· 综述 ·

HDAC3在认知功能障碍中的研究进展

蔡凌宇 刘媛媛 任江滨 苏鸿 孙晓阳
223001 南京医科大学附属淮安第一医院神经外科(蔡凌宇、任江滨、孙晓阳、苏鸿),
内分泌科(刘媛媛)
通信作者:孙晓阳,Email:sunxiaoyangHA@163.com
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【摘要】 组蛋白去乙酰化酶3(HDAC3)是与认知功能障碍相关的表观遗传负性调节因子,在杏仁核、海马和皮层等部位广泛表达。激活后的HDAC3具有神经毒性作用,负性调控认知和记忆的形成。本文对HDAC3在认知功能障碍中的作用机制进行综述,并探讨HDAC3抑制剂治疗的发展前景。

【关键词】 认知功能障碍; 组蛋白乙酰化酶3; 神经毒性; 靶向抑制; 综述
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Research progress of HDAC3 in cognitive impairment *Cai Lingyu, Liu Yuanyuan, Ren Jiangbin, Su Hong, Sun Xiaoyang*
Neurosurgery, the Affiliated Huaian First People's Hospital of Nanjing Medical University, Huaian 223001, China(Cai LY, Ren JB, Sun XY, Su H); Department of Endocrinology, the Affiliated Huaian First People's Hospital of Nanjing Medical University, Huaian 223001, China(Liu YY)
Corresponding author: Sun Xiaoyang, Email: sunxiaoyangHA@163.com

【Abstract】 Histone deacetylase 3 (HDAC3) is an epigenetic negative regulatory factor associated with cognitive impairment, widely expressed in the amygdala, hippocampus, and cortex. The activated HDAC3 has neurotoxic effects and negatively regulates the formation of cognition and memory. This paper reviews the mechanism of HDAC3 in cognitive impairment and explores the development prospects of HDAC3 inhibitor therapy.

【Key words】 Cognitive dysfunction; Histone deacetylase 3; Neurotoxicity; Targeted inhibition; Review
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认知功能障碍是指学习、记忆、感知以及思维判断等大脑高级信息加工过程出现异常,从而引起学习障碍、记忆障碍、执行障碍。2019年,全球因认知功能障碍相关疾病而死亡的人数约为162.3万例,我国死亡人数约占全球总死亡人数的19.8%[1]。我国老年认知功能障碍患病率较高,约为20%[2],并且患病率随着老龄化进程加快而逐渐上升[3]。探索认知功能障碍的影响机制、预防措施具有重要意义。

现有研究表明,神经炎症、代谢紊乱、基因突变、线粒体损伤和氧化应激等多种机制影响认知功能障碍的发生、发展[4-7],其中表观遗传机制如组蛋白乙酰化与认知形成过程有关[8-9]。组蛋白去乙酰化酶(histone deacetylase, HDAC)是促使组蛋白以及大量其他细胞核、细胞质和线粒体蛋白去乙酰化的一组酶,其家族成员众多,其中HDAC3与认知功能障碍关系密切,是已知与认知功能障碍相关的表观遗传负性调节因子[10]。本文回顾了HDAC3在认知功能障碍中的相关文献,对其作用机制进行综述,并探讨HDAC3抑制剂治疗认知功能障碍疾病的发展前景,以期为未来疾病的研究和防治提供参考。

一、HDAC3的分布

表观遗传机制如DNA甲基化和组蛋白修饰参与了基因表达变化[11],HDAC家族则是组蛋白修饰过程中的关键酶。迄今为止,HDAC家族成员在哺乳动物中共有4类、18种亚型[12-13]:Ⅰ类家族成员包括HDAC1、2、3和8,HDAC1、2和8主要分布在所有组织的细胞核内,HDAC3存在于细胞质;Ⅱ类包括HDAC4~7、9、10,在细胞核和细胞质内穿梭;Ⅲ类为SIRT1~7,存在于线粒体、细胞核和细胞质中;Ⅳ类为HDAC11,存在于细胞质和细胞核中。不同亚型

的HDAC在认知形成相关的不同脑结构区表达[14-15]，Ⅰ类和Ⅳ类HDAC家族成员广泛分布于与认知功能密切相关的大脑区域，如杏仁核、海马、皮层等部位，其中Ⅰ类家族成员中的HDAC3表达更为丰富[16]。

二、HDAC3负性调控认知功能

HDAC3是与认知功能障碍相关的负性调节因子[10]，调控机制可能与其神经毒性、基因表达水平有关。

(一)HDAC3的神经毒性作用

神经毒性作用能促使神经元凋亡，导致认知功能障碍的发生。研究认为HDAC3通过细胞蛋白协同作用、改变磷酸化水平、自身酶促功能等多种方式产生神经毒性作用，释放炎性因子，导致认知功能障碍。

1. HDAC3与HDAC1的协同作用：两者的协同作用可加重神经元的毒性损伤，促进神经元凋亡[17]。即刻早期基因(immediate early genes，IEGs)受神经元活动的调节，常与HDAC3相互作用，并抑制其神经毒性作用[18]。当IEGs表达减少时，HDAC3与HDAC1的相互作用显著增强。一些研究认为HDAC1会影响轴突运输和降低线粒体活性，产生神经毒性作用；HDAC3可与HDAC1形成神经毒性复合物，诱导皮质和颗粒神经元的细胞死亡[19-20]。在R6/2转基因小鼠中，皮质和纹状体中的HDAC1、3相互作用加速神经元丢失，导致运动功能缺陷[21-22]。Bardai等[22]通过免疫共沉淀表明HDAC3和HDAC1的伴侣蛋白——亨廷顿蛋白之间存在相互作用。当亨廷顿蛋白与HDAC3分离时，HDAC3神经毒性的抑制作用则被解除。目前的研究大多探讨了HDAC3与HDAC1间的联系，与其他细胞蛋白之间的作用机制较少，有待进一步研究。

2. HDAC3的磷酸化：Bardai和D'Mello[23]发现，葡萄糖稳态的负性调节因子糖原合酶激酶3β可介导HDAC3磷酸化，从而发挥神经毒性作用。在多种神经退行性疾病中，糖原合酶激酶3β活性增强，但是如何导致神经元凋亡，机制尚不明确[24-27]。此外，富含亮氨酸的重复激酶2通过直接磷酸化刺激HDAC3产生神经毒性作用，这是遗传性帕金森病的主要病因[28-29]。

3. HDAC3的酶促功能：HDAC3的激活离不开视黄酸和甲状腺激素受体的沉默介质SMRT和核受体共阻遏物N-CoR[30]，两者在大脑的发育中发挥着关键作用[31-33]。目前证实HDAC3可以通过SMRT和N-CoR与HDAC 4、5和7形成共沉淀复合物，发挥酶促功能[34-35]。也有研究报道，在发育过程中，神经系统之外的HDAC3独立于其酶活性[36]。鉴于此，仍需更多的研究证实HDAC3的神经毒性作用是否依赖于其酶活性。

4. HDAC3参与神经炎性反应：HDAC3通过调节炎性反应，释放炎性因子，从而负性调控认知功能。Durham等[37]发现，选择性抑制HDAC可减少TNF-α和IL-6的表达。此外，Chen等[38]证明HDAC抑制剂VPA可导致小胶质细胞从M1到M2的表型转变，抑制HDAC3活性和炎性因子TNF-α、IL-1、IL-6及干扰素的释放。肠道微生物群改善认知功能障碍的相关研究较多，Wang等[39]研究发现肠道菌群分泌的丁酸盐可干扰HDAC3与核因子和受体之间信号通路，从而减少海马区的炎性反应和神经元凋亡，改善认知功能障碍。Zhang等[40]通过黄芪素介导小鼠小胶质细胞HDAC3与其上游蛋白间的信号传递，影响IL水平，再次论证了认知行为与炎性细胞因子和炎性相关菌群相关。因此，未来对于脑–肠轴的信号分子、抗炎因子的探索及应用可能成为改善认知功能障碍的方向之一。

(二)HDAC3参与调节记忆基因表达

神经元基因表达变化是认知功能障碍的基础。HDAC3是表观遗传修饰的关键酶，参与了染色质的重塑和记忆基因的表达。研究表明，基因Nr4a2和IEGs促进突触的可塑性、参与记忆的形成，抑制IEGs和Nr4a2的转录水平即可影响记忆能力；HDAC3与IEGs和Nr4a2的启动子密切相关，HDAC3缺失会增加IEGs、Nr4a2的表达，从而改善认知[41-44]。在此基础上，Suelves等[45]发现在亨廷顿小鼠模型中，通过注射抑制剂RGFP966可有效抑制海马和纹状体中的HDAC3活性，使海马记忆依赖基因的表达正常化，预防海马长期记忆缺陷。Amin等[46]发现，上调海马中的Nr2B基因和cAMP反应元件结合的磷酸化水平可选择性抑制HDAC3表达，从而改善长期记忆功能。此外，Guan等[47]在2022年就证实组蛋白3、4的乙酰化可诱发神经元长时程增强(long-term potentiation，LTP)，即LTP是两个神经元之间的突触连接持续性增强的一种现象，为认知的功能基础。miR-132通过降低HDAC3活性促进LTP并改善海马记忆和突触功能障碍[48]，但是亦有研究结果与上述结果不一致。Zhou等[49]通过对核受体辅助阻遏物1、2缺失的小鼠实验后发现下丘脑外侧神经元中HDAC3水平下降会导致学习和记忆障碍，并通过

小分子调节剂或化学遗传学操作对成年实验小鼠进行治疗，成功逆转了认知和记忆缺陷。Norwood等[50]发现，HDAC3条件基因敲除后，前脑兴奋性神经元中HDAC3的缺失会导致小鼠多项神经行为测试中的认知缺陷。上述研究表明，HDAC3对参与记忆基因表达的参与过程是多元化的，其兴奋-抑制失衡是可能导致认知功能障碍的重要因素之一。

三、HDAC3抑制剂改善认知功能障碍的研究进展

近年来，人们发现越来越多的HDAC抑制剂如异羟肟酸盐、苯甲酰胺和酰肼及天然化合物褪黑激素等均可延缓多种疾病相关认知功能障碍的进展[51-54]，丙戊酸、丁酸盐、苯基丁酸盐和氢氧化物酸已被证明对Ⅰ类HDAC家族成员有较强的抑制作用，但是其抑制选择性不理想。

选择性HDAC3抑制剂主要根据其化学修饰而设计，其中RGFP966通常被用作HDAC3学术研究的分子工具[55-56]。RGFP966通过影响长期记忆和突触可塑性相关基因如 Arc、Egr1 和IEGs的表达、抑制小鼠纹状体CAG的重复扩增、降低突变亨廷顿蛋白的寡聚化等，延缓亨廷顿模型小鼠的识别和空间长期记忆障碍[55, 57-58]。Krishna等[59]证明，RGFP966可恢复淀粉样蛋白-β 寡聚物诱导的海马CA1锥体神经元的可塑性缺陷。

相较于RGFP966，抑制剂RGFP963和RGFP968在刺激突触发生、增加海马棘密度等方面的能力则更为突出[57]。在小鼠背侧海马内递送HDAC3选择性抑制剂RGFP136，可以观察到组蛋白4赖氨酸8水平升高，从而显著地促进小鼠长期记忆的形成，表明该抑制剂是一种有前途的治疗认知功能障碍的药物[10]。此外，抑制剂BRD3308通过激活细胞焦亡因子GSDMD相关信号通路，可显著减少神经元丢失，改善脑室出血后海马区的神经行为表现[60]。

目前，选择性HDAC3抑制剂大多局限于直观设计或酶与配体的相互作用，部分学者基于分子建模技术增强了HDAC3抑制剂的抑制效力和选择性[61]。但是新型选择性HDAC3抑制剂与认知功能之间的研究仍有限，未来可能需要分子生物学研究进行进一步探索。

综上所述，HDAC3作为经典的HDAC家族成员，通过多种方式产生神经毒性作用，参与记忆基因的形成，调控认知功能，但是其缺乏明确的上下游机制，甚至部分学者的研究结果也不尽相同。目前，HDAC3抑制剂对认知功能障碍的改善作用已明确，但是HDAC3存在选择性差的问题，可能会对其他家族成员产生抑制，从而干扰实验结果。未来可能需要进一步提高抑制剂的选择性，排除其他细胞蛋白干扰，明确上下游机制。随着研究的深入，关于HDAC3的认识将对认知功能障碍发生、发展的研究提供新思路，也为预防、干预和治疗认知功能障碍提供新的策略和方案。

利益冲突 文章所有作者共同认可文章无相关利益冲突

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