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Review

Vitamin D and the paraventricular nucleus: Relevance for type 2 diabetes

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ABSTRACT

Vitamin D deficiency is linked to type 2 diabetes and we recently showed this may be through action of vitamin D in the paraventricular nuclei (PVN) in the hypothalamus of the brain. This review focuses on the known roles of the PVN in glucose control and how previously discovered actions of vitamin D in other tissues may translate to action in the PVN. Specifically, we focus on the role of insulin and inflammation in the hypothalamus and how these may be modified through vitamin D action.

Type 2 diabetes (T2DM) affects over 400 million adults worldwide [1], often occurs on a background of insulin resistance in obesity, and is a leading risk factor for cardiovascular disease [2]. While insulin resistance is known to be a contributing factor to the development of T2DM, the full mechanisms behind the development of T2DM have not been elucidated. Genetics has a confirmed role in the development of T2DM as well as other factors, such as epigenetics, diet, and environmental substances [3]. Vitamin D deficiency has been linked to the development of T2DM [4,5], although reversing/preventing diabetes with vitamin D treatment clinically has not shown consistent results [6,7]. Recently, our lab published that vitamin D action in the brain is an essential pathway to halt glucose intolerance in an obese animal [8]. In this article, we will synthesize the known literature on vitamin D action to explain a possible model by which vitamin D may affect peripheral glucose levels. We will also suggest key areas important to advancing our knowledge of the link between vitamin D deficiency and T2DM.

1. Hypovitaminosis D and T2DM

As early as 1988, low 25-hydroxyvitamin D (the storage form of vitamin D, 25OHD) serum levels were noted in obese subjects and eventually, 25OHD was shown to be negatively correlated in obese patients [9]. T2DM, in turn, has also been associated with a lower circulating levels of 25OHD independent of weight status [10,11]. Insulin resistance, hyperinsulinemia, and adipocyte dysfunction have well-established ties to T2DM [12] and have been implicated in how vitamin D may affect glucose control [13,14].

While vitamin D is well known for its regulatory effects on bone health and calcium levels, it also has important roles in glucose control. Vitamin D is made, either in the skin after UV exposure or ingested, and then becomes hydroxylated in the liver to become 25OHD. A second hydroxylation step in the kidney, via the 1α-hydroxylase enzyme, renders the active form of vitamin D, 1α,25-dihydroxyvitamin D. Both 1α,25-dihydroxyvitamin D receptors (VDR) and 1-alpha-hydroxlase enzyme have been found in pancreatic beta cells [15,16], suggesting that circulating 1α-25-dihydroxyvitamin D regulates extracellular calcium concentrations and flux through cell membranes in beta cells. Animal model studies have confirmed that vitamin D enhances insulin secretion and synthesis – but not other islet hormones [17]. Rats fed a diet deficient in vitamin D have impaired glucose tolerance, insulin secretion [18], and insulin sensitivity [19]. Additionally, mice lacking vitamin D receptors have impaired glucose tolerance and a reduction in insulin levels [20]. This may be secondary to rapid, membrane-bound VDR actions instead of typical genomic/transcriptional actions of the VDR as a transcription factor since mice with VDRs that are transcriptionally inactive have normal insulin secretion from islets [21].

Given the clinical associations of vitamin D with obesity and T2DM and the animal models showing effects of vitamin D on insulin secretion, it follows that low vitamin D levels in patients may be a contributing factor to their development of T2DM or lack of proper glucose homeostasis. Multiple clinical studies have used vitamin D as a therapeutic agent in T2DM. Vitamin D given at 2000 IU per day for 16 weeks increased the disposition index (measure of beta cell function) in adults [22]. Vitamin-D fortified yogurt giving 1000 IU per day for 12 weeks also significantly decreased HgbA1c and HOMA-IR [7]. However, no association was observed between 25OHD and insulin sensitivity or disposition index in obese adolescents [23]. Sixteen weeks of

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supplementation with 4000 IU per day of vitamin D in vitamin D-deficient obese adults also resulted in no significant differences in insulin sensitivity or secretion [24]. An article using mathematics and VDR polymorphisms concludes that there is likely no causal relationship between vitamin D deficiency and diabetes, although the differences in vitamin D levels in this study were of little clinical significance [25]. These discrepant findings necessitate a closer examination of the therapeutic potential of vitamin D on glucose intolerance within vitamin-D deficient models.

2. CNS control of glucose

We (and others) have previously published more extensive reviews on the ability of the brain to control peripheral glucose levels [26–28]. In brief, the brain can directly control hepatic glucose production, insulin secretion, and glucose handling by the muscle and kidney [28,29]. While many areas of the brain are implicated in the aforementioned pathways, the hypothalamus of the brain contains multiple nuclei that are key, including the arcuate, ventromedial hypothalamic (VMH), lateral hypothalamic area (LHA), and paraventricular nuclei (PVN).

The PVN is a critical hypothalamic nuclei that integrates signals from a variety of brain regions and has important regulatory functions for hepatic glucose control. Stimulation of the sympathetic nervous system, via direct norepinephrine injection, in the PVN causes hyperglycemia [30]. The PVN directly projects to the liver through both the parasympathetic and sympathetic nervous system [31,32]. Intra-PVN thyroid hormone (T3) increases hepatic glucose production, an effect blocked by hepatic sympathectomy [33]. The PVN also plays a large role in integrating signals from other areas of the brain, including the suprachiasmatic nucleus, ventromedial hypothalamus, and arcuate. AgRP neurons of the arcuate are necessary for insulin-mediated changes in hepatic glucose production [34] but these effects are blocked by vagotomy. Given that AgRP neurons are known to synapse with neurons in the PVN, it is likely that the effects of insulin in the arcuate nucleus are mediated through second-order neurons in the PVN.

The PVN may also alter peripheral glucose levels by modifying pancreatic function. The pancreatic islets receive both parasympathetic and sympathetic innervation and viral tracing studies have shown that the PVN is one of the major sources of this innervation [35]. Antagonism of GABAergic neurons in the PVN (via bicuculline) caused hyperglycemia in mice secondary to increased glucagon secretion via sympathetic nervous system activation [36]. Thus, the PVN has multiple modalities by which it can influence peripheral glucose levels.

3. Vitamin D and the brain

Vitamin D is well known to be integral to normal brain development [37]. Vitamin D can increase important neurotrophic proteins such as nerve growth factor and neurotrophins NT-3 and 4 [38,39]. Rats lacking vitamin D prenatally have altered brain morphology, defining the importance of vitamin D in the embryonic stage. Additionally, vitamin D has been shown to be potentially important in other brain related diseases such as schizophrenia, Parkinson's disease, and autism, among others [40,41]. Vitamin D can cross the blood-brain barrier, although the transport of cholecalciferol and calcitriol is likely limited [42,43]. Interestingly, neurons possess the critical enzymes to convert precursor vitamin D into its active form and some parts of the brain can catabolize vitamin D into its inactive form [44]. Vitamin D influences neurotransmitters and evidence suggests it likely increases dopamine, noradrenaline, and serine levels while decreasing glutamine and serotonin in the brain [45,46]. Excellent reviews on the effects of vitamin D in the brain from a molecular level [47] and also related to psychological/neurological manifestations [40,48] have been previously published. Important for this review, the vitamin D receptors (VDR) in the adult brain have been mapped to multiple brain regions including the hypothalamus [49]. In humans, the PVN and supraoptic nuclei contained intense staining for the VDR, suggesting that vitamin D may also influence hormone regulation by the PVN.

4. Glucose regulation & vitamin D in the hypothalamus

Our lab recently demonstrated the importance of vitamin D action in the PVN on glucose regulation [8]. In diet-induced obese rats, treatment with 1α,25-dihydroxyvitamin D_3 (calcitriol) into the third-ventricle of the brain decreased hepatic glucose production and improved whole-body insulin sensitivity. When 1α,25-dihydroxyvitamin D_3 was directly administered into the PVN, animals had improvement in glucose tolerance during an intraperitoneal glucose tolerance test. However, 1α,25-dihydroxyvitamin D_3 had no effect when delivered to animals with a lentiviral-mediated knockdown of VDRs, demonstrating that the action of calcitriol in the brain was through the VDR. Additionally, mice treated with an AAV-Cre virus to knockdown VDRs in the PVN displayed an impairment of glucose tolerance. This demonstrated that VDR action in the PVN is not only important pharmacologically but also is necessary physiologically. Additionally, our data showed that effects of vitamin D on glucose regulation only occur in a high-fat diet fed state, not in chow-fed animals.

How vitamin D can alter glucose regulation through the PVN is unknown. Since central vitamin D improved peripheral insulin sensitivity, it is possible that central vitamin D may act by improving insulin action within the hypothalamus. Insulin receptors are expressed in the hypothalamus [50] and brain-specific deletion of insulin receptors (IR) confers insulin resistance, leptin resistance, and obesity [51]. Insulin is well-known to activate phosphatidylinositide-3′-kinase (PI3K), which in turn phosphorylates AKT. 1α-25-dihydroxyvitamin D increased phosphorylation of AKT in osteosarcoma cell lines in a PI3K-dependent manner [52]. Recently, vitamin D supplementation has been shown to increase CSF concentration of insulin in obese rats [53]. Whether this effect was secondary to weight loss or a direct effect of vitamin D in the brain was not determined. Insulin, and its downstream target KATP channels, can suppress hepatic glucose production through signaling directly in the brain [27,28]. Of interest, insulin action in the brain has been shown to increase hepatic IL-6, which causes a cascade of events leading to decreased hepatic glucose production via the STAT3 pathway [54]. We have unpublished data showing an increase in hepatic IL-6 after calcitriol administration into the third ventricle of obese rats, which occurred concurrently with a decrease in phosphoenoylpyruvate carboxykinase (PEPCK), a rate limiting step of gluconeogenesis in the liver. Thus, vitamin D may act in the brain to augment insulin signaling through the PI3K pathway thereby decreasing hepatic glucose production possibly through STAT3 activation. Nameni et al. recently showed that peripheral vitamin D treatment increased the ratio of CSF to peripheral insulin concentration, which would suggest improved insulin action in the brain [53]. This is also supported by data showing that vitamin D treatment enhances insulin action in mouse islets [55] while vitamin D deficiency impairs insulin signaling in islets of obese mice [56]. Thus, vitamin D may act in the brain to improve insulin action, which would result in decreased hepatic glucose production.

Another possibility is that vitamin D may act as an anti-inflammatory agent in the hypothalamus.

It is generally accepted that inflammatory changes are detectable in the hypothalamus of high-fat diet-fed animals. Proinflammatory cytokines, such as IL-1β, TNF-α, and IL-6 have an altered hypothalamic expression after both short and long-term feeding with high-fat diet [57,58]. Moreover, evidence suggests that hypothalamic inflammation is a key contributor to hepatic insulin resistance. In wild-type animals, central administration of antibodies to Toll-like Receptor 4 (TLR4) and TNF-α improved glucose tolerance and insulin signaling in the liver [59]. Interestingly, this effect is blocked with a vagotomy or inhibition of the parasympathetic nervous system. Hypothalamic administration of TNF-α or a TLR4 activator also causes defective insulin secretion, which is likely mediated through increased sympathetic nervous system