Neurosteroid vitamin D system as a nontraditional drug target in neuropsychopharmacology

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Vitamin D is becoming increasingly recognized as a nontraditional drug target for different brain pathologies. Although widely known for their role in calcium metabolism, vitamin D and its receptor have been linked to several brain disorders, including cognitive decline, epilepsy, affective disorders, and schizophrenia. Here we discuss mounting evidence, and parallel recent clinical and animal behavioral, genetic and pharmacological data to emphasize the emerging role of the neurosteroid vitamin D system in brain function. *Behavioural Pharmacology* 21:420–426 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Vitamin D has traditionally been known for its role in calcium and bone homeostasis, cell proliferation, and modulation of parathyroid hormone secretion (Cranney *et al.*, 2007; Aloia *et al.*, 2010). Mounting evidence indicates that vitamin D and its receptors play an important role in the brain, from neuroprotection to immunomodulation (Garcion *et al.*, 2002; Kalueff *et al.*, 2006d; Kalueff and Tuohimaa, 2007; McCann and Ames, 2008). Vitamin D also maintains a robust antiproliferative activity, thereby making it an important regulator of brain cell proliferation and differentiation (Eyles *et al.*, 2003; Ko *et al.*, 2004), and implicating it in brain development (Banerjee and Chatterjee, 2003). With the large part of the global population still suffering from vitamin D deficiency (DVD) (Gloth *et al.*, 1999; Berk *et al.*, 2007; Barnard and Colon-Emeric, 2010; Lips, 2010), it is now time to discuss the role of this hormone in brain functioning and behavioral regulation (also see Ref. McCann and Ames (2008) for a recent comprehensive review).

Vitamin D is produced by the skin upon ultraviolet light exposure. It is a lipid-soluble secosteroid hormone, which is biologically inert by itself. Vitamin D is metabolized in the liver to produce 25-hydroxyvitamin D (25-D), which is the major circulating form of this hormone. 25-D is further oxidized in the kidneys and brain to produce 1,25-D (Garcion *et al.*, 2002; Kalueff *et al.*, 2006d; Kalueff and Tuohimaa, 2007). Ultimately, 25-D and 1,25-D are oxidized in the kidneys (and other tissues) to form the inactive metabolites of 24,25-D and 1,24,25-trihydroxyvitamin D. The enzyme responsible for the catabolism, vitamin D-24-hydroxylase, is downregulated by high levels of calcium and phosphate and upregulated by 1,25-D, thereby playing an important role in maintaining the physiological concentrations of 1,25-D (Armbrecht *et al.*, 1998; Hamamoto *et al.*, 2006; Kalueff *et al.*, 2006d).

As the endocrine vitamin D system is tightly linked to calcium and parathyroid hormone, the autocrine and paracrine systems are controlled by 25-D concentration (Reichel and Norman, 1989; St-Arnaud, 2008). Furthermore, the widespread distribution of 1α-hydroxylase (the enzyme that produces 1,25-D) and the nuclear vitamin D receptor (VDR) in both neurons and glial cells suggests that vitamin D may have autocrine and paracrine properties in the brain (Eyles *et al.*, 2005).

1,25-D binds to the VDR, which acts as a typical transcription factor and regulates gene expression (Ogunkolade *et al.*, 2006). VDR is highly expressed in the animal (Stumpf and O'Brien, 1987; Prufer *et al.*, 1999) and human (Eyles *et al.*, 2005) brain. Upon binding, VDR undergoes a conformational change to form a complex with a retinoid X receptor. This complex controls gene expression by binding to the DNA elements in the promoter regions of the target genes – vitamin D response elements (Arbelle *et al.*, 1996; Thompson *et al.*, 1998).

There are five important common polymorphisms within the *VDR* gene region that are likely to exert functional effects: *Cdx2*, *Fok*I, *Bsm*I, *Apa*I, and *Taq*I (Chen *et al.*, 2009). For example, *Cdx2* polymorphism in the promoter region of the *VDR* gene is important for proper vitamin D/VDR signaling (Fang *et al.*, 2003). Several single nucleotide polymorphisms of the promoter region of the *VDR* gene,

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such as 1521 (G/C) and 1012 (A/G), modulate the formation of the protein–DNA complex, thereby regulating the circulating levels of 25-D (D'Alesio *et al.*, 2005).

Among several hundreds of genes activated by 1,25-D (Kalueff *et al.*, 2006d), the *CYP27B1* gene coding 1α-hydroxylase is of particular interest (Cannell, 2008; Currenti, 2010). On account of the unique pharmacokinetics of vitamin D, variations of CYP27B1 interact with differing levels of environmentally determined 25-D. This results in neural concentrations that are under genetic organization, but that vary widely with human behavior. That is, although vitamin D operates under genetic organization, these variations may fail to fully signal the genetic expression encoding neural proteins regulated by vitamin D (Cannell, 2008). Polymorphisms in the *CYP27B1* gene are important in vitamin D metabolism, implicating this gene in a variety of pathologies (Lopez *et al.*, 2004; Bailey *et al.*, 2007; Dong *et al.*, 2009).

The generation of VDR-deficient mice (Yoshizawa *et al.*, 1997) has emphasized the role of vitamin D as an important neurosteroid hormone. In 2004, our laboratory was the first to report neurobehavioral abnormalities in VDR mutant mice (Kalueff *et al.*, 2004, also see subsequent phenotypical findings in Burne *et al.*, 2005; Kalueff *et al.*, 2005b, 2006a, 2006b, 2006c). VDR null mice fail to thrive, developing alopecia, hypocalcemia, infertility, and severely impaired bone formation, and ultimately die within 15 weeks after birth (Yoshizawa *et al.*, 1997). However, when supplemented with a high calcium diet, they survive, although the lack of functional VDR leads to a variety of neurobehavioral phenotypes, including increased anxiety, reduced social behavior, abnormal grooming, pup cannibalism, impaired nest building, and neophobia (Kalueff *et al.*, 2004, 2005a, 2006b; Minasyan *et al.*, 2007). These mice also display abnormal motor phenotypes, increased proneness to epilepsy, impaired vestibular functions, prolactin dysregulation (Kalueff *et al.*, 2006c, 2006d; Keisala *et al.*, 2007, 2009), and abnormally high brain angiotensin II, resulting in increased water intake (Kong *et al.*, 2008).

Recently, the developmental DVD model has emerged as a useful approach to the mechanisms underlying vitamin D-related brain pathologies. Rodents deprived of sufficient vitamin D during embryogenesis later express altered gene expressions for maintenance (MAP2, NF-L), neurotransmission (GABA-Aα4), and cell cycle control (GADD45) in the brain (Feron *et al.*, 2005; Eyles *et al.*, 2007, 2009). They also have altered brain morphology and reduced levels of nerve growth factor expression in adulthood (Eyles *et al.*, 2003, 2009; Feron *et al.*, 2005). DVD causes dysregulation of multiple brain proteins involved in different biological pathways including oxidative phosphorylation, redox balance, cytoskeleton maintenance, calcium homeostasis, chaperoning, post-translational modifications, synaptic plasticity, and neurotransmission in the prefrontal cortex and hippocampus (Almeras *et al.*, 2007). Protein expression is also altered in the nucleus accumbens, affecting proteins involved in calcium binding (calbindin 1 and 2, hippocalcin and calreticulin) and mitochondrial function (McGrath *et al.*, 2008). Finally, with its expansive roles in the brain, the vitamin D neuroendocrine system seems to be involved in various neurobehavioral disorders (Carswell, 1997; Kalueff *et al.*, 2006d), several of which will be discussed here.

Although this article aims to serve as an encompassing summary of the most current neurobehavioral research, several pathologies have been purposely excluded here. For example, the role of vitamin D and VDR in multiple sclerosis is widely accepted in the literature (Hayes *et al.*, 1997; Cantorna, 2006, 2008; Smolders *et al.*, 2009). As our review focuses on the behavioral aspects of the vitamin D/VDR neuroendocrine system, its well-known role in the pathogenesis of multiple sclerosis is not addressed here (however, see Refs. Cantorna, 2008; Smolders *et al.*, 2009) for recent reviews on this topic).

Brain aging

Brain aging is triggered by genomic instability, neuroendocrine dysfunctions, oxidative stress, altered calcium metabolism, and neuroinflammation (Lee *et al.*, 2000; Tuohimaa *et al.*, 2009). VDR and vitamin D have a regulatory effect on all these phenomena, rendering vitamin D a candidate for longevity regulation (Tuohimaa *et al.*, 2009). For example, cacitriol has also been shown to induce the expression of GADD45α, a protein involved with DNA repair and global genome stability, indicating that vitamin D may have genoprotective action (Akutsu *et al.*, 2001; Galbiati *et al.*, 2003). Notably, VDR mutant mice display symptoms of premature physiological and brain aging, such as wrinkling of the skin, hair and weight loss, muscle atrophy (Keisala *et al.*, 2009), progressive hearing loss (Tuohimaa, 2009), thalamic calcification (Kalueff *et al.*, 2006a), and age-dependent motor and vestibular abnormalities (Minasyan *et al.*, 2009).

Cognitive deficits are the key phenotype of brain aging (Grady and Craik, 2000; Drag and Bieliauskas, 2010). The importance of vitamin D in preserving cognitive function in aging adults is receiving the growing support in clinical literature (Przybelski and Binkley, 2007; Bjorkman *et al.*, 2008; Buell *et al.*, 2009; Lee *et al.*, 2009; Wilkins *et al.*, 2009; Barnard and Colon-Emeric, 2010). With VDR heavily expressed in the cortex and hippocampus, this steroid hormone has a significant influence on cognition, such as episodic memory (Annweiler *et al.*, 2009). Mechanisms that may underlie how vitamin D affects cognition (Kuningas *et al.*, 2009) include downregulation of L-type voltage-sensitive calcium channels in hippocampal neurons, which reduces the influx and excitotoxic effects of calcium (Brewer *et al.*, 2001) known to impair cognitive functioning (Veng *et al.*, 2003). However, although VDR polymorphisms have been linked to impaired cognition, none

of them is associated with calcium levels (Kuningas *et al.*, 2009). Other suggested mechanisms for the beneficial role of vitamin D in cognition include the possibility that it may increase acetylcholine concentration or neurotrophin synthesis (Przybelski and Binkley, 2007).

DVD is also associated with impaired cognitive performance (Wilkins *et al.*, 2006; Wilkins *et al.*, 2009) including dementia (Buell *et al.*, 2010). Interestingly, the incidence of osteoporosis seems to be higher in patients with Alzheimer's disease than in nondemented individuals (Tysiewicz-Dudek *et al.*, 2008), whereas the high prevalence of DVD is associated with Alzheimer's disease (Sato *et al.*, 1998). Altogether, these data indicate that the vitamin D neuroendocrine system emerges as an important factor in preserving brain aging (Lee *et al.*, 2009).

Epilepsy

Maternal vitamin D insufficiency is rather common, often leading to DVD and hypocalcemia in newborns. Researchers have long considered there to be a correlation between neonatal hypocalcemic seizures and corresponding vitamin D levels (Camadoo *et al.*, 2007). Thus, with an emerging link between seizures and vitamin D, there is a growing interest in its possible involvement in epilepsy. Several studies have shown a link between vitamin D dysfunction and epilepsy (Ali *et al.*, 2004; Kalueff *et al.*, 2005b, 2006c), confirming an association between low vitamin D levels and seizures (Janjoppi *et al.*, 2008). Siegel *et al.* (1984) were the first to show the effect of vitamin D against epilepsy in a rodent model, showing that vitamin D delivered to the hippocampus lowers the threshold for chemically induced seizures. However, it took more than two decades before further strides were made. Recently, our group has linked VDR function to epilepsy by showing an increased susceptibility to pentylenenetrazole-induced seizures in VDR knockout mice (Kalueff *et al.*, 2006c). In line with this, 1,25-D indices rapid antiseizure effects in wild-type mice (Kalueff *et al.*, 2005b), whereas pilocarpine-induced seizures elevated VDR mRNA expression (Janjoppi *et al.*, 2008). Collectively, these findings confirm that the vitamin D/VDR endocrine system may play an important role in the regulation of seizures, and may represent a potential drug target to treat this disorder.

Schizophrenia

The observation that humans born in the winter and spring, and those living at higher latitudes, have an increased risk of developing schizophrenia initially implied the role of hypovitaminosis D (Torrey and Miller, 1997; McGrath, 1999; Davies *et al.*, 2003; Saha *et al.*, 2006). The possibility that low prenatal vitamin D could be a risk factor for psychosis was proposed more than a decade ago (McGrath, 1999), as vitamin D supplementation in the first year of life significantly reduces the risk of schizophrenia (McGrath *et al.*, 2004). Although the possibility of genetic variation in the determination of the pathogenesis of schizophrenia has also been examined, genetic polymorphisms in VDR have not emerged as a contributing factor to the susceptibility for schizophrenia (Yan *et al.*, 2005; Handoko *et al.*, 2006). A recent study of a multigenerational family with a mutated VDR also failed to establish the link between VDR mutation and psychotic phenotypes (Ozer *et al.*, 2004).

Vitamin D-deficient animals have been developed to model this link by mimicking the features associated with schizophrenia (McGrath, 1999). For example, transient prenatal DVD in female rats causes morphological, cellular, and molecular changes in the brain, which alters behavior and nerve growth factor expression in their offspring (Grecksch *et al.*, 2009). Newborn rats exposed to prenatal DVD also show altered brain morphology (such as enlarged lateral ventricles and cortical thinning) and evidence of increased cell proliferation in the brain tissue (Eyles *et al.*, 2003). The ventriculomegaly, characteristic of the DVD model, strikingly parallels increased ventricle volume observed in patients with schizophrenia (Kesby *et al.*, 2006). As adults, these rats show significantly impaired latent inhibition and reduced habituation, and spontaneous hyperlocomotion (Becker *et al.*, 2005; Kesby *et al.*, 2006). DVD has also been shown to impair learning in mice (De Abreu *et al.*, 2010). Furthermore, hypovitaminosis D affects several proteins, reported to be disrupted in the postmortem brain tissue from patients with schizophrenia, such as malic enzyme 2 and mitogen-activated protein kinase 1 (McGrath *et al.*, 2008). Importantly, the DVD model is associated with the dysregulation of numerous calcium-binding proteins (calbindin 1 and 2, hippocalcin and calreticulin) (Lewis and Hashimoto, 2007; McGrath *et al.*, 2008). For example, calmodulin has been found to be underexpressed in the hippocampus of adult rats born to vitamin D-deficient mothers (Almeras *et al.*, 2007). Calcium-binding proteins modulate a wide range of key cellular functions, and aberrant calcium buffering, specifically in the nucleus accumbens, may lead to the disruption of adaptive and goal-directed behaviors, consistent with the symptoms of schizophrenia (McGrath *et al.*, 2008).

In line with the DVD model, the absence of vitamin D during development alters the way dopaminergic neurons develop (Eyles *et al.*, 2010). Recent rat studies confirmed that vitamin D targets dopaminergic systems and increases the dopamine transporter density and affinity in the caudate putamen and nucleus accumbens (Kesby *et al.*, 2010). Other studies have shown the modulation of MK 801-induced hyperlocomotion by haloperidol (Kesby *et al.*, 2006) and amphetamine (Kesby *et al.*, 2010) in DVD rats. Amelioration of DVD-induced reduction in neurogenesis by haloperidol (Keilhoff *et al.*, 2010) further supports the link between vitamin D and schizophrenia-like states. Overall, the role of vitamin D in schizophrenia continues to be supported by a growing amount of behavioral, genetic, and pharmacological evidence.

Affective disorders

The role of vitamin D in depression, originally proposed almost a decade ago (Lansdowne and Provost, 1998), has recently received strong support in the largest study to date (Hoogendijk *et al.*, 2008; also see Gloth *et al.*, 1999; Feldman *et al.*, 2004; Berk *et al.*, 2007; Bertone-Johnson, 2009; Barnard and Colon-Emeric, 2010 for details). The role of vitamin D in depression was supported by several recent studies indicating that supplemental vitamin D reduces depressive symptoms (Jorde *et al.*, 2008; Shipowick *et al.*, 2009), with levels of 25-D found to be significantly lower in patients with minor or major depression (Hoogendijk *et al.*, 2008; Arvold *et al.*, 2009). The effectiveness of light therapy (that normalizes vitamin D levels: Sato *et al.*, 2003) in alleviating depression is also in line with these findings (Manber *et al.*, 2002; Shirani and St Louis, 2009; Deligiannidis and Freeman, 2010). The variants in the *VDR* gene have recently been established as possible contributors to susceptibility to age-related changes in cognitive functioning and depressive symptoms (Kuningas *et al.*, 2009). Furthermore, although not directly examining the link, a recent study reported a high number of individuals with bipolar or unipolar depression in a multigenerational family with a mutated *VDR* gene (Ozer *et al.*, 2004).

The role of vitamin D in depression is further corroborated by microarray data showing vitamin D response elements in the promoter regions of serotonin receptors and tryptophan hydroxylase, both of which are strongly associated with depression (Wang *et al.*, 2005; Fernandes de Abreu *et al.*, 2009). A recent study screening thalamic transcriptome found an association between VDR expression and bipolar depression (Chu *et al.*, 2009), offering yet further evidence to support the role of the vitamin D/VDR neuroendocrine system in clinical depression.

Unlike human data, vitamin D has not been directly linked to depression in animal models. For example, VDR mutant mice do not exhibit the baseline depressive-like symptoms, but do show significant anxiety-like behavior (Kalueff *et al.*, 2004, 2006b; Minasyan *et al.*, 2007), including decreased exploratory behavior and stress-induced grooming (Kalueff *et al.*, 2004). The idea that VDR is involved in anxiety has been further confirmed by Kas' group, implicating the *VDR* gene in neophobia in mice (De Mooij-van Malsen *et al.*, 2009). The quantitative trait locus found in this study and associated with mouse avoidance behavior contains *VDR* gene regions, and is homologous to the human locus linked to affective pathogenesis (Segurado *et al.*, 2003; De Mooij-van Malsen *et al.*, 2009). Finally, a correlation has also been noted between DVD and anxiety in humans (Armstrong *et al.*, 2007), collectively supporting the role of vitamin D in affective disorders.

Brain calcification is a common consequence of dysregulated calcium metabolism, and may be triggered by hypocalcemia and hypovitaminosis D. Calcification of the basal ganglia, such as Fahr's syndrome, is known to produce neurological and psychological phenotypes, including movement disorders, seizures, dementia, psychoses, and mood disorders (Senoglu *et al.*, 2007; Brunoni *et al.*, 2009). Associated with genetic defects in VDR, vitamin D-resistant rickets type II has recently been reported to lead to basal ganglia calcification in humans, associated with depression, mental retardation, and aggression (Brunoni *et al.*, 2009). Our earlier studies with VDR mutant mice (Kalueff *et al.*, 2006a) showed a strikingly similar phenotype, with progressive thalamic calcification in these mutants. Altogether, this raises the possibility that various neuropsychiatric symptoms associated with vitamin D/VDR deficiency may be linked to benign brain calcification. Importantly, such calcification can be easily detected by brain imaging methods and corrected by vitamin D/calcium supplementation.

Conclusion

The recognition of vitamin D and VDR as novel drug targets in the brain continues to be supported by a growing amount of clinical and experimental data. The understanding of the mechanisms and role played by vitamin D in neurobiology and behavior is crucial in developing innovative therapeutic approaches for treating a variety of brain pathologies. Although vitamin D supplementation as a therapy has long been associated with a clear benefit in preventing numerous brain pathologies, especially when administered during pregnancy, one of the major problems is its toxicity because of hypercalcemia (Carswell, 1997). Therefore, the development of novel drugs with low-calcemic analogs, and those with synthetic vitamin D ligands with tissue-specific uptake, may provide the needed progression in therapeutics (Kalueff *et al.*, 2006d). Finally, there is increasing genomic and genetic evidence, briefly summarized here, suggesting the important role of brain genes in the vitamin D action. Therefore, new therapeutic strategies may include both traditional pharmacological and gene therapy approaches to the vitamin D/VDR neuroendocrine system.

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