

磷酸二酯酶4抑制剂在中枢神经系统疾病中的作用研究进展

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[摘要] 磷酸二酯酶(PDE)通过催化细胞内的环磷酸腺苷(cAMP)和环磷酸鸟苷(cGMP)的水解参与调节神经元可塑性、突触发生、突触传递、记忆形成和认知功能等细胞生理过程及功能发挥。大量基础和临床研究证明PDE4抑制剂主要通过抑制cAMP水解、提高cAMP含量,增强其下游效应,从而改善中枢神经系统疾病的发生和发展。PDE4抑制剂可提高长时程增强效应、海马神经元cAMP反应元件结合蛋白(CREB)的磷酸化和记忆相关Arc基因的表达,从而改善认知和记忆障碍以及阿尔茨海默病样症状;通过减轻 α -突触核蛋白诱导的细胞毒性,增加miR-124-3p对细胞活性的作用而抵抗帕金森病的发生发展;可激活cAMP/PKA/CREB通路,从而减弱神经炎症和氧化应激,增强神经可塑性,改善精神分裂症;通过抑制海马的晚期糖基化终末产物受体(RAGE)、Toll样受体4和NOD样受体热蛋白结构域相关蛋白3通路降低小胶质细胞激活和IL-1 β 产生,下调HMGB1/RAGE信号通路和抑制炎症因子,在抑郁症中发挥作用;通过减少小脑神经胶质细胞损伤,增加伤害性感受阈值,改善相互学习和记忆缺陷,从而在孤独症谱系障碍的治疗中发挥作用;通过调节cAMP含量影响脆性X智力低下蛋白表达,有望应用于脆性X染色体综合征治疗;促进少突胶质祖细胞分化并增强髓鞘形成而影响多发性硬化症治疗。PDE4与双向情感障碍也有关,可能作为治疗靶点之一。目前还有不少PDE4抑制剂处于中枢神经系统疾病的临床试验阶段。本文综述了PDE4抑制剂治疗中枢神经系统疾病的基础研究和临床试验进展,以期为中心神经系统疾病的预防和治疗提供新的思路,为中心神经系统药物的研发提供新策略。



[关键词] 磷酸二酯酶4抑制剂;中枢神经系统疾病;基础研究;临床试验;综述

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Research progress on phosphodiesterase 4 inhibitors in central nervous system diseases

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[**Abstract**] Phosphodiesterases (PDE) are involved in the regulation of cellular physiological processes and neurological functions, including neuronal plasticity, synaptogenesis, synaptic transmission, memory formation and cognitive functions by catalyzing the hydrolysis of intracellular cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP). Many basic and clinical studies have shown that PDE4 inhibitors block or ameliorate the occurrence and development of central nervous system (CNS) diseases by inhibiting cAMP hydrolysis, increasing cAMP content and enhancing its downstream effects. PDE4 inhibitors have long-term potentiation effect, which can enhance phosphorylation of cAMP response element binding protein (CREB) and upregulate expression of memory related Arc genes in hippocampal neurons, thereby improving cognitive impairment and Alzheimer's disease-like symptoms. They can also delay the occurrence and development of Parkinson's disease by reducing the cytotoxicity induced by α -syn and increasing the effect of miR-124-3p on cell functions. Alteration of PDE4 activity is the molecular basis for psychosis and some cognitive disorders, therefore it is considered as a therapeutic target for schizophrenia. PDE4 inhibitors play a role in depression by inhibiting the advanced glycation end product receptor (RAGE), TLR4 and NLRP3 pathways in the hippocampus, reducing the activation of microglia and the production of IL-1 β , down-regulating HMGB1/RAGE signaling pathway and inhibiting inflammatory factors. PDE4 inhibitor plays a role in the treatment of autism spectrum disorder by reducing the damage of cerebellar glial cells, increasing nociceptive threshold, and improving mutual learning and memory deficits. PDE4 inhibitors might be used in the treatment of fragile X syndrome by regulating the level of cAMP and affecting the expression of fragile X mental retardation protein (FMRP). PDE4 inhibitors can also promote the differentiation of oligodendrocyte progenitor cells and enhance myelination, which has potential in the treatment of multiple sclerosis. PDE4 is also related to bipolar disorder, which may be one of the therapeutic targets. At present, several PDE4 inhibitors are in clinical trials for the treatment of CNS diseases. This article reviews and discusses the progress on basic research and clinical trials of PDE4 inhibitors in CNS diseases, providing a reference for the prevention and treatment of CNS diseases and the development of new drugs.

[**Key words**] Phosphodiesterase 4 inhibitors; Central nervous system diseases; Basic research; Clinical trial; Review

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[缩略语] 磷酸二酯酶(phosphodiesterase, PDE); 环磷酸腺苷(cyclic adenosine monophosphate, cAMP); 环磷酸鸟苷(cyclic guanosine monophosphate, cGMP); 蛋白激酶 A(protein kinase A, PKA); cAMP 反应元件结合蛋白(cAMP response element binding protein, CREB); α -氨基-3-羟基-5-甲基-4-异唑丙酸(α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, AMPA); 脑源性神经营养因子(brain-derived neurotrophic factor, BDNF); 沉默信息调节因子(silent information regulator, SIRT); 蛋白激酶 B(protein kinase B, Akt); B 淋巴瘤(B cell lymphoma, Bcl); Bcl-2 相关 X 蛋白(Bcl-2-associated X protein, Bax); β -淀粉样蛋白(amyloid β -protein, A β); 肿瘤坏死因子(tumor necrosis factor, TNF); 突触核蛋白(synuclein, syn); cAMP 激活的交换蛋白(exchange protein activated by cAMP, EPAC); 1-甲基-4-苯基-吡啶离子(1-methyl-4-phenylpyridinium ion, MPP⁺); 丝裂原激活蛋白激酶(mitogen activation protein kinase, MAPK); 核富集转录本(nuclear enriched abundant transcript, NEAT); 微 RNA(microRNA, miR); 单核苷酸多态性(single nucleotide polymorphism, SNP); 晚期糖基化终末产物受体(advanced glycation end product receptor, RAGE); NOD 样受体热蛋白结构域相关蛋白(NOD-like receptor thermal protein domain associated protein, NLRP); 脆性 X 染色体综合征(fragile X syndrome, FXS); 脆性 X 智力低下蛋白(fragile X mental retardation protein, FMRP); 少突胶质祖细胞(oligodendrocyte precursor cell, OPC); 信使 RNA(messenger RNA, mRNA); 咯利普兰低亲和力结合位点(low affinity rolipram binding state, LARBS); 咯利普兰高亲和力结合位点(high affinity rolipram binding state, HARBS)

PDE 是专属水解 cAMP 和 cGMP 的超级酶家族,通过催化细胞内 cAMP 和 cGMP 的水解,参与调节细胞生理过程和神经功能,包括神经元可塑性、突触发生、突触传递、记忆形成和认知功能等^[1]。目前已知的 PDE 超级酶家族包括至少 21 个基因和 100 多个独立亚型,基于基因序列相似性、调节模式、cAMP 或 cGMP 底物的亲和性分为 11 个亚家族,其中 PDE4、PDE7、PDE8 水解 cAMP, PDE5、PDE6、PDE9 水解 cGMP, PDE1、PDE2、PDE3、PDE10、PDE11 水解 cAMP 和 cGMP^[2]。已有不少研究结果证明 PDE 抑制剂可治疗中枢神经系统疾病,如 PDE1 抑制剂可改善阿尔茨海默病的临床症状^[3]; PDE2 抑制剂^[4]、PDE3 抑制剂^[5]和 PDE5 抑制剂^[6]均具有增强记忆的效果; PDE9 抑制剂可改善认知功能^[7],但对精神分裂症无明显效果^[8]; PDE10 抑制剂对皮质纹状体疾病和精神分裂症均有一定的治疗作用^[9]。

PDE4 是 11 个 PDE 家族中最大的亚家族,由四个基因(*Pde4a*、*Pde4b*、*Pde4c* 和 *Pde4d*)编码,且剪接变异体多,分布于胞浆和亚细胞器中^[10]。

PDE4 在脑内各区域均存在,分布有所不同,如在顶叶和颞叶部位, PDE4A 的表达量较高;在海马、黑质、丘脑等部位, PDE4B 的表达量最高,而 PDE4C 和 PDE4D 的表达量低^[11]。PDE4 亚型可能参与了中枢神经功能紊乱的病理生理过程,因此在脑内各区的表达量有所变化。目前,已有大量证据支持 PDE4 抑制剂可改善认知功能,在阿尔茨海默病、亨廷顿病、睡眠障碍和多发性硬化症的治疗上也具有较好的应用前景^[12]。本文综述了 PDE4 抑制剂在中枢神经系统疾病中的基础研究和临床试验进展,讨论 PDE4 抑制剂潜在的应用方向和不足,旨在为中枢神经系统疾病药物的研发提供新策略和视角。

1 磷酸二酯酶 4 抑制剂改善认知和记忆障碍

认知和记忆障碍的主要表现是注意力不集中、学习困难、记忆力下降、思维能力减弱等。海马体和前额皮层负责形成、储存长期记忆和认知功能。cAMP 在记忆的形成中起重要作用。cAMP 激活 PKA,进而磷酸化 CREB^[13],磷酸化的

CREB负责神经元可塑基因的转录、AMPA受体和BDNF的编码^[14];激活的PKA还可促进AMPA受体嵌入突触前膜^[15]。此外,cAMP在神经元刺激和长时程增强的维持中起关键作用,而抑制海马神经元的PDE4可以加强长时程增强^[13]。动物研究发现,第一代PDE4抑制剂咯利普兰可有效改善认知功能^[16]。研究显示,PDE4B对认知、记忆形成具有重要作用^[17]。近年来,PDE4D在认知和记忆方面的作用也受到关注。体内研究发现,PDE4D选择性变构抑制剂BPN14770可在PDE4D基因人源化的小鼠中逆转东莨菪碱诱导的记忆和认知缺陷,抑制PDE4D可以改变PKA、SIRT1、Akt、Bcl-2/Bax表达,从而调节内分泌反应、应激抵抗、神经元自噬和凋亡,发挥改善神经功能的作用^[18]。

临床研究显示,PDE4抑制剂罗氟司特能改善老年人(60~80岁)和精神分裂症患者的记忆形成,且无明显的副作用^[19-20]。目前,罗氟司特已进入Ⅱ期临床试验(NCT04658654)。综上,PDE4抑制剂在认知功能障碍和记忆障碍的治疗中可能具有潜在的临床应用价值。

2 磷酸二酯酶4抑制剂有效治疗阿尔茨海默病

阿尔茨海默病是一种慢性进行性神经系统疾病,主要表现为记忆力减退、思维能力下降、行为和情绪变化等症状。其病因尚未完全明确,但主要病理改变为A β 和微管相关蛋白 τ 蛋白的异常沉积。研究表明,阿尔茨海默病患者颞叶PDE4D1、PDE4D3、PDE4D5和PDE4D8表达量增加^[21],可能与阿尔茨海默病的发生发展密切相关。PDE4抑制剂已经成为治疗阿尔茨海默病的热门药物之一^[22]。PDE4的作用靶点cAMP是PKA等多种信号通路的中心;PDE4也是cAMP、PKA、CREB的主要正调节因子,其中CREB是一种核转录因子,调节与神经元生存和功能相关基因表达,并在一些物种的记忆形成及保持中发挥重要作用^[13]。

细胞水平研究提示,抑制PDE4B可使溶解性A β 刺激小胶质细胞释放的TNF- α 降低70%左右,从而减轻炎症反应和细胞损伤^[23]。动物实验研究显示,罗氟司特也可能通过PDE4B/PDE4D介导的cAMP/CREB和BDNF信号转导改善阿尔茨海默病小鼠的学习和记忆,并减轻其抑郁样行为^[24]。在PDE4D基因敲除的A β ₄₂诱导记忆缺陷

和认知障碍小鼠模型中发现pSer133-CREB和BDNF上调,记忆缺陷恢复^[25],提示PDE4D可能在阿尔茨海默病的发生发展中起关键作用。临床研究显示,PDE4抑制剂咯利普兰以剂量依赖性方式逆转A β 引起的记忆缺陷,增强了CREB磷酸化和记忆相关的Arc基因的表达,从而显著减缓记忆缺失等阿尔茨海默病样症状^[26]。目前,PDE4D变构抑制剂BPN14770正在进行阿尔茨海默病治疗的Ⅱ期临床试验(NCT03817684)。因此,抑制PDE4可能为阿尔茨海默病相关的记忆缺失提供一种有效的治疗方法。

3 磷酸二酯酶4抑制剂可能有效治疗帕金森病

帕金森病是一种慢性进行性神经系统疾病,由多巴胺神经元的丧失、谷氨酸神经元兴奋性增加等多种因素共同作用所致,主要特征是运动障碍,包括肌肉僵硬、震颤、运动迟缓和姿势平衡障碍。典型病理特征为黑质Lewy小体,是由 α -syn聚集而成。PDE4B在黑质表达最高^[11],可能与帕金森病的发生有关。

氧化应激引起的多巴胺能神经元的凋亡是帕金森病发生发展的主要原因之一。FCPR16是一种PDE4抑制剂,通过cAMP/PKA/CREB和EPAC/Akt信号通路,限制活性氧的产生和线粒体膜电位的改变,防止氧化应激,从而抑制人神经母细胞瘤细胞SH-SY5Y中的多巴胺能变性和凋亡^[27]。此外,FCPR16增加微管相关蛋白轻链3Ⅱ的水平,以及激活一磷酸腺苷依赖的蛋白激酶自噬来保护SH-SY5Y细胞免受MPP⁺诱导的氧化损伤^[28]。另外,在 α -syn干预PDE4B过表达的SH-SY5Y细胞中,线粒体膜电位降低,细胞凋亡增加。PDE4抑制剂罗氟普兰可逆转p38 MAPK磷酸化,减少p38 MAPK和E3泛素连接酶的结合,减轻 α -syn诱导的SH-SY5Y细胞毒性^[29]。提示PDE4抑制剂可能是治疗 α -syn诱导的神经退行性病变的有效途径之一。体外研究发现,MPP⁺诱导的帕金森病细胞模型中NEAT1和PDE4B的表达量升高,miR-124-3p的表达下降;敲除NEAT1或过表达miR-124-3p可增加细胞活性,减轻细胞损伤;miR-124-3p是NEAT1的直接靶点,PDE4B是miR-124-3p的下游靶点,过表达PDE4B可以减弱miR-124-3p过表达对细胞的影响,说明MPP⁺诱导的帕金森病细胞模型中NEAT1能通过

miR-124-3p 调控 PDE4B 表达, 从而造成细胞损伤和炎症反应^[30]。

4 磷酸二酯酶 4 抑制剂有效治疗精神分裂症

精神分裂症是一种严重的精神疾病, 通常表现为现实感知和思维模式的严重紊乱。精神分裂症的发病机制尚未清楚, 涉及遗传、神经递质、环境和社会压力等多种因素, 与多个脑区(前额叶、颞叶、顶叶、杏仁核等)的发育和多种神经递质(多巴胺、谷氨酸、 γ 氨基丁酸等)的功能异常有关^[31]。研究显示, 精神分裂症患者小脑外侧组织 PDE4B2、PDE4B4 的表达量下降^[32]。PDE4 活性改变可能是影响精神错乱和认知紊乱的分子基础^[33]。抑制 PDE4 可激活 cAMP/PKA/CREB 通路, 从而减弱神经炎症和氧化应激, 增强神经可塑性, 改善精神分裂症^[9]。研究显示, 罗氟司特不仅可以改善精神分裂症患者的认知功能和语言记忆, 且可作为辅助药物显著改善稳定性精神分裂症患者的认知紊乱^[19]。另一项临床报道, 罗氟司特可改善精神分裂症患者的脑电图认知信号^[33]。

PDE4B 的多态性与精神分裂症的易感性相关^[34]。PDE4B 的多个 SNP 和一个双 SNP 单倍型与精神分裂症发病率的增加有关; 相关 SNP 出现在一个关键剪接连接附近的内含子序列中, 这导致不同调节功能的 PDE4B 亚型高表达^[32]。这些证据提示 PDE4B 在精神分裂症预防和治疗中可能具有潜在的临床价值。

5 磷酸二酯酶 4 抑制剂有效治疗抑郁症

抑郁症是一种常见的心理疾病, 其主要特征是持续的、严重的抑郁情绪和对日常活动的兴趣丧失。研究显示, 重度抑郁症患者脑部背外侧前额叶皮层 PDE4A 表达量升高^[35], 前扣带皮层 PDE4B、PDE4D 表达下调^[36]。长期使用氟西汀、舍曲林、地昔帕明、反苯环丙胺等抗抑郁药可导致抑郁症大鼠模型额叶皮层 PDE4A 和 PDE4B 表达增加, 同时伏隔核 PDE4B 表达增加, 这些可能是对治疗的补偿性反应^[37]。

已有大量临床前研究证明, 第一代 PDE4 抑制剂咯利普兰能有效治疗抑郁症^[9, 16]。PDE4 抑制剂通过抑制海马中 RAGE、Toll 样受体 4 和 NLRP3 通路减少小胶质细胞激活和 IL-1 β 产生, 下调高迁移

率蛋白 B1/RAGE 信号通路和抑制炎症因子, 参与抗抑郁过程^[38]。PDE4 抑制剂还能逆转大脑皮层和海马中 p38 MAPK 和 C-Jun 氨基端激酶的磷酸化, 在激活 cAMP/CREB/BDNF 通路的同时减少海马中 IL-1 β 的产生, 也可以减少慢性不可预知性温和应激诱导的炎症小体信号通路中的 NLRP3、凋亡相关斑点样蛋白和胱天蛋白酶-1 的水平^[38-39]。目前, PDE4D 变构抑制剂 BPN14770 已完成抑郁症治疗的 II 期临床试验(NCT03861000)。我国自主研发的高选择性 PDE4D 变构调节剂 LS21031 也于 2023 年 3 月在国内获批应用于抑郁症治疗。因此, PDE4 抑制剂非常有希望成为治疗抑郁症的药物之一。

6 磷酸二酯酶 3/4 抑制剂有效治疗孤独症谱系障碍

孤独症谱系障碍是一种具有相当大临床异质性的神经发育障碍, 具有多种病因和表型特征, 通常在儿童期即有症状, 主要包括社交困难、语言和沟通障碍、重复性行为等^[40]。与健康对照组比较, 孤独症谱系障碍患者小脑中 PDE4A5、PDE4B1、PDE4B2、PDE4B3、PDE4B4 明显减少, 而额叶皮层中 PDE4AX、PDE4A1 和 PDE4B2 增加^[41], 提示小脑和大脑中 PDE4 表达的失调可能参与了孤独症谱系障碍的病理过程。目前, 临床上使用氟西汀可减少患儿的重复行为^[42], 地西帕明可减轻患儿的多动症^[43]。研究提示长期使用地西帕明、氟西汀治疗可导致大鼠额叶皮层 PDE4A 和 PDE4B 表达增加^[37]。在丙戊酸诱导的孤独症谱系障碍大鼠模型的研究中发现, PDE3/4 抑制剂异丁司特干预可显著缓解丙戊酸暴露诱导的交互学习/记忆缺陷、焦虑、多动症, 增加伤害性感受阈值, 降低促炎标志物(IL-1 β 、TNF- α 、IL-6)及小脑神经胶质细胞原纤维酸性蛋白阳性神经元损伤, 提示异丁司特通过神经保护作用可改善孤独症谱系障碍相关的行为异常^[44]。目前, 异丁司特已完成孤独症谱系障碍的 I 期临床试验(NCT01031186)。综上, PDE4 抑制剂有望成为治疗孤独症谱系障碍的药物之一。

7 磷酸二酯酶 4D 变构抑制剂有效治疗脆性 X 染色体综合征

FXS 是一种常见的遗传性神经发育障碍, 由

脆性X染色体上 *Fmr1* 基因突变引起,主要表现为智力发育迟缓、语言发育延迟、社交困难、注意力不集中、焦虑、孤独症、特殊的面部特征等。由 *Fmr1* 编码的FMRP是一种RNA结合蛋白,在神经元和胶质细胞中均高表达,参与RNA代谢的不同过程,调节RNA出核转运和蛋白质翻译^[45]。血液细胞和血小板中cAMP降低是FXS的分子特征之一^[46]。FMRP水平与cAMP水平呈正相关^[47]。研究显示,在果蝇和哺乳动物中,cAMP通过激活PKA调节转录因子CREB,从而正向调控 *Fmr1* 基因的转录^[48-49],可见PDE4抑制剂通过调节cAMP含量而影响FMRP表达。随着PDE4变构抑制剂的深入研究,变构抑制剂成为治疗FXS和其他脑部疾病的新方法^[50]。PDE4D变构抑制剂BNP14770在治疗 *Fmr1* 基因敲除小鼠两周后可改善小鼠社会互动和筑巢、躲避等自然行为,同时恢复 *Fmr1* 基因缺乏神经细胞引起的树突棘形态改变^[51]。BNP14770治疗FXS的Ⅱ期临床试验已完成(NCT03569631),结果显示FXS患者口服BNP14770(一次25 mg,一日两次)可改善其认知、语言和日常行为,药物安全性和耐受性与安慰剂相似^[52]。上述研究提示PDE4D抑制剂在FXS的治疗中具有很好的应用前景。

8 磷酸二酯酶4抑制剂改善多发性硬化症的疾病进程

多发性硬化症是以慢性神经炎症和脱髓鞘为特征的自身免疫性疾病,主要是少突胶质细胞、轴突和神经元受损,其临床表现主要为视力障碍、肢体无力、感觉异常、平衡失调、疲劳、认知障碍等,且在不同患者中的症状和病程各不相同。cAMP参与调控促炎性细胞因子的产生,cAMP类似物可减少炎症和细胞凋亡^[53],还可通过聚集内源性神经干细胞促进其分化并修复多发性硬化症中的髓磷脂^[54]。PDE4D1/2和PDE4D6是诱导OPC分化的关键目标^[55]。抑制PDE4D可促进OPC分化并增强小鼠OPC、诱导人多能干细胞衍生OPC的髓鞘形成。此外,抑制PDE4D可促进双环己酮草酰二胺诱导的脱髓鞘小鼠模型中的体内髓鞘再生,同时改善空间记忆并缩短视觉诱发电位潜伏期^[53]。体外实验证明咯利普兰能增加MAPK磷酸酶-1的表达和活性,选择性抑制自身抗原和有丝分裂原诱导的促炎性细胞因子基

因表达,减少TNF- α 产生,从而发挥抗炎作用^[55]。体外实验研究还显示咯利普兰减少了器官特异性自身抗原髓鞘碱性蛋白诱导的多发性硬化症患者外周血单个核细胞中 γ 干扰素和TNF- α 的mRNA表达,而不影响IL-4、IL-10以及转化生长因子- β 的mRNA表达^[56]。一项临床试验结果显示,PDE4抑制剂咯利普兰不能抑制多发性硬化症患者血脑屏障的破坏,反而增加脑内炎症活性^[57]。而PDE3/4抑制剂异丁司特对进行性多发性硬化症患者具有神经保护作用^[58]。上述研究结果表明,PDE4亚型或双重抑制剂具有靶向多发性硬化症不同过程的潜力。

9 磷酸二酯酶4抑制剂可能加重双相情感障碍

双相情感障碍又称躁郁症,是一种严重的心理疾病。双相情感障碍患者在病程中会交替出现躁狂发作和抑郁发作,与遗传、神经递质、大脑结构及其功能异常、神经炎症、免疫系统异常和环境等因素相关^[59]。许多研究都试图寻找人体中双相情感障碍有关的遗传标志物^[9]。在双相情感障碍患者病理检查中发现,大脑前扣带回靶向 *PDE4B* mRNA的miR-34a表达增加^[60]。另一项研究发现PDE4A在双相情感障碍患者中低表达^[61]。也有研究提示双相情感障碍患者小脑外侧组织PDE4B3表达减少^[32]。

与其他精神疾病不同,双相情感障碍与PDE酶尤其是PDE4的减少有关。可以推测PDE4抑制剂会加重双向情感障碍的症状,尤其体现在躁狂阶段。另外,双相情感障碍每个阶段PDE4的表达是否有差异也值得进行深入研究^[62]。

10 结 语

除上述中枢神经系统疾病之外,PDE4抑制剂对亨廷顿病也有治疗效果。PDE4抑制剂通过调节cAMP和BDNF促进神经元发生和功能恢复,减少细胞毒性,抑制免疫炎症因子,从而发挥治疗亨廷顿病的作用^[63]。

虽然PDE4抑制剂在临床前研究中表现出良好的神经保护作用,但是大部分PDE4抑制剂由于呕吐等不良反应在临床试验早期就被淘汰。早先认为PDE4抑制剂两个不同的结合点LARBS和HARBS与其不良反应有关,尤其是HARBS结合点^[64],因此关于PDE4抑制剂的研究侧重于

LARBS。随着对PDE4亚型的深入研究,发现PDE4亚型PDE4D是引起呕吐的主要原因,目前认为PDE4D4和PDE4D5与呕吐有关^[65]。近年来研发的PDE4D变构抑制剂BPN14770对胃肠道无明显影响,具有良好的耐受性^[56]。另外,多效PDE抑制剂也是解决药物不良反应的有效方法。异丁司特是PDE3/4抑制剂,也能抑制PDE10和PDE11,可减弱中枢神经系统少突胶质细胞的活性以及促炎性细胞因子的形成,在肌萎缩性脊髓侧索硬化症的Ⅱ期临床试验中表现出稳定、安全的治疗效果^[66]。这些研究为PDE4抑制剂的研发提供了新的方向。

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