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MINI-REVIEW

Mechanisms of Neuroprotective Action of Vitamin D_3

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Abstract—This review considers modern data on the mechanisms underlying the neuroprotective effect of the neurosteroid vitamin D_3 and its receptors in the nervous system. Special attention is paid to Ca^{2+} regulation, stimulation of neurotrophin release, interaction with reactive oxygen and nitrogen species, and neuroimmunomodulatory effects of calcitriol, the main biologically active form of vitamin D_3, in the nervous system.

Key words: vitamin D_3, calcitriol, nervous system, neuroprotection

Vitamin D designates a group of calcitriols, fat-soluble hormones of secosteroid nature [1-3]. The calcitriols include vitamins D_2, D_3, D_4, D_5, and their derivatives [3]. Vitamin D_3 (cholecalciferol) synthesized in skin during photolysis of 7-dehydrocholesterol or ingested with food is the most important [1, 4]. Vitamin D_3 itself is biologically inert, and its bioactivation involves double hydroxylation in liver (yielding prohormone calcidiol) followed by subsequent formation of calcitriol (figure) [4-6].

Calcitriol is the main biologically active form of vitamin D_3. Together with calcidiol, vitamin D_3 circulates in blood as complexes with vitamin D-binding protein, albumin, α-fetoprotein, and lipoproteins [1, 3, 7, 8].

Physiological concentrations of calcitriol and calcidiol vary within 50-100 pM and 30-50 nM, respectively [8, 9]. In kidneys, calcidiol and calcitriol undergo subsequent hydroxylation followed by formation of the almost inactive metabolites 24,25-dihydroxy-D_3 and calcicetrol (figure) [4-6]. Biological effects of calcitriol are mediated by specific nuclear receptors [7, 10]. The nuclear vitamin D_3 receptors are ligand-activated transcription factors; they belong to a common family of steroid receptors, which also includes steroid, glucocorticoid, and retinoic acid receptors [5, 11, 12]. Nuclear vitamin D_3 receptor is a protein of ~51 kD that consists of four domains (A/B, C, D, and E) typical for all nuclear receptors of steroid hormones [1, 5]. The E-domain of vitamin D_3 nuclear receptor is responsible for ligand binding [1, 13]. It is formed by 12 α-helical regions arranged into three β-sheets forming the ligand-binding pocket [13]. Calcitriol (K_d ~ 0.5 nM) is the main ligand of vitamin D_3 nuclear receptors [12]. Although affinity of these receptors to calcidiol is ~700 times less than to calcitriol, calcidiol concentrations in blood are much (700-1000-fold) higher than those of calcitriol [1]. The mechanism of the genome effect of vitamin D_3 is similar to that of steroid hormones (see for review [11, 14]).

Besides the genome effect, calcitriol exhibits non-genomic effects realized via membrane vitamin D_3 receptors [11, 15]. These proteins of 60 kD exhibit high affinity to calcitriol (K_d of 0.5 nM) [12]. However, they have not been cloned yet and their domain structure remains unknown [5, 16]. The non-genomic effects occur within a few seconds or minutes and their signal transduction involves formation of second messengers: cyclic nucleotides, diacylglycerol, inositol-trisphosphate, and arachidonic acid (for details see [5, 15-17]).

Traditionally, vitamin D_3 was considered as a hormone-regulator of Ca^{2+} and phosphate homeostasis [1, 3, 18]. However, results of recent studies provide convincing evidence on the role of vitamin D_3 in other biochemical processes in various tissues including the nervous system [2, 3]. Physiological concentrations of calcitriol in brain are around 10 pM; this vitamin can cross the blood–brain barrier and bind to nuclear vitamin D_3 receptors in the brain [19, 20]. Nuclear vitamin D_3 receptors have been found in brain neurons, glial cells, spinal cord, and the peripheral nervous system [20-24]. Membrane vitamin

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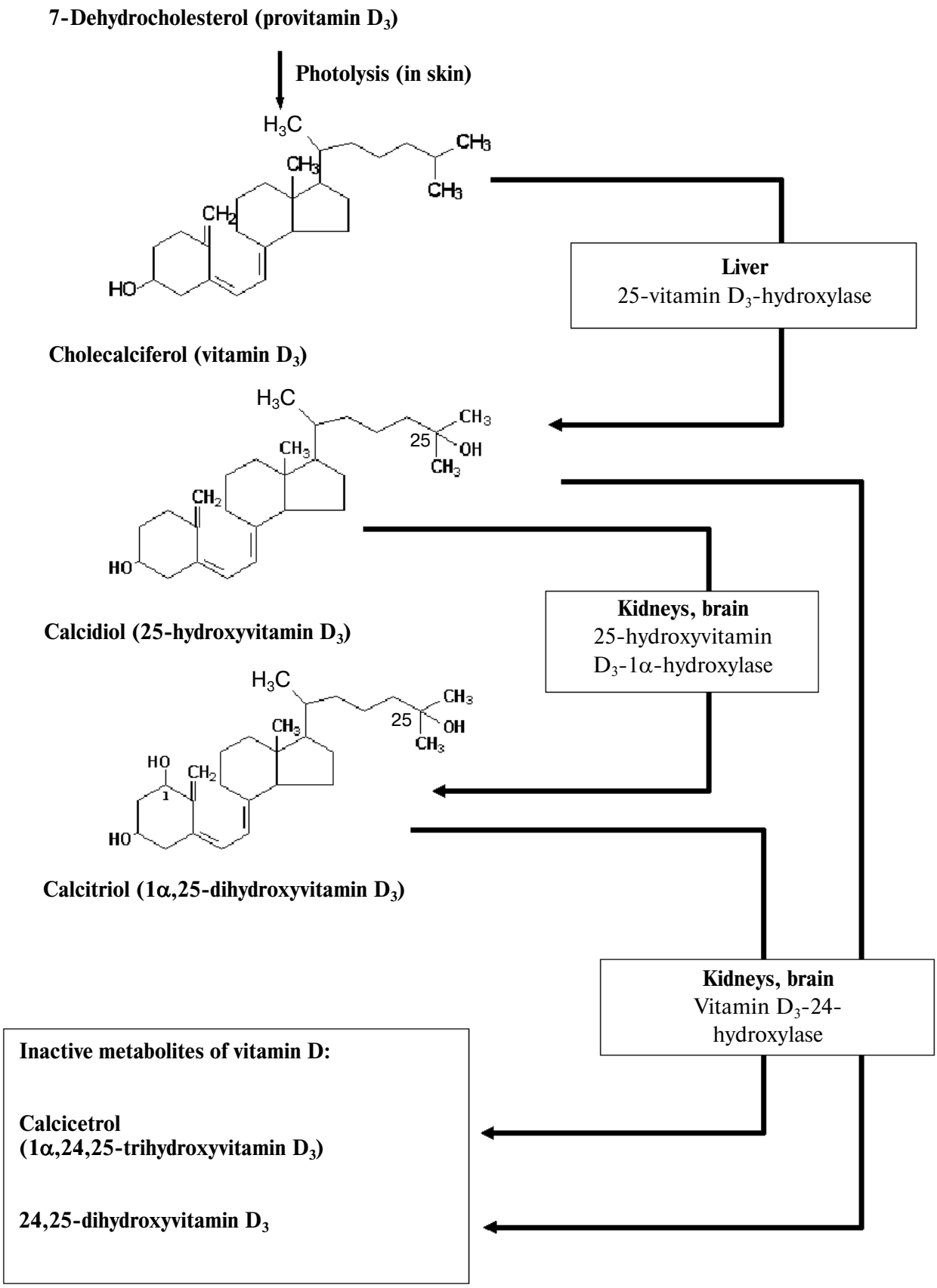

Synthesis and metabolism of vitamin D

D_3 receptors have also been identified in the brain [25], which also contains enzymes of biosynthesis and metabolism of active forms of vitamin D_3 (figure) [6, 26]. So, vitamin D_3 can be considered as para- and autocrine hormone neurosteroid playing an important role in the nervous system [3, 4, 23, 27, 28]. Here we consider modern data on the role and mechanisms underlying the neuroprotective effect of vitamin D_3.

The neuroprotective effect of vitamin D_3 is associated with reduction of Ca^{2+} level in the brain [3, 27, 29]. High level of this ion increases manifestations of neurotoxicity [8], which is attenuated by administration of calcitriol [27, 29]. Vitamin D_3-induced decrease in brain Ca^{2+} may involve two distinct mechanisms. Calcitriol stimulates expression of Ca^{2+} binding proteins—parvalbumin and calbindins D9k and D28k [11, 14, 22, 30, 31]; it also inhibits expression of L-type Ca^{2+} channels in hippocampus [11, 14]. Both effects protect neurons against toxic damage by reducing cell calcium [11, 22, 30].

The second mechanism of the neuroprotective action of vitamin D_3 is related to inhibition of brain γ-glutamyl transpeptidase, the key enzyme of glutathione metabolism [3, 19]. Increasing antioxidant defense by increasing brain glutathione, 1-100 pM calcitriol decreased hydrogen peroxide and exerted a neuroprotective effect during brain damage caused by iron and zinc ions [32, 33]. Neuroprotective effect of calcitriol was also demonstrated using experimental brain ischemia, administration of glutamate, 6-hydroxydopamine, and other neurotoxic agents [8, 27, 29, 34].

The interaction of vitamin D_3 with reactive oxygen and nitrogen species is also important for neuroprotection. Nanomolar concentrations of calcitriol (0.1-100 nM) protected neurons against direct effects of superoxide and hydrogen peroxide [29, 33, 35]. However, reactive oxygen and nitrogen species modulate effects of vitamin D_3: they inhibit association of nuclear vitamin D_3 receptors with DNA; singlet oxygen, superoxide, and peroxynitrite cause irreversible inhibition, whereas the effect of peroxide is partially reversible [36]. In contrast to these reactive species, nitric oxide causes reversible inhibition of receptor association with DNA. This suggests that nitric oxide (NO) might act as a natural modulator of genome effects of vitamin D_3 in the brain [36]. Calcitriol can reduce NO level by inhibiting expression of inducible nitric oxide synthase in the spinal cord and brain [3, 19]. Thus, one of the important mechanisms of neuroprotective action of vitamin D_3 involves inhibition of production of an oxidant (NO) molecule in the brain [3].

The neuroprotective role of vitamin D_3 is also associated with neutrophin induction [32]. In brain neurons and glial and Schwann cells, calcitriol stimulates expression of nerve growth factor, NT3 neurotrophin, glial neurotrophic factor, and also neurotrophin receptor $p75^{NTR}$ [4, 21, 22, 28, 34, 37, 38]. Calcitriol stimulates neuritogenesis and its deficit results in decreased expression of $p75^{NTR}$ and the neurotrophins [18, 27]. Neurotrophin induction underlies the neuroprotective effect of vitamin D_3 in brain ischemia [13] and the general anti-neurodegenerative properties of this vitamin [3]. For example, D_3 prevents death of dopaminergic neurons in experimental models of Parkinson's disease in animals [7, 29, 34]. The development of Alzheimer's disease is characterized by significant reduction in nuclear vitamin D_3 receptors [31]. Administration of vitamin D_3 (accompanied by induction of nerve growth factor) decreases the progression of Alzheimer's disease [12, 29]. Chronic administration of vitamin D_3 to rats decreases degenerative processes in hippocampus during aging [20]. This suggests the importance of anti-neurodegenerative activity of vitamin D_3 for manifestation of its neuroprotective effect.

Results of recent studies provide convincing evidence for involvement of vitamin D_3 in immunological processes protecting the nervous system [16, 39, 40]. In the central nervous system, calcitriol plays the role of an immunosuppressor. It acts as inducer of anti-inflammatory cytokine interleukin-4 and transforming growth factor; calcitriol also decreases expression of proinflammatory cytokines interleukin-6, tumor necrosis factor, and macrophage colony stimulating factor [19, 41-43]. Calcitriol decreases expression of proteins of major histocompatibility complex class II and cofactor CD4, which play important roles in autoimmune processes in the nervous system [3, 39]. In a model of experimental allergic encephalomyelitis (in mice or rats), calcitriol inhibited autoimmune damage of nervous system, whereas deficit of this vitamin increased the autoimmune damage [19, 39]. The neuroprotective effect of calcitriol was lower in interleukin-4 knockout mice [40]. This effect obviously involved nuclear vitamin D_3 receptor, because knockout of the gene encoding this receptor resulted in loss of calcitriol activity as neuroprotector-immunosuppressor [40]. Thus, the immunomodulating properties of vitamin D_3 represent another mechanism of neuroprotective effect of this vitamin.

Summarizing all the data considered in this review, we conclude that biological functions of vitamin D_3 in the body include potent neuroprotective effect that involves several independent mechanisms [3, 8, 44]. Since vitamin D_3 exhibits numerous effects in the nervous system, this neurosteroid hormone and its analogs can be considered as promising for development of new therapeutic neuroprotectors [8, 29, 34].

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