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维生素D对脑内多巴胺神经系统的调节作用*

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摘要 维生素D（vitamin D，VD）是一种神经活性类固醇，可以调节神经递质合成、维持细胞内钙稳态，在脑内发挥调节神经元兴奋性、保护神经细胞等作用。新近研究表明，VD与多巴胺（dopamine，DA）能神经元介导的动机、奖赏、学习和运动等行为有关，VD不仅可促进DA合成，调节脑内DA水平，还从多种角度对DA能神经元发挥神经保护作用。本文将介绍VD的合成、代谢及作用途径，探讨VD对DA能神经元调控机制，为动机、奖赏等行为的研究提供理论参考。

关键词 维生素D，多巴胺神经系统，调控功能，突触可塑性
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维生素D（vitamin D，VD）是人体重要的营养素，缺乏VD可导致各种慢性疾病发生，如佝偻病、骨质疏松等，并降低自身免疫功能，增加患精神障碍和癌症的风险[1-3]。人体外周及中枢的VD合成均依靠阳光照射、饮食来源和各类补剂[4-5]。大脑中的VD是一种重要的神经活性小分子，参与神经递质和营养因子的合成、预防细胞氧化损伤并能够维持细胞内钙的稳态，发挥神经保护作用[6]。新近研究发现，VD可以增强神经元的兴奋性，促进细胞增殖和神经发生[7]，中脑腹侧被盖区（ventral tegmental area，VTA）和黑质致密部（substantia nigra pars compacta，SNc）是脑内多巴胺（dopamine，DA）能神经元的主要聚集地，VTA与伏隔核（nucleus accumbens，NAc）构成的神经通路，是大脑中奖赏机制的核心通路，在动机、运动和成瘾中发挥重要的神经调节作用。

1 VD的发现及其生物代谢

1645年Whistler[8]首次描述了佝偻病高发于阴雨多雾的英格兰地区。1922年McCollum等[9]发现了鱼肝油具有抗佝偻病的特性，并将抗佝偻病因子命名为VD。同时临床研究表明，光照或人工紫外线B（ultraviolet B，UVB）照射可以预防或治愈佝偻病[10-11]。1928年Windaus[12]确定了麦角固醇是植物中VD的有效化学成分，1937年首次在动物和人体皮肤中分离出VD的有效成分7-脱氢胆固醇（7-DHC）[13]。

人体中80%~90%的VD_3是在紫外线（290~315 nm）照射作用下合成。皮肤中的7-DHC发生光解作用，合成维生素D前体（图1a）[14-15]，在8 h内被体温异构化为VD_3，并释放进入毛细血管至肝脏，经25-羟基化酶（25-OHase）作用形成25-羟基维生素D_3（$25(OH)D_3$）（图1b），其半衰期较长，约为15 d，$25(OH)D_3$是体内VD的主要存在形式[16]。

$25(OH)D_3$在体内主要通过两条途径生成$1,25(OH)_2D_3$，即VD活性形式。一条是被维生素D结合蛋白（vitamin D binding protein，VDBP）转运到肾脏[17]，进行羟基化；一条是通过血脑屏障，经热休克蛋白70（heat shock protein 70，HSP70）转运至脑内线粒体进行羟基化（图1c）。24-OHase是VD的分解代谢酶，$1,25(OH)_2D_3$在肾脏中经24-OHase催化为$24,25(OH)_2D_3$，是其主要分解代谢途径。UVB照射人体皮肤后16 h内可检测到$1,25(OH)_2D_3$，其半衰期为4~20 h[18]，大脑也可调节$1,25(OH)_2D_3$水平，在维持正常神经系统功能中发

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挥重要作用[19]。敲除体内VDBP会降低25(OH)D_3和1,25$(OH)_2D_3$水平，实验证明$VDBP^{-/-}$（敲除）小鼠无法通过UVB照射产生VD，说明VDBP在VD合成中发挥重要作用[20]。

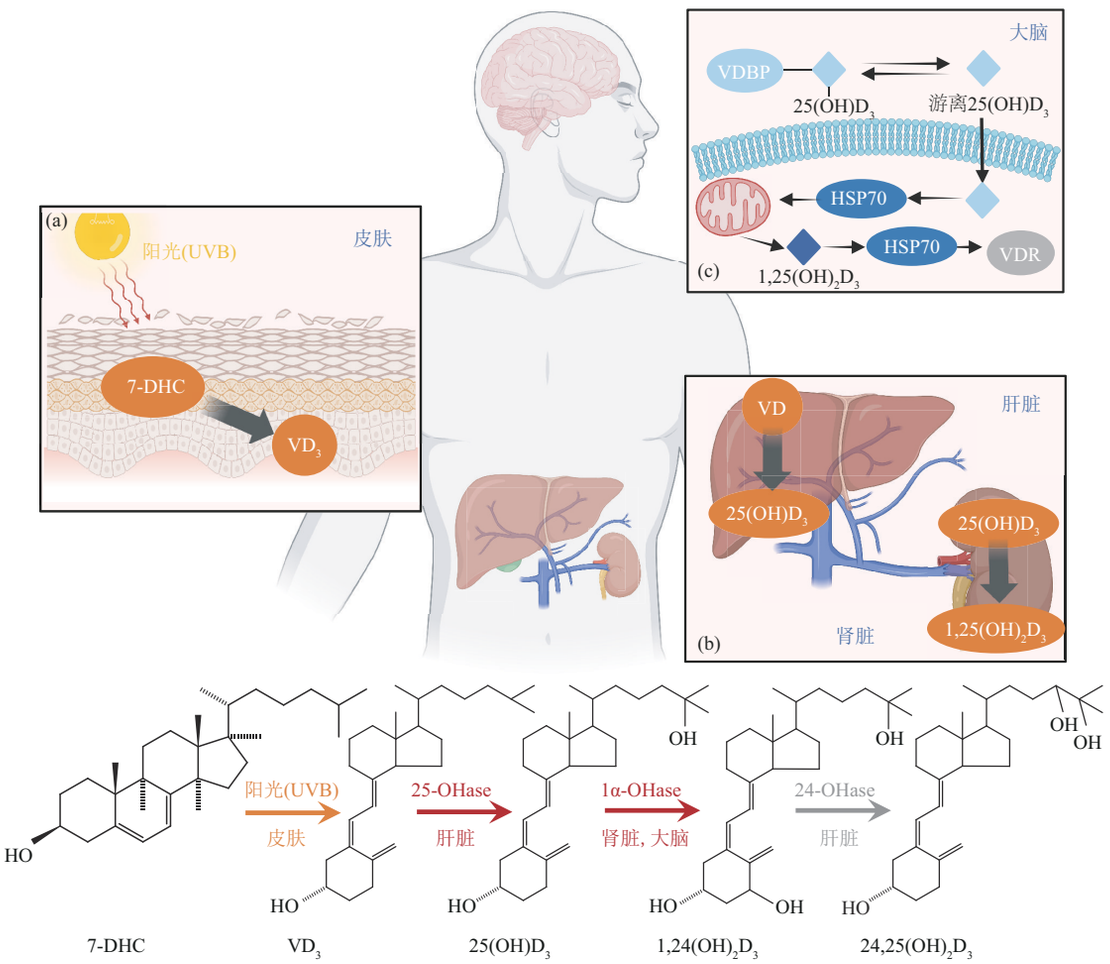

Fig. 1　The synthesis process of vitamin D in biological organisms

图1　体内维生素D的生物合成及代谢过程

2　VD的信号转导通路及突触可塑性调节

VD是大脑功能的有效调节剂，在中枢神经系统中通过与维生素D受体（vitamin D receptor，VDR）和膜受体（MARRS，mVDR）的结合进行信号转导调节（图2）[21]。VDR主要存在于与钙稳态维持有关的组织如肠道、肾脏和骨骼中，也存在于脑内神经元与神经胶质细胞中，VDR是核受体转录因子家族的成员，1,25$(OH)_2D_3$与其结合时，诱导基因转录。VD与MARRS结合主要调节Ca^{2+}、Cl^-通道的开放，发挥非基因组作用[22]。同时，MARRS受体也具有基因调节效应，能够结合DNA并调控基因转录[23]。

研究表明，VD可上调与突触可塑性相关的多种基因表达，也可提高神经递质的受体表达，维持突触正常功能，如DA、谷氨酸和血清素[24-25]，通过多种途径影响神经系统的突触可塑性，VD缺乏可能导致学习和记忆缺陷。VD还可以影响电压依赖性钙通道（voltage-dependent calcium channels，VDCC）发挥促进神经递质释放、调控神经元兴奋性等生理功能[6]。同时，VD通过激活蛋白质激酶C（PKC）、蛋白激酶A（PKA）、磷脂酰肌醇3激酶（PI3K）等，调节L型VDCC（L-VDCC）开放，诱导Ca^{2+}内流[26]。实验观察到，产前缺乏VD的大鼠脑中，脑发育调节蛋白和生长相关蛋白43基因表达失调，这两类基因均与突触可塑性调节有关[27]。免疫荧光染色观察到，D1-Cre和D2-Cre转基因小鼠NAc和背侧纹状体中，VDR与多巴胺D1

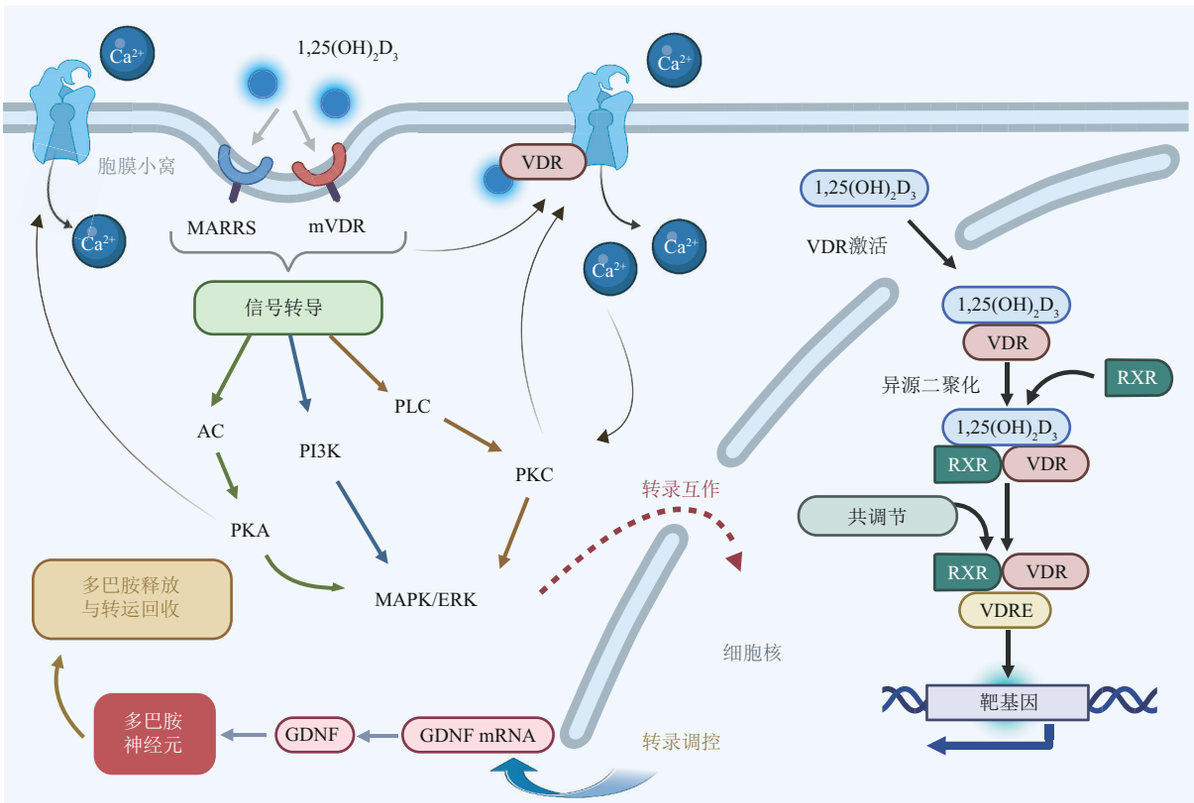

Fig. 2　The signal transduction pathway of vitamin D

图2　维生素D的信号转导通路

AC：腺苷酸环化酶（adenylyl cyclase）；PI3K：磷脂酰肌醇3激酶（phosphoinositide 3-kinase）；PLC：磷脂水解酶C（phospholipase C）；PKA：蛋白激酶A（protein kinase A）；PKC：蛋白质激酶C（protein kinase C）；ERK：细胞外调节蛋白激酶（extracellular regulated protein kinases）。

型受体-中型多棘神经元（D1R-MSN）和D2R-MSN高度共定位，提示VDR可能是调节DA的靶点[28]。

3　VD对DA神经环路功能的调节

3.1　DA神经投射通路及VD的调节功能

脑内DA神经投射通路主要包括以下4条（图3）。VTA至NAc的投射通路（VTA→NAc）是大脑奖赏机制的核心通路，负责激励动机、强化学习、愉悦寻求等功能[29-31]。NAc区域的DA释放能够驱使机体寻求奖励的行为，是形成动机导向行为的核心枢纽，该神经通路异常诱发药物成瘾或抑郁症等情绪障碍的发生[32-34]。VD缺乏会导致VTA中DA水平降低，影响DA能神经元兴奋性[35]。

VTA至海马脑区（hippocampus，Hipp）的投射通路（VTA→Hipp）在学习记忆中具有重要的调节作用，VTA的DA能神经元和海马之间形成闭合环路[36-37]。当接收需要储存的信息时，VTA神经元兴奋，在海马投射区释放DA，海马区的D_1/D_5受体激活有助于记忆编码，同时对短时程记忆向长时程记忆的转化有重要意义，补充VD可增加海马神经元的兴奋性，减轻与年龄相关的认知能力下降[24]，VD可能提高VTA核团神经元兴奋性，影响海马神经元放电频率。

VTA至前额叶皮质（prefrontal cortex，PFC）的投射通路（VTA→PFC）在决策、注意力、社交行为等高级认知功能与情绪调控中发挥关键作用。DA不仅调控PFC区域的中间神经元的兴奋性和突触可塑性，而且还影响情绪调节与社交功能。当PFC区域的DA水平及其相关受体出现异常时，这些功能可能受到损害[38-39]。VD调节DA活性并维持和增强PFC功能，还可提高PFC区域神经元突触可塑性，促进认知功能改善。

SNc至纹状体（striatum，Str）的投射通路

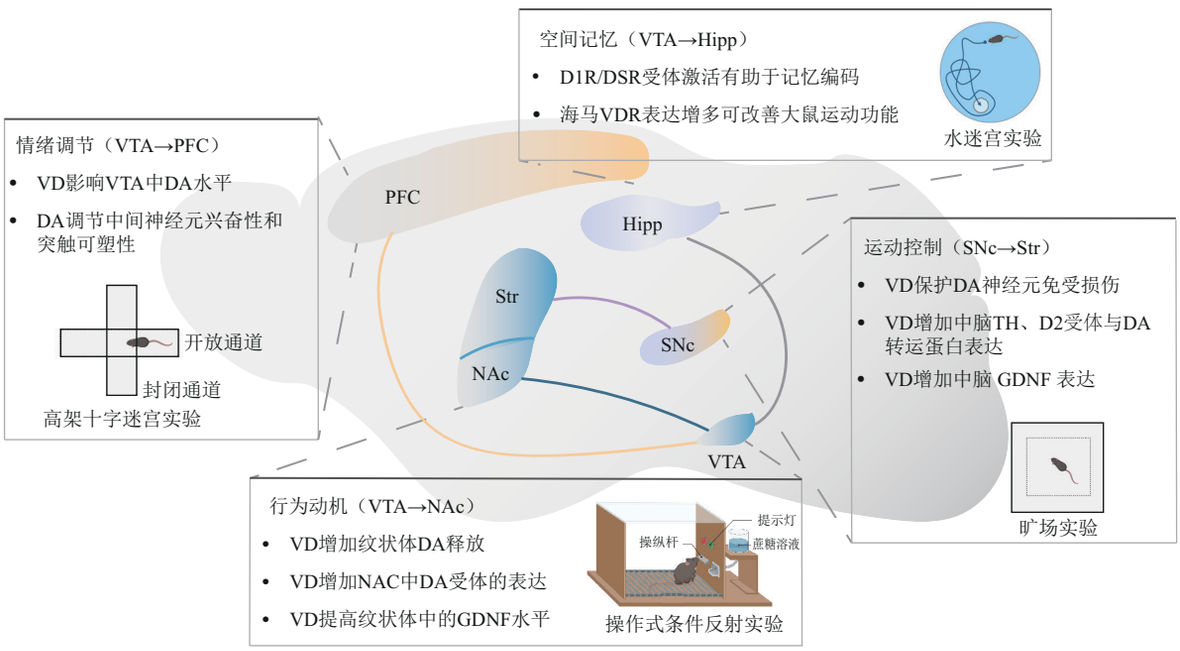

Fig. 3　The regulatory function of VD on the DA neural projection pathway

图3　维生素D对多巴胺神经投射通路的调节功能

（SNc→Str）则发挥运动控制的作用，通过与纹状体D1受体（D1R）结合兴奋直接通路增强运动，与D2受体（D2R）结合抑制间接通路抑制运动，该通路DA能神经元的缺失将导致机体出现帕金森病（Parkinson's disease，PD）运动功能症状，如运动迟缓、僵硬和静止性震颤等[40-41]。VD可增加纹状体中的DA释放，促进神经递质的传递和接收，提高DA转运蛋白表达及DA的重摄取和循环利用。

3.2　VD对DA能神经元功能的调节

VD可诱导酪氨酸羟化酶（tyrosine hydroxylase，TH）基因表达增强，促进DA合成，并调节脑内DA水平。TH作为DA合成的限速酶，在DA回路中与VDR高度共定位，VD可通过VDR调节DA能神经元发生过程中的重要神经黏附分子N-cadherin，提高TH的表达[42]。通过定量PCR（qPCR）实验发现，腹腔注射VD后，小鼠脑内DA相关区域的多巴胺转运蛋白显著上调，NAc中的D2R表达显著增加，同时Str中DA的释放增加，表明VD不仅影响突触前DA的产生和再摄取，还可调节突触后DA神经通路下游的信号转导。在VD注射2 h内，安非他明组小鼠的运动距离显著增加，表明VD通过局部激活中脑神经元中的VDR，实现DA释放以及运动能力的快速调节[28]。

VD作为一种关键的神经发育类固醇，对DA能神经元的发育产生直接影响[43]。VDR在大鼠胚胎的第12天出现于中脑，即DA能神经元产生的高峰期[42]。随着DA能神经元的成熟，VD的信号转导能力在发育的中脑逐步显现。在培养的中脑神经元中，包含大部分处于发育中的DA能神经元，VD孵育后，胶质细胞源性神经营养因子（glial cell- derived neurotrophic factor，GDNF）表达增加，DA细胞数量增多，当GDNF的合成被阻断时，VD介导的DA生长受到影响[44]。此外，NAc内DA的释放还受到GDNF的调节，表明VD可能通过调节GDNF的表达，影响脑内DA投射通路的功能。VD还增加脑内DA的主要代谢酶儿茶酚-O-甲基转移酶（catechol-O-methyl transferase，COMT）对VDR的调节，并提高Nurr1和p57kip2的表达水平，协同调节DA能神经元分化和成熟[45-46]。

3.3　VD对DA能神经元的保护作用

VD对DA能神经元的神经保护包括抗炎作用、抗氧化作用和神经营养作用。在PD小鼠模型中，VD治疗降低小胶质细胞的活化，抑制促炎细胞因子白介素-6和肿瘤坏死因子α的释放，对黑质DA能神经元产生保护作用[14]。VD具有一定的抗氧化特性，可减轻氧化应激升高导致的DA变性。VD

通过清除活性氧类（ROS）来减轻PD模型大鼠的运动功能减退和DA神经毒性[47-48]，还可保护中脑DA免受谷氨酸毒性的影响，可提高谷胱甘肽水平，抑制诱导型一氧化氮合酶的表达[49-50]。VD还发挥神经营养作用，细胞实验观察到，VD可增加胞内GDNF表达，增强GDNF释放，提高脑内GDNF的表达和蛋白质水平[51]。GDNF参与DA通路的调节，在DA存活和药物滥用的调节中发挥作用[52-54]。VD参与神经营养因子NT-3的合成，进一步促进神经元存活、生长和分化[55-56]。

新近研究表明，每天补充VD，癌症死亡风险降低12%，患痴呆症的风险降低40%[57]。摄入较高剂量VD的糖尿病前期患者，患II型糖尿病的风险降低15%，恢复正常血糖调节的可能性增加30%[58]。VD可促进注意力缺陷多动障碍儿童血清DA的增加[59]，促进抑郁症患者血清素的增加[60]。此外，VDR表达可增加DA能神经元的分化，增加DA的产生[61]。VD还能抑制血清素再摄取转运蛋白和单胺氧化酶A基因的表达，表明VD和抗抑郁药可能具有共同的作用机制[62]。在大鼠PD模型中，脑部给予VD可部分增加Str和SNc中TH蛋白和GDNF蛋白的表达水平。在大鼠糖尿病模型中，小脑D2R表达增加，D1R表达减少，VD补充后使这些神经递质受体表达恢复到非糖尿病水平[63-64]。聚集早期形成的α突触核蛋白（α-synuclein，α-Syn）寡聚物具有细胞毒性，与脑神经退行性疾病有关，单细胞安培法测定结果表明，VD可恢复细胞中α-Syn寡聚物诱导胞外释放过程中神经递质的释放量，进一步验证了VD对DA能神经元的神经保护作用[65]。

4 VD缺乏对DA神经系统的影响

脑内VD稳态紊乱与抑郁、自闭症、精神分裂症等神经精神疾病有关[66-68]。流行病学调查结果显示，母亲孕期VD缺乏会直接影响后代的大脑发育，增加DA系统异常相关疾病的风险[69-71]。VD缺乏的后代大脑皮层变薄，导致与细胞骨架维持、突触可塑性、神经传递、细胞增殖和生长相关的基因表达减少，以及神经生长因子（NGF）水平降低[72]。发育性维生素D缺乏症（developmental vitamin D deficiency，DVD）会导致前脑DA能神经元代谢紊乱，影响DA在发育过程中的循环[73]。在DVD模型鼠的胎鼠大脑中，TH的基因表达和蛋白质含量显著降低。DVD不仅会降低DA能神经元的关键因子表达，还降低DA能神经元代谢酶表达，诱导中脑DA能神经元早期发育异常，引发DA相关行为障碍[74]。

在VD缺乏的小鼠模型中，VTA中DA能神经元水平降低，影响DA信号转导[35]。PD患者的VD水平不足，血清VD缺乏程度与疾病的严重程度有关，VDR基因的多态性也影响PD的发病风险，补充VD和晒太阳是预防PD的有效措施。VD缺乏小鼠对PD诱导毒素的神经毒性作用表现出更大的易感性，与VD水平充足的小鼠相比，表现出更严重的运动缺陷和DA损失，表明VD缺乏会加剧PD的神经退行性过程[75]。缺乏VD还会增加老年人认知障碍的风险，补充VD可降低老年PD患者的骨折风险，改善年轻PD患者的身体平衡控制，减少摔倒的发生[7]。此外，缺乏VD时DA还能诱导VDR介导的信号转导，表明VD和DA之间存在着复杂的相互作用关系。

5 小　结

VD在大脑的神经生理和病理过程中扮演重要角色，作为一种关键的化学小分子物质，通过其信号转导通路影响神经递质的活动和突触可塑性。VD在调节DA功能方面尤为显著，DA是一种重要的神经递质，对动机、奖赏感知等高级认知功能至关重要，VD通过不同机制影响DA系统并对其进行功能调节。在多种DA神经投射通路中，VD可能改变上游神经核团兴奋性水平，使得DA受体表达上调，导致通路兴奋性发生变化。还可能提高神经元突触可塑性，改善神经通路调控功能，对高级认知和情绪调节产生积极影响。DA能神经元易受氧化应激和炎症的伤害，VD的神经保护作用可维护DA能神经元的健康，有助于为DA能神经元创造有利的生存环境。VD还可调节DA的合成和释放，影响脑内多种DA神经投射通路的信号传递，提示脑内DA神经系统可作为VD直接或间接调控靶点，影响动机、奖赏等高级认知功能。

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Vitamin D Plays a Crucial Role in Regulating Dopamine Nervous System in Brain*

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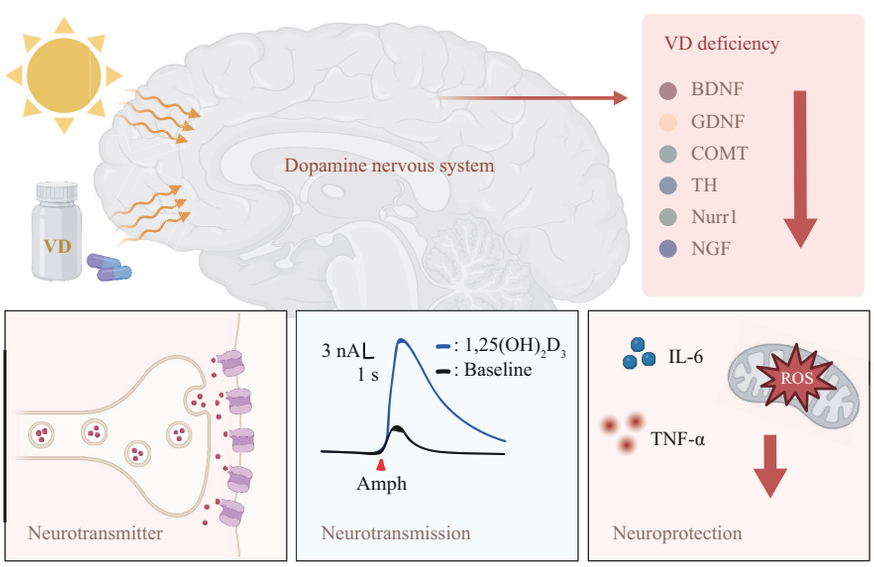
Graphical abstract



Abstract　Vitamin D is a unique fat-soluble vitamin that plays an indispensable role in human health. It exists in various forms, the most significant being vitamin D_2 (derived from plant sources) and vitamin D_3 (synthesized naturally in human skin upon exposure to sunlight). Vitamin D's primary function is to facilitate the absorption of calcium and phosphorus, which are crucial for maintaining healthy bones. Beyond its role in bone health, vitamin D significantly influences the immune system, muscle function, cardiovascular health, and the regulation of brain functions. A deficiency in vitamin D can lead to various chronic diseases such as rickets, osteoporosis, decreased immunity, increased risk of mental disorders, and cancers. The synthesis of vitamin D in the human body, both peripherally and centrally, relies on sunlight exposure, dietary sources, and various supplements. As a neuroactive steroid, vitamin D impacts both the physiological and pathological processes of the nervous system and plays a key role in brain health. It profoundly affects the brain by regulating neurotransmitter synthesis and maintaining intracellular calcium balance. As an essential chemical molecule, vitamin D participates in complex signal

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transduction pathways, impacting neurotransmitter functions and synaptic plasticity. Vitamin D's role in regulating dopamine (DA)—a neurotransmitter critical for motivation, reward perception, and other higher cognitive functions—is particularly noteworthy. Recent studies have revealed that vitamin D not only promotes the synthesis of DA but also plays a role in regulating DA levels within the brain. It exerts neuroprotective effects on DA neurons through anti-inflammatory, antioxidant actions, and neurotrophic support, thereby creating an optimal environment for DA neurons, influencing neuronal structure, and affecting the movement of calcium ions within nerve cells, positively impacting the overall health and functionality of the DA system. Furthermore, vitamin D can regulate the synthesis and release of DA, thus affecting the signal transmission of various DA neural projection pathways in the brain. This function is vital for understanding the complex interactions between neural mechanisms and their effects on key behaviors and cognitive functions. This review aims to delve deeply into the synthesis, metabolism, and pathways of vitamin D's action, especially its regulatory mechanisms on DA neurons. Through this exploration, this article seeks to provide a solid theoretical foundation and research framework for a deeper understanding of vitamin D's role in motivation and reward behaviors. This understanding is crucial for appreciating the broader significance of vitamin D in the fields of neuroscience and neurology. In summary, research and discoveries regarding vitamin D's impact on the nervous system highlight its importance in neural health and function. These insights not only enhance our understanding of the complex workings of the nervous system but also open new avenues for the prevention and treatment of neurological diseases. The exploration of vitamin D's multifaceted roles offers promising prospects for developing new therapeutic strategies, underscoring the compound's potential in addressing a range of neural dysfunctions and diseases. As research continues to evolve, the profound implications of vitamin D in the field of neurology and beyond become increasingly apparent, marking it as a key target for ongoing and future scientific inquiry.

Key words vitamin D, dopamine nervous system, regulatory function, neuroplasticity
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