A, et al, and EMAS study group. Association between 25-hydroxyvitamin D levels and cognitive performance in middle-aged and older european men. J Neurol Neurosurg Psychiatry. 2009; 80:722–29. https://doi.org/10.1136/jnnp.2008.165720 PMID:19460797

156. Buell JS, Scott TM, Dawson-Hughes B, Dallal GE, Rosenberg IH, Folstein MF, Tucker KL. Vitamin D is associated with cognitive function in elders receiving home health services. J Gerontol A Biol Sci Med Sci. 2009; 64:888–95. https://doi.org/10.1093/gerona/glp032 PMID:19377013

157. Silin Y, Paudel ML, Taylor BC, Fink HA, Ishani A, Canales MT, Yaffe K, Barrett-Connor E, Orwoll ES, Shikany JM, Leblanc ES, Cauley JA, Ensrud KE, and Osteoporotic Fractures in Men (MrOS) Study Research Group. 25-hydroxyvitamin D levels and cognitive performance and decline in elderly men. Neurology. 2010; 74:33–41. https://doi.org/10.1212/WNL.0b013e3181c7197b PMID:19940271

158. Lee DH, Chon J, Kim Y, Seo YK, Park EJ, Won CW, Soh Y. Association between vitamin D deficiency and cognitive function in the elderly korean population: a korean frailty and aging cohort study. Medicine (Baltimore). 2020; 99:e19293. https://doi.org/10.1097/MD.0000000000019293 PMID:32080146

159. Lanske B, Razzaque MS. Vitamin D and aging: old concepts and new insights. J Nutr Biochem. 2007; 18:771–77. https://doi.org/10.1016/j.jnutbio.2007.02.002 PMID:17531460

160. Montero-Odasso M, Duque G. Vitamin D in the aging musculoskeletal system: an authentic strength preserving hormone. Mol Aspects Med. 2005; 26:203–19. https://doi.org/10.1016/j.mam.2005.01.005 PMID:15811435

161. Kuningas M, Mooljaart SP, Jolles J, Slagboom PE, Westendorp RG, van Heemst D. VDR gene variants associate with cognitive function and depressive symptoms in old age. Neurobiol Aging. 2009; 30:466–73. https://doi.org/10.1016/j.neurobiolaging.2007.07.001 PMID:17714831

162. Gatto NM, Paul KC, Sinsheimer JS, Bronstein JM, Bordelon Y, Rausch R, Ritz B. Vitamin D receptor gene polymorphisms and cognitive decline in parkinson’s disease. J Neurol Sci. 2016; 370:100–06. https://doi.org/10.1016/j.jns.2016.09.013 PMID:27772376

163. Sutherland MK, Somerville MJ, Yoong LK, Bergeron C, Haussler MR, McLachlan DR. Reduction of vitamin D hormone receptor mRNA levels in alzheimer as compared to huntington hippocampus: correlation with calbindin-28k mRNA levels. Brain Res Mol Brain Res. 1992; 13:239–50. https://doi.org/10.1016/0169-328x(92)9032-7 PMID:1317496

164. Eyles DW, Smith S, Kinobe R, Hewison M, McGrath JJ. Distribution of the vitamin D receptor and 1 alpha-hydroxylase in human brain. J Chem Neuroanat. 2005; 29:21–30. https://doi.org/10.1016/j.jchemneu.2004.08.006 PMID:15589699

165. Groves NJ, McGrath JJ, Burne TH. Vitamin D as a neurosteroid affecting the developing and adult brain. Annu Rev Nutr. 2014; 34:117–41.
166. Groves NJ, Burne TH. Sex-specific attentional deficits in adult vitamin D deficient BALB/c mice. Physiol Behav. 2016; 157:94–101. https://doi.org/10.1016/j.physbeh.2016.01.033 PMID:26836278

167. Zhu Y, Zhou R, Yang R, Zhang Z, Bai Y, Chang F, Li L, Sokabe M, Goltzman D, Miao D, Chen L. Abnormal neurogenesis in the dentate gyrus of adult mice lacking 1,25-dihydroxy vitamin D3 (1,25-(OH)2 D3). Hippocampus. 2012; 22:421–33. https://doi.org/10.1002/hipo.20908 PMID:21125584

168. Cataldi S, Arcuri C, Hunot S, Mecca C, Codini M, Laurenti ME, Ferri I, Loreti E, Garcia-Gil M, Traina G, Conte C, Ambesi-Impiombato FS, Beccari T, et al. Effect of vitamin D in HN9.10e embryonic hippocampal cells and in hippocampus from MPTP-induced parkinson’s disease mouse model. Front Cell Neurosci. 2018; 12:31.

169. Pertile RA, Cui X, Eyles DW. Vitamin D signaling and the differentiation of developing dopamine systems. Neuroscience. 2016; 333:193–203. https://doi.org/10.1016/j.neuroscience.2016.07.020 PMID:27450565

170. Morello M, Landel V, Lacassagne E, Baranger K, Annweiler C, Féron F, Millet P. Vitamin D improves neurogenesis and cognition in a mouse model of alzheimer’s disease. Mol Neurobiol. 2018; 55:6463–79. https://doi.org/10.1007/s12035-017-0839-1 PMID:29318446

171. Shah S, Islam MN, Dakshanamurthy S, Rizvi I, Rao M, Herrell R, Zinser G, Valrance M, Aranda A, Moras D, Norman A, Welsh J, Byers SW. The molecular basis of vitamin D receptor and beta-catenin crossregulation. Mol Cell. 2006; 21:799–809. https://doi.org/10.1016/j.molcel.2006.01.037 PMID:16543149