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Review

The Putative Role of $1,25(OH)_2D_3$ in the Association of Milk Consumption and Parkinson's Disease

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Abstract
The consumption of dairy products, particularly of low fat milk, has been shown to be associated with the occurrence of Parkinson's disease. This association does not necessarily reflect a pathophysiological role of milk intake in the development of Parkinson's disease. Nevertheless, the present review discusses a potential mechanism possibly mediating an effect of milk consumption on Parkinson's disease. The case is made that milk is tailored in part to support bone mineralization of the suckling offspring and is thus rich in calcium and phosphate. Milk intake is thus expected to enhance intestinal calcium phosphate uptake. As binding to fatty acids impedes Ca^{2+} absorption, low fat milk is particularly effective. Calcium and phosphate uptake inhibit the formation of $1,25(OH)_2D_3$ (1,25-dihydroxy-vitamin D_3 = calcitriol), the active form of vitamin D. Calcium inhibits $1,25(OH)_2D_3$ production in part by suppressing the release of parathyroid hormone, a powerful stimulator of $1,25(OH)_2D_3$ formation. Phosphate excess stimulates the release of fibroblast growth factor FGF23, which suppresses $1,25(OH)_2D_3$ formation, an effect requiring Klotho. $1,25(OH)_2D_3$ is a main regulator of mineral metabolism, but has powerful effects apparently unrelated to mineral metabolism, including suppression of inflammation and influence of multiple brain functions. In mice, lack of $1,25(OH)_2D_3$ and excessive $1,25(OH)_2D_3$ formation have profound effects on several types of behavior, such as explorative behavior, anxiety, grooming and social behavior. $1,25(OH)_2D_3$ is produced in human brain and influences the function of various structures including substantia nigra. In neurons $1,25(OH)_2D_3$ suppresses oxidative stress, inhibits inflammation and stimulates neurotrophin formation thus providing neuroprotection. As a result, $1,25(OH)_2D_3$ is considered to favorably

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influence the clinical course of Parkinson's disease. In conclusion, consumption of milk could in theory accelerate the downhill course of neuronal function in Parkinson's disease by lowering 1,25(OH)$_2$D$_3$ formation. However, substantial additional experimentation is required to define the putative causal role of 1,25(OH)$_2$D$_3$ in the pathophysiology of Parkinson's disease and its sensitivity to milk consumption.

Introduction

Several studies uncovered an association of milk consumption and risk of Parkinson's disease [1-8]. According to analysis of 2 large prospective cohort studies (n = 80,736 and 48,610, resp., follow up 26 and 24 years, resp.), consumption of skim and low fat milk was more influential than consumption of full fat milk [2]. The association does not necessarily reflect a causal role of milk consumption in the pathogenesis of Parkinson's disease. Instead, consequences of Parkinson's disease may impact on milk consumption. For instance, early loss of smell (anosmia) during the course of Parkinson's disease [9] may in theory influence eating habits of the patient. Moreover, a common cause could in theory account for Parkinson's disease and alterations of eating habits. Nevertheless, the observation of an association may reflect a causal relationship and deserves considerations about potential underlying mechanisms. The present review discusses the possibility that milk consumption triggers Parkinson's disease by interference with the formation of calcitriol or 1,25-dihydroxy-vitamin D3 (1,25(OH)$_2$D$_3$) [10-12], which not only stimulates intestinal and renal Ca^{2+} and phosphate transport [10, 12], but has a multitude of effects unrelated to mineral metabolism including neuroprotection [13].

Milk consumption enhances intestinal calcium and phosphate uptake thus suppressing formation of 1,25(OH)$_2$D$_3$, a major regulator of mineral metabolism

In order to support bone mineralization of the suckling offspring, milk is rich in calcium phosphate [8]. Thus, milk consumption is expected to enhance intestinal uptake of calcium and phosphate.

Calcium and phosphate uptake impacts on formation of 1,25(OH)$_2$D$_3$, a powerful regulator of mineral metabolism [10-12]. 1,25(OH)$_2$D$_3$ is generated from vitamin D by hydroxylation to 25(OH)D$_3$ [10, 11] followed by second hydroxylation to 1,25(OH)$_2$D$_3$ [10, 11, 13, 14]. The second hydroxylation is accomplished by a 25-hydroxyvitamin D$_3$ 1α-hydroxylase (1α-hydroxylase) [10, 11, 15], which is stimulated by calcium- and phosphate deficiency and parathyroid hormone [11-13, 16, 17]. Phosphate excess up-regulates fibroblast growth factor 23 (FGF23) [12, 18], which activates the co-receptor Klotho [19-21], a powerful inhibitor of 25-hydroxyvitamin D$_3$ 1α-hydroxylase [19]. Thus excess phosphate suppresses 1,25(OH)$_2$D$_3$ formation and thus further phosphate accumulation [18, 22, 23]. Hypercalcemia inhibits 1α-hydroxylase by suppressing release of parathyroid hormone [11-13, 16, 17]. The sensitivity of 25-hydroxyvitamin D$_3$ 1α-hydroxylase to calcium- and phosphate aims to adjust the 1,25(OH)$_2$D$_3$ formation exactly to the requirements of mineral metabolism. Further factors regulating 1,25(OH)$_2$D$_3$ formation include dehydration [24], volume depletion, mineralocorticoids, lithium, high fat diet, iron deficiency, CO-releasing molecule 2 (CORM-2) [25], leptin, catecholamines, tumor necrosis factor alpha (TNFα) and transforming growth factor beta 2 (TGFβ2) [13, 26-29]. To the extent that any of those regulators of 1,25(OH)$_2$D$_3$ formation is modified by milk consumption, it could contribute to the impact of milk consumption on Parkinson's disease. Moreover, in theory alterations of calcium and phosphate homeostasis may affect the development of Parkinson's disease by mechanisms other than formation of 1,25(OH)$_2$D$_3$.

$1,25(OH)_2D_3$ participates in the regulation of multiple processes seemingly unrelated to mineral metabolism

$1,25(OH)_2D_3$ is not only a powerful regulator of mineral metabolism but participates in the regulation of diverse further functions [13], including inflammation and immune response [30-33], glucose metabolism [34], platelet activation [35], suicidal cell death [36-42], as well as neuronal function and survival [43-45]. Moreover, 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, lymph nodes, thymus, skin (keratinocytes, hair follicles), placenta, lung, colon (epithelial cells and parasympathetic ganglia), stomach, pancreatic islets, adrenal medulla and brain [13, 46-54].

The $1,25(OH)_2D_3$-binding vitamin D receptor (VDR) regulates the expression of as many as 500-1000 genes, which are involved in the regulation of a wide variety of cellular functions including transport, growth, differentiation and apoptosis [13, 55, 56].

$1,25(OH)_2D_3$ is generated in the brain and influences neuronal function and survival

Neurons, microglia and pericytes in several structures of the brain (including prefrontal cortex, hippocampus, cingulate gyrus, thalamus, hypothalamus, and substantia nigra [13, 48]) express 25-hydroxyvitamin D_3 1α-hydroxylase and are thus capable to generate $1,25(OH)_2D_3$ from $25(OH)D_3$ [46-48, 57]. Neurons are further able to produce $25(OH)D_3$ from cholecalciferol [57]. Similar to kidney, choroid plexus of the brain expresses klotho [19], which presumably participates in the regulation of cerebral $1,25(OH)_2D_3$ formation.

Neurons, microglia and pericytes may further express the vitamin D receptor (VDR) and are thus sensitive to $1,25(OH)_2D_3$ [58]. Upon binding of $1,25(OH)_2D_3$ the VDR enters nuclei and modifies the expression of a wide variety of genes [58]. VDR-regulated genes detected in hippocampus include CCAAT/enhancer-binding protein beta (CEBPB), Peripheral myelin protein 22 (PMP22), Plasma membrane calcium-transporting ATPase 3 (ATP2B3), Glutamate receptor AMPA 3 (GRIA3), Neurotrophic Receptor Tyrosine Kinase 2 (NTRK2), DNA Methyltransferase 3 Alpha (DNMT3A), Tenascin R (TNR), and Glutamate ionotropic receptor NMDA type subunit 2A (GRIN2A) [13, 59], genes implicated in the pathophysiology of Parkinson's disease [60-67]. As $1,25(OH)_2D_3$ is a powerful regulator of neuronal gene expression, it has been considered a neurosteroid [57].

$1,25(OH)_2D_3$ confers neuroprotection, an effect in part due to counteraction of oxidation, inflammation, and vascular injury, as well as up-regulation of neurotrophins, improvement of metabolism and favorable influence on cardiovascular function [13, 44, 68].

$1,25(OH)_2D_3$ stimulates differentiation of dopaminergic neurons [68-70] leading to reduced expression of Neurogenin-2 (NEUROG2), a marker of immature dopaminergic neurons [69]. $1,25(OH)_2D_3$ up-regulates N-cadherin [70], tyrosine hydroxylase, catechol-O-Methyltransferase (COMT) [69, 70], dopamine synthesis and dopamine metabolism [68-70]. $1,25(OH)_2D_3$ supports the survival of dopaminergic neurons by up-regulation of glial cell-derived neurotrophic factor (GDNF) and its receptors [71, 72].

In neuroblastoma cells, $1,25(OH)_2D_3$ has been shown to decrease cell proliferation and to stimulate differentiation [73]. $1,25(OH)_2D_3$ has further been shown to up-regulate nerve growth factor (NGF) expression [73], TGFβ2 expression [74] and protein kinase C (PKC) activity [74]. $1,25(OH)_2D_3$, has been shown to down-regulate myc expression [75].

$1,25(OH)_2D_3$ stimulates expression of several neurotrophic and neuroprotective factors including neurotrophin 3 (NT-3) [76], brain-derived neurotrophic factor (BDNF) [76], glial cell-derived neurotrophic factor (GDNF) [76], ciliary neurotrophic factor (CNTF) [76], and neuroprotective cytokine IL-34 [77]. The neurotrophic factors support neural cell survival and differentiation [76]. $1,25(OH)_2D_3$ thus supports growth, survival, proliferation and differentiation of neurons and of neural stem cells [68]. Vitamin D deficiency may compromise neuronal development, dopamine transport and metabolism [78].

1,25(OH)$_2$D$_3$ may counteract inflammation, demyelination and neuron loss [79, 80]. 1,25(OH)$_2$D$_3$ decreases nitrite formation and oxidative stress [81]. Conversely, 1,25(OH)$_2$D$_3$ may support formation of neural stem cells, oligodendrocyte precursor cells and oligodendrocytes [79]. 1,25(OH)$_2$D$_3$ may down-regulate pro-inflammatory mediators, such as interferon gamma (IFN-γ), granulocyte macrophage colony-stimulating factor (GM-CSF), macrophage inflammatory protein 2 (MIP-2) as well as interleukins 6 (IL-6) and 17A (IL-17A). Conversely, 1,25(OH)$_2$D$_3$ may up-regulate anti-inflammatory interleukins 4 (IL-4) and 10 (IL-10) [79, 81]. 1,25(OH)$_2$D$_3$ suppresses activity of T-cells [82]. 1,25(OH)$_2$D$_3$ is a powerful suppressor of cyclooxygenase (COX) [83, 84], an inflammatory enzyme apparently involved in the pathophysiology of Parkinson's disease [85].

Further mechanisms invoked in the cerebral effects of 1,25(OH)$_2$D$_3$ include up-regulation of Beclin1 and of B-cell lymphoma 2 (Bcl-2)/Bcl-2-associated X protein (Bax) ratio [80], Amyloid beta (Aβ) – scavenger receptor low density lipoprotein receptor related protein (LRP-1) [86], sphingosine kinase activity and thus the sphingosine-1-phosphate (S1P)/ceramide (Cer) ratio [72], as well as downregulation of lipid modified form of microtubule-associated proteins 1A/1B light chain 3B (LC3-II) [80], p38 mitogen-activated protein kinases (p38-MAPK), extracellular signal-regulated kinases (ERK), and c-Jun N-terminal kinase (JNK) activation [81], the ratio p38-MAPK/activating transcription factor 4 (ATF4) [72] and endoplasmatic reticulum (ER) stress damage [72].

1,25(OH)$_2$D$_3$ may further be effective by modifying cytosolic Ca^{2+} activity in neurons and/or glial cells [58, 87-89]. 1,25(OH)$_2$D$_3$ has been shown to up-regulate Ca^{2+} -binding protein in the pineal gland [90]. 1,25(OH)$_2$D$_3$ may further be effective by suppressing glucocorticoid sensitivity of the brain [91].

Table 1. 1,25(OH)$_2$D$_3$-regulated molecules and mechanisms suggested to participate in the pathophysiology of Parkinson´s disease (for references see text)

Molecules	CCAAT/enhancer-binding protein beta (CEBPB)
	Peripheral myelin protein 22 (PMP22)
	Plasma membrane calcium-transporting ATPase 3 (ATP2B3)
	Glutamate receptor AMPA 3 (GRIA3)
	Neurotrophic Receptor Tyrosine Kinase 2 (NTRK2)
	DNA Methyltransferase 3 Alpha (DNMT3A)
	Tenascin R (TNR)
	Glutamate ionotropic receptor NMDA type subunit 2A (GRIN2A)
	Neurogenin-2 (NEUROG2)
	N-cadherin
	Tyrosine hydroxylase
	Catechol-O-Methyltransferase (COMT)
	Glial cell-derived neurotrophic factor (GDNF) and its receptors
	Neurotrophin 3 (NT-3)
	Brain-derived neurotrophic factor (BDNF)
	Ciliary neurotrophic factor (CNTF)
	Interleukin IL-34
	Cyclooxygenase (COX)
Mechanisms	Anti-oxidation
	Anti-inflammation
	Protection against vascular injury
	Anti-apoptosis
	Differentiation of dopaminergic neurons
	Dopamine synthesis, transport and metabolism

$1,25(OH)_2D_3$ influences behavior and mood: In mice, excessive $1,25(OH)_2D_3$ leads to an amazing increase of exploratory behavior and to a shortening of floating in the forced swimming test which reflects decreased depression [92]. Vitamin D deficiency downregulates explorative behavior and leads to anxiety, aberrant grooming, submissive social behavior, social neglect and maternal cannibalism [93-95]. Vitamin D deficiency before birth impacts on murine self-grooming [96]. Vitamin D receptor (VDR) deficiency exerts similar effects as Vitamin D deficiency [94, 97-102]. $1,25(OH)_2D_3$ similarly affects human behavior [44, 45], emotions [103] and anxiety [103]. Vitamin D deficiency may trigger [104, 105] and vitamin D supplementation may counteract [106-108] depression. Vitamin D deficiency fosters the development of bipolar disorder and schizophrenia [103, 109-111]. $1,25(OH)_2D_3$ may influence extraversion [112], social phobia, cluster C personality disorders and suicide risk [111, 113]. Seasonal variations of sun exposure may alter cutaneous vitamin D formation and thus trigger seasonal affective disorders [106-108, 114]. Vitamin D deficiency during brain development may foster [115] and vitamin D supplementation may counteract [110] development of schizophrenia. Vitamin D supplementation may further reduce ± 3,4-methylenedioxymethamphetamine (Ecstacy) toxicity [59]. Human behavior [116, 117] as well as age-related decline of cognitive function and appearance of depression [116] are affected by certain VDR gene variants.

Conclusions

At least in theory, skim milk may accelerate development and progression of Parkinson's disease by suppression of $1,25(OH)_2D_3$ formation. $1,25(OH)_2D_3$ is generated in the brain and influences neuronal function and survival by a variety of mechanisms. $1,25(OH)_2D_3$ is partially effective by counteracting oxidative stress, inflammation, and neuronal cell death. $1,25(OH)_2D_3$ downregulates inflammatory mediators and up-regulates neuroprotective neurotrophins. As a result, $1,25(OH)_2D_3$ protects against Parkinson's disease. At least in theory, disease onset and clinical course of the disease could be favorably influenced by avoidance of skim milk and/or by treatment of affected patients with $1,25(OH)_2D_3$ or synthetic VDR-agonists, such as paricalcitol, maxacalcitol, doxercalciferol, and falecalcitriol [118-122]. The evidence presently available is, however, suggestive, but not conclusive and additional experimentation is warranted further dissecting the pathophysiological role of $1,25(OH)_2D_3$ in onset and course of Parkinson's disease. Moreover, further clinical studies are required to define the impact of milk consumption, dietary phosphate, mineral metabolism, $1,25(OH)_2D_3$ and/or synthetic VDR-agonists on the clinical course of Parkinson's disease.

Disclosure Statement

The authors have no conflicts of interests.

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