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Review

$1,25(OH)_2D_3$ in Brain Function and Neuropsychiatric Disease

Florian Lang[a] Ke Ma[b] Christina B. Leibrock[c]

[a]Department of Physiology, Eberhard-Karls-University of Tübingen, Germany, [b]Department of Pharmacology, Experimental Therapy & Toxicology, Eberhard-Karls-University of Tübingen, Germany, [c]Fresenius Kabi Deutschland GmbH, Bad Homburg, Germany

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Abstract
$1,25(OH)_2D_3$ (1,25-dihydroxy-vitamin D3 = calcitriol) is a powerful regulator of mineral metabolism. The hormone increases calcium and phosphate plasma concentrations in part by stimulation of intestinal absorption and renal reabsorption of calcium and phosphate. It is primarily, but not exclusively, produced in the kidney. Renal $1,25(OH)_2D_3$ formation is stimulated by calcium and phosphate deficiency and by parathyroid hormone which is up-regulated by hypocalcemia. $1,25(OH)_2D_3$ formation is inhibited by fibroblast growth factor FGF23, which is up-regulated by phosphate excess and requires Klotho to become effective. Klotho- or FGF23-deficiency leads to excessive plasma $1,25(OH)_2D_3$-, Ca^{2+}- and phosphate-concentrations with severe soft tissue calcification and accelerated aging. Tissue calcification and premature aging are prevented by NH_4Cl without affecting $1,25(OH)_2D_3$-formation. $1,25(OH)_2D_3$ has powerful effects apparently unrelated to mineral metabolism, including anti-inflammatory actions and modification of multiple brain functions. Excessive $1,25(OH)_2D_3$ formation in klotho-deficient NH_4Cl-treated mice leads to an amazing surge of exploratory behavior, lack of anxiety and decreased depression, effects dissipated by low vitamin D diet. Conversely, vitamin D deficient mice display reduced explorative behavior, enhanced anxiety, aberrant grooming, submissive social behavior, social neglect and maternal cannibalism. $1,25(OH)_2D_3$ is generated in human brain, and acts on diverse structures including prefrontal cortex, hippocampus, cingulate gyrus, thalamus, hypothalamus, and substantia nigra. In neurons $1,25(OH)_2D_3$ suppresses oxidative stress, inhibits inflammation, provides neuroprotection, down-regulates a variety of inflammatory mediators and up-regulates a wide variety of neurotrophins. Diseases postulated to be favorably modified by $1,25(OH)_2D_3$ include multiple sclerosis, Parkinson´s disease, Alzheimer´s disease, depression, bipolar disorder and schizophrenia. Clearly,

Florian Lang
Department of Vegetative and Clinical Physiology
University of Tübingen, Wilhelmstr. 56, 72074 Tübingen (Germany)
Tel. +49707129-72194, Fax +49707129-5618, E-Mail florian.lang@uni-tuebingen.de

substantial additional experimentation is required to fully understand the neuro-psycho-pathophysiological role of $1,25(OH)_2D_3$ and to exploit $1,25(OH)_2D_3$ or related agonists in the treatment of neuro-psychiatric disorders.

Introduction

Calcitriol or 1,25-dihydroxy-vitamin D3 ($1,25(OH)_2D_3$), a hormone generated from the vitamin D metabolite $25(OH)D_3$ (25-hydroxy-vitamin D3), is one of the major regulators of mineral metabolism [1-3] effective in part by stimulation of intestinal and renal Ca^{2+} and phosphate transport [1, 3]. $1,25(OH)_2D_3$ can be generated from vitamin D by hydroxylation to 25(OH)D3 [1, 2] and second hydroxylation to $1,25(OH)_2D_3$ [1, 2, 4]. The second decisive hydroxylation is accomplished by a 25-hydroxyvitamin D_3 1α-hydroxylase (1α-hydroxylase) [1, 2, 5]. The renal 25-hydroxyvitamin D_3 1α-hydroxylase is under tight control [1, 2, 5]. It is up-regulated by calcium- and phosphate deficiency and parathyroid hormone [2, 3, 6, 7]. 25-hydroxyvitamin D_3 1α-hydroxylase is inhibited by fibroblast growth factor 23 (FGF23) [3, 8], an effect requiring the co-receptor Klotho [9]. The FGF23 released from bone is stimulated by excess phosphate and disrupts further $1,25(OH)_2D_3$ formation and phosphate accumulation [8, 10, 11]. The fine tuning of renal 1α-hydroxylase aims to adjust the $1,25(OH)_2D_3$ formation exactly to the requirements of mineral metabolism. However, the components are sensitive to factors unrelated to mineral metabolism. For instance, $1,25(OH)_2D_3$ formation is further up-regulated by dehydration [12] and inhibited by CO-releasing molecule 2 (CORM-2) [13], FGF23 is up-regulated by $1,25(OH)_2D_3$, phosphate excess, Ca^{2+}, PTH, leptin, catecholamines, mineralocorticoids, volume depletion, lithium, high fat diet, iron deficiency, tumor necrosis factor alpha (TNFα) and transforming growth factor beta 2 (TGFß2) [14-17].

$1,25(OH)_2D_3$ contributes to the regulation of multiple functions seemingly unrelated to mineral metabolism, such as suicidal cell death [18-24], inflammation and immune response [25-28], glucose metabolism [29], platelet activation [30], neuroprotection and multiple brain functions [31] including mood [32, 33]. Along those lines 25-hydroxyvitamin D_3 1α-hydroxylase is expressed and thus $1,25(OH)_2D_3$ produced in several extra-renal tissues including dendritic cells/macrophages, skin (keratinocytes, hair follicles), lymph nodes (granulomata), thymus, placenta, lung, colon (epithelial cells and parasympathetic ganglia), stomach, pancreatic islets, adrenal medulla, and brain (pericytes, cerebellum and cerebral cortex) [34-42], Neurons can possibly transform the inactive cholecalciferol into $25(OH)D_3$, which is activated to $1,25(OH)_2D_3$, by neurons or microglia [43]. $1,25(OH)_2D_3$ enters neuronal nuclei and is thus expected to modify neuronal gene expression [44]. In view of its neuronal effects it is considered as a neurosteroid [43].

Effect of excessive $1,25(OH)_2D_3$ formation in klotho deficient mice on brain function

Klotho is not only expressed in the kidney, but is highly expressed as well in choroid plexus of the brain [9]. The extracellular domain of the transmembrane protein may be cleaved off and enter blood or cerebrospinal fluid [9]. Negative 1α-hydroxylase regulation by FGF23 is disrupted by klotho-deficiency [9, 45, 46]. Consequences of subsequent excessive formation of $1,25(OH)_2D_3$ include hyperphosphatemia and severe soft tissue calcification eventually leading to diverse age related disorders including vascular calcifications, thymus atrophy, pulmonary emphysema, hypoglycemia, infertility, skin thinning, osteoporosis, sarcopenia, hypoactivity, hearing loss, and ataxia [9, 45, 46] as well as severe reduction of life span [9, 45]. Conversely, klotho overexpression in mice extends the life span [47]. By the same token life span of humans is affected by specific klotho gene variants [48]. Tissue calcification and premature aging is prevented by ammonium chloride (NH_4Cl) treatment, which disrupts osteogenic signaling and almost normalizes the lifespan of klotho deficient mice without affecting excessive $1,25(OH)_2D_3$-formation [49, 50]. NH_4Cl has been shown to

be effective by alkalinizing acidic cellular compartments thus disrupting TGFß maturation [49]. Unlike the severely ill untreated klotho-deficient mice, NH_4Cl treated klotho deficient mice are able to undergo behavioral studies [50].

Excessive $1,25(OH)_2D_3$ formation in klotho deficient mice leads to profound behavioral effects [50]. Open field, dark-light box, and O-maze revealed significantly higher exploratory behavior in NH_4Cl-treated klotho-deficient mice than in NH_4Cl-treated or untreated wild-type mice, differences abrogated by low vitamin D diet (LVD). Moreover, the time of floating in the forced swimming test was significantly shorter in NH_4Cl-treated klotho-deficient mice on standard diet than in untreated wild-type mice or NH_4Cl-treated klotho-deficient mice on LVD. The altered behavior of NH_4Cl-treated klotho-deficient mice thus resulted from excessive $1,25(OH)_2D_3$ formation and were not due to behavioral effects of klotho or of NH_4Cl treatment [50]. Nevertheless, those observations do not exclude a more direct role of klotho in the regulation of depression and cognitive function [51-55], oligodendrocyte maturation and myelination [56] as well as neurodegeneration [57]. Klotho is apparently required for the suppressive effect of fibroblast growth factor 21 (FGF21) on sugar or alcohol preference/addiction [58-63].

Effects of vitamin D deficiency on murine behavior

Vitamin D deficiency of mice has been shown to reduce explorative behavior and enhance anxiety, aberrant grooming, submissive social behavior, social neglect and maternal cannibalism [64-66]. Vitamin D deficiency before birth impacts on murine self-grooming [67]. Murine behavior is similarly affected by deletion of the vitamin D receptor (VDR) [65, 68-73].

Evidence for impact of $1,25(OH)_2D_3$ in human brain function

In human brain, VDR and vitamin D metabolizing enzymes are expressed by several cerebral structures including prefrontal cortex, hippocampus, cingulate gyrus, thalamus, hypothalamus, and substantia nigra [36]. VDR gene variants are associated with altered behavior [74, 75] as well as susceptibility to age-related changes in cognitive function and depressive symptoms [74].

Similar to observations in mice, $1,25(OH)_2D_3$ has been shown to affect human behavior [32, 33], emotions and anxiety [76]. Vitamin D deficiency fosters the development of several psychiatric diseases including depression, bipolar disorder and schizophrenia [76-79]. $1,25(OH)_2D_3$ serum concentrations correlate with extraversion [80], which is in turn negatively correlated with social phobia, cluster C personality disorders and suicide risk [79, 81]. In patients suffering from depression decreased serum levels of $25(OH)D_3$ presumably compromising $1,25(OH)_2D_3$ formation have been reported [82, 83]. Conversely, vitamin D supplementation has been shown to reduce depressive symptoms [84-86]. Seasonal variations of sun exposure presumably leading to respective alterations of cutaneous vitamin D formation and $1,25(OH)_2D_3$ production have been associated with seasonal affective disorders [84-86] and vitamin D deficiency may contribute to the desynchronisation in those disorders [87]. Vitamin D deficiency during brain development has been identified as a risk factor for the development of schizophrenia, a condition associated with enhanced neuroticism and decreased extraversion [88]. Conversely vitamin D supplementation has been reported to decrease the risk of developing psychotic-like symptoms [78]. VDR-regulated genes presumably contribute to the pathophysiology of ±3, 4-methylenedioxymethamphetamine (ecstacy) intoxication, which may, at least in theory, be suppressed by vitamin D supplementation [89].

$1,25(OH)_2D_3$ in neuroinflammation

In experimental autoimmune encephalomyelitis, a murine model for multiple sclerosis, $1,25(OH)_2D_3$ treatment suppresses inflammation, demyelination as well as neuron loss [90, 91] and increases numbers of neural stem cells, oligodendrocyte precursor cells as well as oligodendrocytes [90], effects accomplished in part by down-regulation of pro-inflammatory interferon gamma (IFN-γ), granulocyte macrophage colony-stimulating factor (GM-CSF) and interleukin 17A (IL-17A) as well as up-regulation of anti-inflammatory interleukin 4 (IL-4) and interleukin 10 (IL-10) [90]. $1,25(OH)_2D_3$ thus decreases the T-cell responsiveness to Myelin-Derived Antigens [92]. $1,25(OH)_2D_3$ further blunts lipopolysaccharide (LPS)-induced nitrite formation, reactive oxygen species (ROS) production and interleukin 6 (IL-6) as well as macrophage inflammatory protein 2 (MIP-2) release [93]. Signaling involved includes up-regulation of Beclin1, increased B-cell lymphoma 2 (Bcl-2)/ Bcl-2-associated X protein (Bax) ratio, and decreased accumulation of lipid modified form of microtubule-associated proteins 1A/1B light chain 3B (LC3-II) [91].

Synthetic VDR agonists

Selective synthetic VDR agonists with relatively small calcemic effect, such as paricalcitol, maxacalcitol, doxercalciferol, and falecalcitriol [94-98], may be particularly interesting for the use in neuropsychiatric disorders. However, still little is known about their effects on cerebral function. Paricalcitol has been shown to exert anti-convulsive and anti-depressive effects [99, 100]. Maxacalcitol, paricalcitol, and doxercalciferol decrease Aβ-production and increase Aβ-degradation in neuroblastoma cells or vitamin D deficient mouse brains [101] and are, thus, candidates for the treatment of Alzheimer´s disease. Clearly, much still needs to be learned about cerebral effects and side effects of this interesting group of drugs.

Mechanisms invoked in the effects of $1,25(OH)_2D_3$ on brain function

Several mechanisms have been suggested to participate in the cerebral effects of $1,25(OH)_2D_3$, including suppression of oxidation, inhibition of inflammation, counteraction of vascular injury, up-regulation of neurotrophins and improvement of metabolic and cardiovascular function [32, 102].

$1,25(OH)_2D_3$ stimulates neuronal cell growth, survival, and proliferation [102]. It supports proliferation of neural stem cells and their differentiation to oligodendrocytes, effects paralleled by expression of neurotrophin 3 (NT-3), brain-derived neurotrophic factor (BDNF), glial cell-derived neurotrophic factor (GDNF) and ciliary neurotrophic factor (CNTF), important neurotrophic factors for neural cell survival and differentiation [103]. Vitamin D deficiency has been suggested to affect cellular development, dopamine transport and metabolism, as well as brain morphology [104].

$1,25(OH)_2D_3$ fosters differentiation of dopaminergic neurons [102, 105, 106], an effect paralleled by up-regulation of N-cadherin [106]. Vitamin D increases expression of tyrosine hydroxylase and catechol-O-Methyltransferase (COMT) [105, 106], dopamine synthesis and metabolism [102, 105, 106], as well as expression of GDNF and its receptors, which is crucial for the survival of dopaminergic neurons [107]. $1,25(OH)_2D_3$ decreases the expression of Neurogenin-2 (NEUROG2), a marker of immature dopaminergic neurons [105].

$1,25(OH)_2D_3$ further stimulates the neuronal formation of the neuroprotective cytokine IL-34 [108]. $1,25(OH)_2D_3$ upregulates the Amyloid beta (Aβ) – scavenger receptor low density lipoprotein receptor related protein (LRP-1) [109] and reduces amyloid beta toxicity in part by enhancing sphingosine kinase activity and thus the sphingosine-1-phosphate (S1P)/ ceramide (Cer) ratio [110]. $1,25(OH)_2D_3$ decreases activities of p38 mitogen-activated protein kinases (p38-MAPK), extracellular signal-regulated kinases (ERK), and c-Jun N-terminal

kinase (JNK) activation [93] and endoplasmatc reticulum (ER) stress damage apparent from the ratio p38-MAPK/activating transcription factor 4 (ATF4) [110]. In neuroblastoma cells, $1,25(OH)_2D_3$ decreases cell proliferation, changes cell morphology, increases expression of protein markers of mature neuronal cells [111], increases expression of nerve growth factor (NGF) [111], up-regulates transforming growth factor-beta2 (TGF-beta2) [112], stimulates protein kinase C (PKC) activity [112], and decreases myc expression [113].

At least in theory, $1,25(OH)_2D_3$ could modify neuronal function by affecting neuronal or glial cytosolic Ca^{2+} activity [44, 114-116]. $1,25(OH)_2D_3$-dependent calcium binding protein has been observed in nuclei influencing the pineal gland [117]. $1,25(OH)_2D_3$ may suppress cerebral effects of glucocorticoids, which contribute to the development of major depression [118].

In other cell types, VDR has been shown to modify the expression of 500-1000 genes engaged in the regulation of a wide variety of cellular functions including transport, growth, differentiation, and apoptosis [119, 120]. VDR-regulated genes in the hippocampus include CCAAT/enhancer-binding protein beta (CEBPB), CD3e molecule, epsilon (CD3E) Calcium/ Calmodulin Dependent Protein Kinase II Inhibitor 2, (CAMK2N2), Krueppel-like factor 1 i (KLF1), peripheral myelin protein 22 (PMP22), Poly(A) Binding Protein Cytoplasmic 1 (PABPC1), Plasma membrane calcium-transporting ATPase 3 (ATP2B3), Glutamate receptor AMPA 3 (GRIA3), solute carrier family 4 (Na^+,HCO_3^- cotransporter) member 4 (SLC4A4) Neurotrophic Receptor Tyrosine Kinase 2 (NTRK2), retinoblastoma-binding protein 6 (E3 ubiquitin ligase) (RBBP6), Latrophilin 1 (LPHN1), DNA Methyltransferase 3 Alpha (DNMT3A), Tenascin R (TNR), and glutamate ionotropic receptor NMDA type subunit 2A (GRIN2A) [89]. However, the role of specific VDR-regulated genes in cerebral function remained largely elusive.

Conclusions and future directions

$1,25(OH)_2D_3$ is generated by and has powerful effects on neurons. The hormone suppresses oxidative stress, inhibits inflammation, provides neuroprotection, and modifies a variety of neuronal and glial cell functions. It is effective in part by down-regulation of inflammatory mediators and up-regulation of neurotrophins. A variety of common diseases are presumably sensitive to $1,25(OH)_2D_3$ including multiple sclerosis, Parkinson´s disease, Alzheimer´s disease, depression, bipolar disorder and schizophrenia. Clearly, substantial additional experimentation is required to fully understand the pathophysiological role of $1,25(OH)_2D_3$ in those and further clinical conditions and to exploit $1,25(OH)_2D_3$ or synthetic VDR-agonists in the treatment of neuropsychiatric disease. Future studies dissecting effects of $1,25(OH)_2D_3$ or synthetic VDR-agonists on function of neurons and glial cells, on murine behavior and cerebral function, as well as on the course of murine neuroinflammation are expected to uncover novel therapeutic opportunities, future neuropsychiatric analysis of patients treated with $1,25(OH)_2D_3$ or synthetic VDR-agonists are expected to define therapeutic efficacy and side effects in the respective patients.

Disclosure Statement

The authors declare they have no conflict of interests.

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