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SHORT REVIEW ARTICLE

Molecular basis of vitamin D action in neurodegeneration: the story of a team perspective

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Abstract
Vitamin D, a secosteroid hormone, has, over the years, mainly been known for its classic role in the maintenance of calcium homeostasis of the human body. However, there is increasing understanding that vitamin D contributes to the regulation of Ca^{2+} homeostasis, especially via voltage-gated calcium channels, in another major organ that uses calcium, the brain. Almost 30 years ago, the role of dysregulation in the aging brain and in Alzheimer's disease (AD) gave rise to the Ca^{2+} hypothesis of brain aging and dementia. We thus made calcium homeostasis the starting point of our studies, proposing the notion that the consequences of long-term deficiency and/or inefficient utilization of vitamin D may cause the disruption of calcium homeostasis in neurons, this creating a vulnerability of neurons to aging and neurodegeneration. In this mini-review, we aim to describe the potential of vitamin D (cholecalciferol) as a neurosteroid based on our findings and conclusions.

Keywords Neurodegeneration · Vitamin D · VDR · Pdia3 · Amyloid beta · Alzheimer's disease · APP · Secretase · Plasma membrane

The start

Sutherland et al. provided the first study indicating the potential role of vitamin D receptor (VDR) in Alzheimer's disease (AD) in 1992 [1], reporting reduced levels of VDR mRNA in the hippocampal CA1 and CA2 pyramidal neurons of AD patients [1]. Following this study, several genetic studies were published reporting identification of a novel AD risk locus on chromosome 12 [2–5]. These studies were, however, particularly important because, although not stated by the researchers, the risk locus also carries the VDR gene. Our initial hypothesis was thus simple: if vitamin D is known for its role in maintenance of calcium homeostasis of the human body, especially in bones, it should also have at least some functions in the brain, the other major organ that uses calcium. On the other hand, verifying this theory was not an easy task due to a lack of equipment in our facilities at that time. Nevertheless, we concluded that if our hypothesis was correct, then we might be able to validly propose a genetic association between VDR and Alzheimer's disease for the very same reason that an association between VDR and other bone diseases had already been established [6]. Our investigation having accordingly supplied valuable evidence, we demonstrated the association of VDR polymorphisms with AD, also publishing this data for the first time in the literature [7]. The study provided the first evidence of a genetic relation of vitamin D and its receptor VDR in AD, thus in brain function. Studies followed, confirming this relationship at both the genetic level [8–14] and the biochemical level [15–21]. Subsequently, the amazing potential of this vitamin D-VDR pathway directed our research further, for the next 10 years, towards investigation into their molecular action.

Where to begin testing the molecular basis of vitamin D action in neurodegeneration?

What was known about the role of vitamin D in the brain, or what at least offered a clue as to this, was its role in the regulation of neurotrophic factors as well as its relation to voltage-sensitive calcium channels [22–24]. On the basis of

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the above, we concluded that neurotrophic factors, particularly nerve growth factor (NGF) and the L-type voltage-sensitive calcium channels alpha 1C and alpha 1D (LVSCC-A1C and LVSCC-A1D), would be good targets for research. Thus, vitamin D and its receptor VDR as well as a potential receptor, namely, protein disulfide isomerase 3 (Pdia3), were tested in our laboratories in two models with two different perspectives: (1) a cellular model of AD in primary cortical neuron cultures in order to test the preventive and treatment effect of vitamin D on a well-known neurodegenerative disorder and (2) a model that uses disruption of the vitamin D-VDR/Pdia3 pathway by small interfering RNAs (siRNA) in primary cortical neuron cultures in order to test the capacity of vitamin D to contribute to regulation of known genes important for neurodegeneration and neuronal survival. Additionally, this gene-silencing approach also helped us to create a partial vitamin D deficiency model.

In 2011, armed with the results of the first model, we demonstrated that amyloid beta (Aβ) induces neurodegeneration by promoting the expression of voltage-sensitive calcium channels and altering NGF synthesis [25]. Even more importantly, we also showed a significant suppression of the expression of VDR protein with a direct effect of one of the pathological hallmarks of AD [25]. This particularly surprising result also provided a possible molecular explanation for the findings of Sutherland et al.

The next issue to be addressed was as follows: Does Aβ itself have an effect on vitamin D catabolism or anabolism? We showed that the induction of 25-hydroxyvitamin D_3 24-hydroxylase (24OHase) [26], the enzyme that accelerates vitamin D catabolism and the attenuation of 1α-hydroxylase [27], is responsible for the production of the active form of vitamin D by Aβ. The high expression of VDR and the 24OHase enzyme in hippocampal neurons led us to speculate that hippocampal neurons require large amounts of vitamin D; this may mean that cognitive functions require large amounts of vitamin D [28]. These results also revealed that there are several overlapping pathways between Aβ pathology and vitamin D action.

What if vitamin D-VDR/Pdia3 pathway disruption is a novel model of neurodegeneration?

We continued our investigations by posing three basic questions to aid us in determining the role of vitamin D in neurodegeneration. The first question was as follows: Might silencing the VDR gene or Pdia3 via siRNAs mimic Aβ toxicity? or Can it generate a novel neurodegeneration model? The disruption of vitamin D pathways via either vitamin D-VDR or vitamin D-Pdia3 by siRNAs, a tool widely used for post-transcriptional gene silencing, regardless of whether it was due to the presence of Aβ, resulted in the induction of voltage-sensitive calcium channels A1C and A1D, inducible nitric oxide synthase (iNOS), and attenuated NGF. Each of these events is known to have the potential to induce Aβ accumulation and neurodegeneration [28–30]. The data indicated that either Aβ or VDR siRNA-treated neurons induced very similar amounts of iNOS and LVSCC-A1C mRNAs compared to untreated ones [25, 26, 29–32].

Can we test this hypothesis in a particular neurodegenerative disorder, namely AD?

Based on the previously reported results, we concluded that the disruption of vitamin D pathway-related mechanisms may trigger neurodegeneration and/or Aβ production. We therefore asked the second question: Does vitamin D or its deficiency have an effect on the enzymes which regulate the production of Aβ? To answer this question, we focused on the effects of disrupted VDR/Pdia3 pathways and/or $1,25(OH)_2D_3$ treatments on the components of secretase complexes and Aβ production. Amyloid precursor protein (APP) processing, which is responsible for Aβ peptide production in AD pathogenesis, includes three enzyme complexes, α-, β-, or γ-secretase. α-secretases are members of the ADAM (a disintegrin and metalloprotease domain) family, including ADAM 10, 9, and 17. β-secretase is an aspartic protease like the beta amyloid-cleaving enzyme (BACE1, 2). The γ-secretase complex consists of presenilin-1 (PS1)/presenilin-2 (PS2), anterior pharynx-defective 1 (Aph-1), presenilin enhancer 2 (Pen2), and nicastrin [33]. First, we examined the possible VDR-dependent transcriptional regulation of the proteins involved in APP processing. The other potential receptor, Pdia3, was also evaluated due to its possible involvement as an endoplasmic reticulum chaperone in the APP processing pathway. Our data indicated that vitamin D and/or its receptors regulate the expression of certain proteins involved in secretases, including presenilin 1, presenilin 2, NICASTRIN, ADAM10, BACE1, and the APP substrate in either VDR, Pdia3, double-silenced neurons, or vitamin D–treated neurons; however, the regulation is time-, concentration-, and receptor-dependent [34].

Although our data indicate the possible regulation of all three secretases and the substrate APP, there was a third question: Is Aβ production affected by vitamin D or its deficiency? We demonstrated the induction of intracellular Aβ1−42 production in VDR, Pdia3, or double-silenced neurons [34]. The results showed that $1,25(OH)_2D_3$ treatments attenuated intracellular Aβ 1−42 production and secretion [34]. Meanwhile, Grimm et al. investigated vitamin D and therapeutically used analogs, including maxacalcitol, calcipotriol, alfacalcidol, paricalcitol, and doxercalciferol, on AD-related mechanisms. They found that D2 and D3 analogs attenuated Aβ production and increased Aβ degradation in neuroblastoma cells and

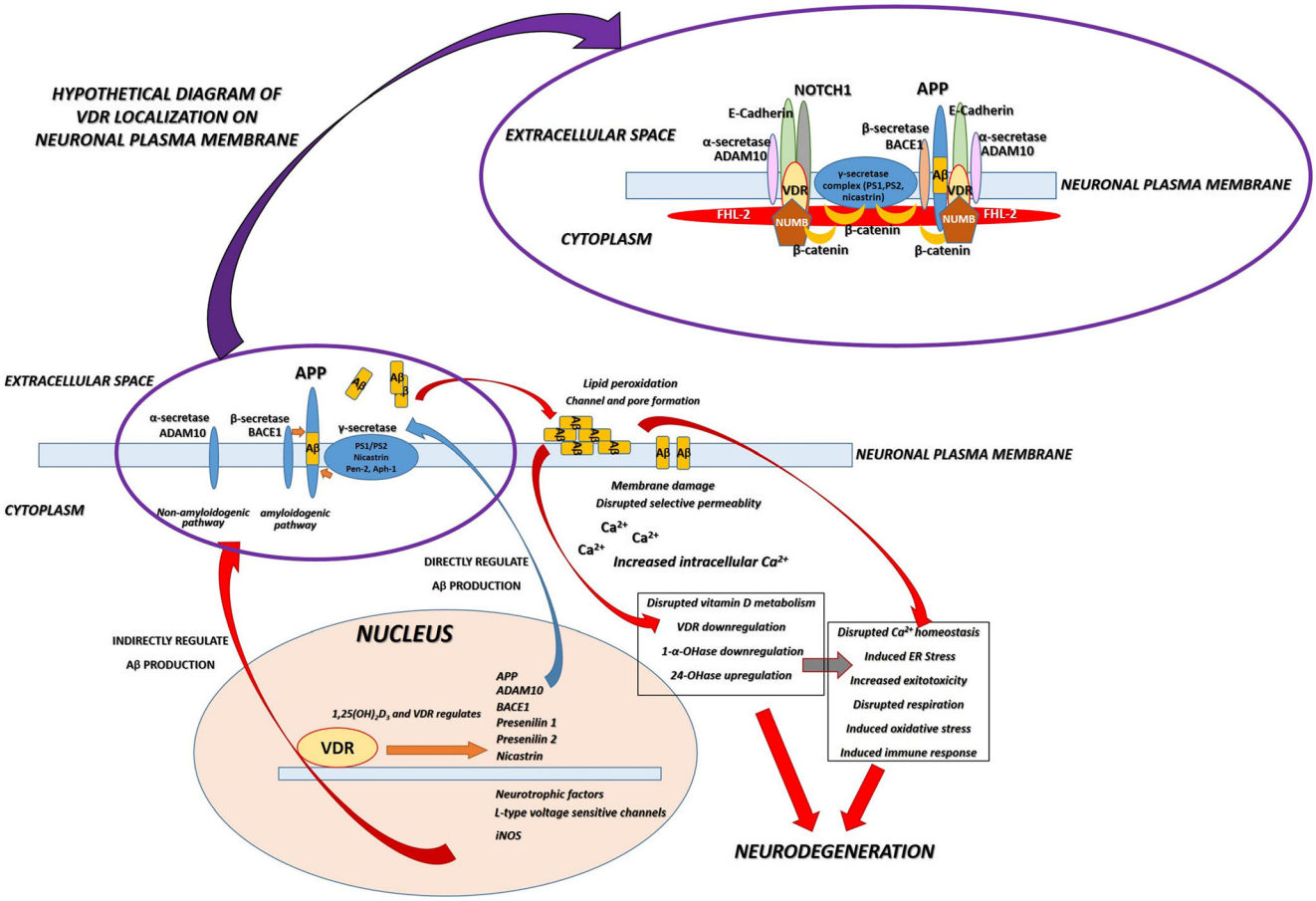

Fig. 1 The hypothesis of the relationship between VDR and Aβ-induced neurodegeneration. Transcriptional regulation data is received from Gezen-Ak et al. [34] and other previous studies [22–24]. Hypothetical diagram of VDR localization on neuronal plasma membrane was drawn based on the cell-based assay and FPClass protein-protein interaction: data from Dursun and Gezen-Ak [39]. VDR and other proteins may be found in lipid rafts in close proximity [39, 46, 47]. APP processing, Aβ production, and its relation to neurodegeneration are based on Pearson et al. [33]

vitamin D deficient mouse brains [35]. Today, a large number of other studies are accumulating, supporting our findings and strongly indicating a role for vitamin D VDR and Pdia3 in the regulation of numerous genes in both brain development and neurodegeneration [36–44].

On the other hand, the role of vitamin D in neuroinflammatory processes, which comprise a particularly important component of neurodegeneration, requires a detailed discussion and has been reviewed by dedicated researchers [22, 45].

Answers that prompted more questions

These findings led us to the conclusion that, due to the great complexity of the relationship between VDR and amyloid pathogenesis, all of the regulative properties of VDR in the production of Aβ cannot be explained solely by its transcriptional regulation. We hence hypothesized that the neuronal plasma membrane might involve VDR in close proximity to APP and secretase complexes. We identified the localization of VDR on the neuronal plasma membranes while also demonstrating the co-localization of VDR and APP or ADAM10 or nicastrin and limited colocalization of VDR and PS1 [39]. According to our FpClass data, E-cadherin interaction with APP or the γ-secretase complex may involve NOTCH1, NUMB, or four and a half LIM domains 2 (FHL2 or DRAL) [39]. The complex that we have proposed might also include VDR, which strongly contributes to Ca^{2+} hemostasis through its vitamin D ligand. In addition, we suggest that VDR is a member of this complex with its own non-genomic action and has the potential to similarly regulate the APP processing pathway also in neurons [39] (Fig. 1).

Conclusion

Considering all the data that has been amassed over the last 10 to 15 years, it is evident that vitamin D is not a "simple vitamin." The involvement of this neurosteroid in the mechanisms of AD and neurodegeneration, though complex and not as yet fully elucidated, can no longer be ignored.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Sutherland MK, Somerville MJ, Yoong LK, Bergeron C, Haussler MR, McLachlan DR (1992) 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 13:239–250
2. Poduslo SE, Yin X (2001) Chromosome 12 and late onset Alzheimer's disease. Neurosci Lett 310:188–190
3. Blacker D, Wilcox MA, Laird NM, Rodes L, Horvath SM, Go RC, Perry R, Watson B Jr, Bassett SS, McInnis MG, Albert MS, Hyman BT, Tanzi RE (1998) Alpha-2 macroglobulin is genetically associated with Alzheimer disease. Nat Genet 19:357–360
4. Hollenbach E, Ackermann S, Hyman BT, Rebeck GW (1998) Confirmation of an association between a polymorphism in exon 3 of the low-density lipoprotein receptor-related protein gene and Alzheimer's disease. Neurology 50:1905–1907
5. Luedecking-Zimmer E, DeKosky S, Nebes R, Kamboh I (2003) Association of the 3'UTR transcription factor LBP-1c/CP2/LSF polymorphism with late-onset Alzheimer's disease. Am J Med Gene B 117:114–117
6. Gezen Ak D, Kahraman H, Dursun E, Süsleyici Duman B, Erensoy N, Alagöl F, Yılmazer S (2005) Polymorphisms at the ligand binding sites of vitamin D receptor gene and osteomalacia. Dis Markers 21:191–197
7. Gezen-Ak D, Dursun E, Ertan T, Hanagasi H, Gurvit H, Emre M, Eker E, Ozturk M, Engin F, Yilmazer S (2007) Association between vitamin D receptor gene polymorphism and Alzheimer's disease. Tohoku J Exp Med 212(3):275–282
8. Lehmann DJ, Refsum H, Warden DR, Medway C, Wilcock GK, Smith DA (2011) The vitamin D receptor gene is associated with Alzheimer's disease. Neurosci Lett 504:79–82
9. Beecham GW, Martin ER, Li YJ, Slifer MA, Gilbert JR, Haines JL, Pericak-Vance MA (2009) Genome-wide association study implicates a chromosome 12 risk locus for late-onset Alzheimer disease. Am J Hum Genet 84:35–43
10. Beydoun MA, Ding EL, Beydoun HA, Tanaka T, Ferrucci L, Zonderman AB (2012) Vitamin D receptor and megalin gene polymorphisms and their associations with longitudinal cognitive change in US adults. Am J Clin Nutr 95:163–178
11. Beydoun MA, Tajuddin SM, Dore GA, Canas JA, Beydoun HA, Evans MK, Zonderman AB (2017) Vitamin D receptor and megalin gene polymorphisms are associated with longitudinal cognitive change among African-American urban adults. J Nutr 147(6):1048–1062
12. Dursun E, Alaylioglu M, Bilgic B, Hanagasi H, Lohmann E, Atasoy IL, Candas E, Araz OS, Onal B, Gurvit H, Yilmazer S, Gezen-Ak D (2016) Vitamin D deficiency might pose a greater risk for ApoEvarepsilon4 non-carrier Alzheimer's disease patients. Neurol Sci 37(10):1633–1643
13. Gezen-Ak D, Alaylioglu M, Genc G, Gunduz A, Candas E, Bilgic B, Atasoy IL, Apaydin H, Kiziltan G, Gurvit H, Hanagasi H, Ertan S, Yilmazer S, Dursun E (2017) GC and VDR SNPs and vitamin D levels in Parkinson's disease: the relevance to clinical features. NeuroMolecular Med 19(1):24–40
14. Gezen-Ak D, Dursun E, Bilgic B, Hanagasi H, Ertan T, Gurvit H, Emre M, Eker E, Ulutin T, Uysal O, Yilmazer S (2012) Vitamin D receptor gene haplotype is associated with late-onset Alzheimer's disease. Tohoku J Exp Med 228(3):189–196
15. Annweiler C, Schott AM, Allali G, Bridenbaugh SA, Kressig RW, Allain P, Herrmann FR, Beauchet O (2010) Association of vitamin D deficiency with cognitive impairment in older women: cross-sectional study. Neurology 74(1):27–32
16. Cherniack EP, Florez H, Roos BA, Troen BR, Levis S (2008) Hypovitaminosis D in the elderly: from bone to brain. J Nutr Health Aging 12(6):366–373
17. Evatt ML, DeLong MR, Khazai N, Rosen A, Triche S, Tangpricha V (2008) Prevalence of vitamin D insufficiency in patients with Parkinson disease and Alzheimer disease. Arch Neurol 65(10): 1348–1352
18. Llewellyn DJ, Langa KM, Lang IA (2009) Serum 25-hydroxyvitamin D concentration and cognitive impairment. J Geriatr Psychiatry Neurol 22(3):188–195
19. Llewellyn DJ, Lang IA, Langa KM, Muniz-Terrera G, Phillips CL, Cherubini A, Ferrucci L, Melzer D (2010) Vitamin D and risk of cognitive decline in elderly persons. Arch Intern Med 170(13): 1135–1141
20. McCann J, Ames BN (2008) Is there convincing biological or behavioral evidence linking vitamin D deficiency to brain dysfunction? FASEB J 22:982–1001
21. Wilkins CH, Sheline YI, Roe CM, Birge SJ, Morris JC (2006) Vitamin D deficiency is associated with low mood and worse cognitive performance in older adults. Am J Geriat Psychiat 14:1032–1040
22. Fernandes de Abreu DA, Eyles D, Féron F, Vitamin D (2009) a neuro-immunomodulator: implications for neurodegenerative and autoimmune diseases. Psychoneuroendocrinology 34(1):265–277
23. Garcion E, Wion-Barbot N, Montero-Menei CN, Berger F, Wion D (2002) New clues about vitamin D functions in the nervous system. Trends Endocrinol Metab 13(3):100–105
24. Brewer LD, Thibault V, Chen KC, Langub MC, Landfield PW, Porter NM (2001) Vitamin D hormone confers neuroprotection in parallel with downregulation of L-type calcium channel expression in hippocampal neurons. J Neurosci 21:98–108
25. Dursun E, Gezen-Ak D, Yilmazer S (2011) A novel perspective for Alzheimer's disease: vitamin D receptor suppression by amyloid-beta and preventing the amyloid-beta induced alterations by vitamin D in cortical neurons. J Alzheimers Dis 23(2):207–219
26. Dursun E, Gezen-Ak D, Yilmazer S (2013) Beta amyloid suppresses the expression of the vitamin d receptor gene and induces the expression of the vitamin d catabolic enzyme gene in hippocampal neurons. Dement Geriatr Cogn Disord 36(1–2):76–86
27. Gezen-Ak D, Atasoy IL, Candas E, Alaylioglu M, Dursun E (2018) The transcriptional regulatory properties of amyloid beta 1-42 may include regulation of genes related to neurodegeneration. NeuroMolecular Med 20(3):363–375
28. Gezen-Ak D, Dursun E, Yilmazer S (2013) Vitamin D inquiry in hippocampal neurons: consequences of vitamin D-VDR pathway disruption on calcium channel and the vitamin D requirement. Neurol Sci 34(8):1453–1458
29. Gezen-Ak D, Dursun E, Yilmazer S (2011) The effects of vitamin D receptor silencing on the expression of LVSCC-A1C and LVSCC-A1D and the release of NGF in cortical neurons. PLoS One 6(3):e17553
30. Dursun E, Gezen-Ak D, Yilmazer S (2013) A new mechanism for amyloid-beta induction of iNOS: vitamin D-VDR pathway disruption. J Alzheimers Dis 36(3):459–474
31. Dursun, E., Gezen-Ak D, Yilmazer S (2014) The influence of vitamin D treatment on the inducible nitric oxide synthase expression in

primary hippocampal neurons. Arch Neuropsych 51(2):163–168. https://doi.org/10.4274/npa.y7089
32. Gezen-Ak D, Dursun E, Yilmazer S (2014) The effect of vitamin D treatment on nerve growth factor release (NGF) in hippocampal neurons. Arch Neuropsych 51(2):157–162. https://doi.org/10.4274/npa.y7076
33. Pearson HA, Peers C (2006) Physiological roles for amyloid beta peptides. J Physiol 575(Pt 1):5–10
34. Gezen-Ak D, Atasoy IL, Candas E, Alaylioglu M, Yilmazer S, Dursun E (2017) Vitamin D receptor regulates amyloid beta 1-42 production with protein disulfide isomerase A3. ACS Chem Neurosci 8(10):2335–2346
35. Grimm MOW, Thiel A, Lauer AA, Winkler J, Lehmann J, Regner L, Nelke C, Janitschke D, Benoist C, Streidenberger O, Stotzel H, Endres K, Herr C, Beisswenger C, Grimm HS, Bals R, Lammert F, Hartmann T (2017) Vitamin D and its analogues decrease amyloid-beta (Abeta) formation and increase Abeta-degradation. Int J Mol Sci 18(12). https://doi.org/10.3390/ijms18122764
36. Mizwicki MT, Menegaz D, Zhang J, Barrientos-Durán A, Tse S, Cashman JR, Griffin PR, Fiala M (2011) Genomic and nongenomic signaling induced by 1α,25(OH)2-vitamin D3 promotes the recovery of amyloid-β phagocytosis by Alzheimer's disease macrophages. J Alzheimers Dis 29(1):51–62
37. Mizwicki MT, Liu G, Fiala M, Magpantay L, Sayre J, Siani A, Mahanian M, Weitzman R, Hayden EY, Rosenthal MJ, Nemere I, Ringman J, Teplow DB (2013) 1alpha,25-dihydroxyvitamin D3 and resolvin D1 retune the balance between amyloid-beta phagocytosis and inflammation in Alzheimer's disease patients. J Alzheimers Dis 34(1):155–170
38. Masoumi A, Goldenson B, Ghirmai S, Avagyan H, Zaghi J, Abel K, Zheng X, Espinosa-Jeffrey A, Mahanian M, Liu PT, Hewison M, Mizwickie M, Cashman J, Fiala M (2009) 1alpha,25-dihydroxyvitamin D3 interacts with curcuminoids to stimulate amyloid-beta clearance by macrophages of Alzheimer's disease patients. J Alzheimers Dis 17(3):703–717
39. Dursun E, Gezen-Ak D (2017) Vitamin D receptor is present on the neuronal plasma membrane and is co-localized with amyloid precursor protein, ADAM10 or nicastrin. PLoS One 12(11):e0188605
40. Landel V, Stephan D, Cui X, Eyles D, Feron F (2018) Differential expression of vitamin D-associated enzymes and receptors in brain cell subtypes. J Steroid Biochem Mol Biol 177:129–134. https://doi.org/10.1016/j.jsbmb.2017.09.008
41. Berridge MJ (2017) Vitamin D and depression: cellular and regulatory mechanisms. Pharmacol Rev 69(2):80–92
42. Landel V, Millet P, Baranger K, Loriod B, Feron F (2016) Vitamin D interacts with Esr1 and Igf1 to regulate molecular pathways relevant to Alzheimer's disease. Mol Neurodegener 11:22
43. Mizwicki MT, Norman AW (2009) The vitamin D sterol-vitamin D receptor ensemble model offers unique insights into both genomic and rapid-response signaling. Sci Signal 2(75):re4
44. Morello M, Landel V, Lacassagne E, Baranger K, Annweiler C, Feron F, Millet P (2018) Vitamin D improves neurogenesis and cognition in a mouse model of Alzheimer's disease. Mol Neurobiol 55(8):6463–6479. https://doi.org/10.1007/s12035-017-0839-1
45. Landel V, Annweiler C, Millet P, Morello M, Feron F (2016) Vitamin D, cognition and Alzheimer's disease: the therapeutic benefit is in the D-tails. J Alzheimers Dis 53(2):419–444
46. Huhtakangas JA, Olivera CJ, Bishop JE, Zanello LP, Norman AW (2004) The vitamin D receptor is present in caveolae-enriched plasma membranes and binds 1 alpha,25(OH)2-vitamin D3 in vivo and in vitro. Mol Endocrinol 18(11):2660–2671
47. Kang MJ, Chung YH, Hwang CI, Murata M, Fujimoto T, Mook-Jung IH, Cha CI, Park WY (2006) Caveolin-1 upregulation in senescent neurons alters amyloid precursor protein processing. Exp Mol Med 38(2):126–133