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综 述

# 组蛋白去乙酰化酶6抑制剂治疗缺血性脑卒中的研究进展

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**摘 要**：组蛋白乙酰化酶(histone acetyltransferases, HATs)和组蛋白去乙酰化酶(histone deacetylases, HDACs)主导的蛋白质乙酰化修饰在神经系统的发育、成熟中具有重要地位。HDAC6属于II类HDACs，能够调节神经细胞的存活、分化和成熟，参与脑认知和情绪调控，在神经系统发育中具有重要作用，并且参与脑缺血损伤的多个病理环节。本文总结了近年来国内外最新研究成果，阐述了HDAC6抑制剂通过降低细胞兴奋性毒性、减轻氧化应激损伤、抑制炎症介质释放、抑制神经细胞凋亡以及促进神经再生和血管新生等多种方式对缺血性脑卒中发挥有效的神经保护作用。

**关键词**：组蛋白去乙酰化酶6；抑制剂；缺血性脑卒中
**中图分类号**：R34；R362；R743.3

# Research progress of histone deacetylase 6 inhibitors in the therapy of ischemic stroke

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**Abstract:** The protein acetylation by histone acetyltransferases (HATs) and histone deacetylases (HDACs) plays a significant role in the development and maturation of the nervous system. HDAC6, belonging to class II HDACs, by regulating the survival, differentiation and maturation of neural cells, plays an important role in the development of the nervous system and participates in multiple pathological processes of cerebral ischemic injury. In addition, HDAC6 participates in the regulation of cognition and emotion of the brain. This article summarized the latest research results in recent years and expounded that HDAC6 inhibitors could produce a positive and effective neuroprotective effect on ischemic stroke by reducing the neuronal damage induced by excitotoxicity and oxidative stress, depressing the release of inflammatory mediators, inhibiting the apoptosis of neurons and promoting the growth of nerve and blood vessel.

**Key words:** histone deacetylase 6; inhibitor; ischemic stroke

脑卒中是脑组织血液循环障碍导致局部神经功能缺失的急性神经系统疾病，缺血性脑卒中是指由于脑供血动脉的狭窄、闭塞或血栓形成引起的脑供血不足导致的脑组织坏死的总称。缺血性脑卒中是临床最常见的类型，约占脑卒中总发病的60%~80%[1]。在我国，随着人口老龄化发展，脑血管病的发病率逐年上升，缺血性脑卒中因其高发病率、高致残率及高致死率给患者家庭和社会造成了沉重的负担。

缺血性脑卒中发病机制至今尚未被完全阐明，但糖尿病、高血压、肥胖、吸烟和酗酒等已被公认为是脑卒中发病的主要独立危险因素[2–6]。短时间内不完全或轻度缺血将导致可逆性的脑部功能障碍，长时间完全或严重缺血则会引起大面积脑梗死甚至坏死。目前临床上普遍在缺血早期使用溶栓剂

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活血化瘀，抗血小板聚集，使用脱水剂降低颅内压进行对症支持治疗，以帮助恢复组织供血，减轻神经损伤，但效果十分有限，且存在再灌注损伤及出血增加的风险，很多患者接受溶栓治疗后仍遗留神经功能缺陷[7–11]。

## 1 组蛋白去乙酰化酶6 (histone deacetylase 6, HDAC6)与缺血性脑卒中

### 1.1 组蛋白修饰及组蛋白去乙酰化酶(histone deacetylases, HDACs)

近年来大量研究显示，表观遗传机制与中枢神经系统的发育有关，其相关信号通路在脑缺血损伤修复过程中亦扮演重要角色[12–14]。表观遗传是指DNA序列不发生变化，而基因表达却发生可遗传改变的现象，包括DNA甲基化、组蛋白修饰、染色质重塑、非编码RNA这4个主要调控机制。其中组蛋白修饰主要包括乙酰化与去乙酰化、甲基化与去甲基化、泛素化与去泛素化、磷酸化与去磷酸化。由组蛋白乙酰化酶(histone acetyltransferases, HATs)和HDACs主导的蛋白质乙酰化修饰对于神经系统的发育、成熟具有重要意义。大量研究表明HDACs参与调控脑缺血的损伤修复[15–19]、神经退行性疾病[20–22]、肿瘤的发生和转移[23–26]、微生物及病毒感染[27–29]、自身免疫性疾病[30–33]等。

目前人们已在哺乳动物中发现18个HDACs成员，根据同源性将它们分为I、II、III、IV类。I类包括HDAC1、2、3、8，主要定位于胞核，参与调控基因转录和细胞增殖分化[34–37]等；II类包括HDAC4、5、6、7、9、10，可调控组蛋白和非组蛋白乙酰化修饰[38–42]；III类包括SIRT1~7，依赖烟酰胺腺嘌呤二核苷酸(nicotinamide adenine dinucleotide, $NAD^+$)发挥作用[43, 44]；IV类目前只有一种，即HDAC11，是最小的HDACs亚型，其通常表达于脑和睾丸组织中，但在各种癌细胞中表达上调，HDAC11也是抗原呈递细胞中白细胞介素-10 (interleukin-10, IL-10)生成的负调节因子[45–47]。

### 1.2 HDAC6与缺血性脑卒中的关系

HDAC6在大脑、心脏、肝、肾等器官高表达，主要定位于胞浆及核周[48]，是HDACs的II类家族中最独特的成员。HDAC6拥有两个完整的催化结构域，它们高度同源且各自均在C末端有一个可以跟泛素结合的锌指结构，具备双重催化反应功能和独立的酶活性[49, 50]。HDAC6不仅具有很强的组蛋白去乙酰化酶活性，而且能够介导非组蛋白(例如：14-3-3ζ)的脱乙酰化进程[51]。HDAC6参与了细胞内的多种生理过程，其主要作用底物有α-微管蛋白(α-tubulin)、Bax、热休克蛋白90 (heat shock protein 90, HSP90)、HIF1α、GRK2、p300、皮层肌动蛋白(cortactin)[52–57]等。它还可与VCP、NF-κB、Foxp3、tau、PP1、Ku70、PCKα等相互作用，参与调控细胞形态、自噬、迁移及氧化应激保护等相关功能[58–62]。

HDAC6调节神经细胞的存活、分化和成熟，参与大脑认知形成和情绪调控，在神经系统的发育中具有重要作用[63–65]。研究表明，在创伤、缺血、毒素及基因突变引起的氧化应激模型中，HDAC6可对神经细胞胞体或轴突中的一个或多个未知蛋白去乙酰化，从而促进神经细胞的凋亡。HDAC6参与脑缺血损伤的多个病理环节，包括前期的兴奋性毒性、氧化应激反应，后期的炎症反应和细胞凋亡。研究显示，缺血再灌注损伤可使HDAC6在术后3 h先出现明显上升，随后下降的趋势；而选择性沉默HDAC6基因可显著减少缺血脑组织皮层神经元细胞凋亡率，提高细胞对缺氧的耐受性[66]，说明缺血早期出现变化的HDAC6是参与神经细胞凋亡的重要因素。Rivieccio等人在氧化应激的原代神经元中诱导HDAC6表达[67]，结果显示，HDAC6的表达在神经元氧化应激12 h后达到峰值，表明HDAC6的表达与氧化应激呈时间依赖性关系，HDAC6可能被氧化应激反应调节或在病理信号中起作用。Yuan等人对大鼠皮质神经元的氧-葡萄糖剥夺(oxygen-glucose deprivation, OGD)模型的研究结果表明，OGD诱导培养的大鼠皮质神经元出现坏死，且HDAC6在神经元中的表达上调[68]，该研究进一步表明HDAC6通过调节活性氧(reactive oxygen species, ROS)和乙酰化微管蛋白的水平参与缺血再灌注过程中神经元坏死的形成。脑缺血损伤发生后的继发性损伤与神经可塑性可共存数天至数周，可能为扩大治疗窗口提供机会。研究表明，HDAC2的表达在小鼠脑中风发生后5~7 d上调，通过减少梗死周围神经元的存活和神经可塑性以及增加神经炎症来介导继发性功能丧失。脑卒中损伤发生后HDAC6和HDAC2水平都上调，但HDAC6上调的时间要早于HDAC2[69]。

脑缺血损伤发生后HDAC6的表达上调，导致了一系列生物大分子的去乙酰化，包括：α-tubulin的去乙酰化破坏微管稳定性，加速微管解聚[57, 70]；

cortactin 的去乙酰化使细胞内部结构趋于稳定，抑制神经元迁移和轴突生长[57, 71]；分子伴侣 HSP90 的去乙酰化促进热休克转录因子 1 (heat shock transcription factor-1, HSF-1) 释放并增加应激反应[52, 72]；过氧化物酶 peroxiredoxin-1 (Prx-1) 和 peroxiredoxin-2 (Prx-2) 的去乙酰化加剧氧化损伤[73, 74]等 ( 图 1)。这些生物大分子的去乙酰化促进了脑卒中的发生。

## 2 HDAC6抑制剂治疗缺血性脑卒中的机制

HDACs 抑制剂最初是作为抗肿瘤新药引起人们关注的，其中辛二酰苯胺异羟肟酸 (suberoylanilide hydroxamic acid, SAHA) 与罗米地辛 (Romidepsin, FK228) 已分别于 2006、2009 年获美国食品药物管理局 (FDA) 批准用于临床治疗皮肤 T 细胞淋巴瘤[75]。目前已上市的 HDACs 抑制剂有 5 种，包括广谱的 HDACs 抑制剂：vorinostat、belinostat、panobinostat 和靶向 I 类 HDACs 抑制剂：romidepsin 和 chidamide[76]。后来研究者在体内外缺血模型中均发现 HDAC6 的表达明显上调，便开始将 HDAC6 抑制剂引入缺血性脑卒中的防治领域进行研究，结果表明：在脑缺血早期，HDAC6 抑制剂可维持甚至提高损伤脑组织的组蛋白乙酰化水平，显著减少脑梗死面积，抑制神经细胞凋亡[19, 64]；在缺血后期则可刺激神经营养因子的分泌[77]，帮助神经元和突触重塑，促进缺血组织的神经和血管发生，促进损伤组织的再生修复。选择性小分子 HDAC6 抑制剂较广谱的 HDACs 抑制剂疗效更佳且毒副作用小[78]，目前研究较多的选择性小分子 HDAC6 抑制剂主要有 Rocilinostat (ACY-1215)、Tubacin、Tubastatin A[79] 等。目前的研究表明，HDAC6 抑制剂通过降低细胞兴奋性毒性、减轻氧化应激损伤、抑制炎症介质释放、抑制神经细胞凋亡以及促进神经再生和血管新生等多种方式对缺血性脑卒中发挥有效的神经保护作用 ( 表 1)。

### 2.1 降低兴奋性毒性

兴奋性毒性是脑缺血病理的首要触发事件，也是脑卒中治疗的首要靶点。脑缺血引起白质损伤后，神经元过度释放具兴奋毒性的谷氨酸，造成大量的 $Na^+$、$Cl^-$ 和水分子内流，导致神经细胞肿胀、溶解，甚至变性坏死，而 $Ca^{2+}$ 超载则使得胞浆内的 $Ca^{2+}$ 依赖性酶类和磷脂酶类大量激活，引起细胞膜的分解和细胞骨架的破坏，激活血小板形成血栓，增加脑缺血面积[80, 81]。研究显示，在大脑中脑动脉栓塞 (middle cerebral artery occlusion, MCAO) 大鼠模型缺血损伤 24 h 后给予广谱 HDACs 抑制剂丙戊酸 (valproic acid, VPA)，可提高谷氨酸转运体 (glutamate transporter, GLT) 的表达，降低兴奋性毒性，减轻脑损伤[82]。HDAC6 抑制剂 Trichostatin A 可减轻 1-甲基 -4- 苯基吡啶 (1-methyl-4-phenylpyridine, MPP) 诱导的 GLT 损伤，增加卒中后缺血周围灶中谷氨

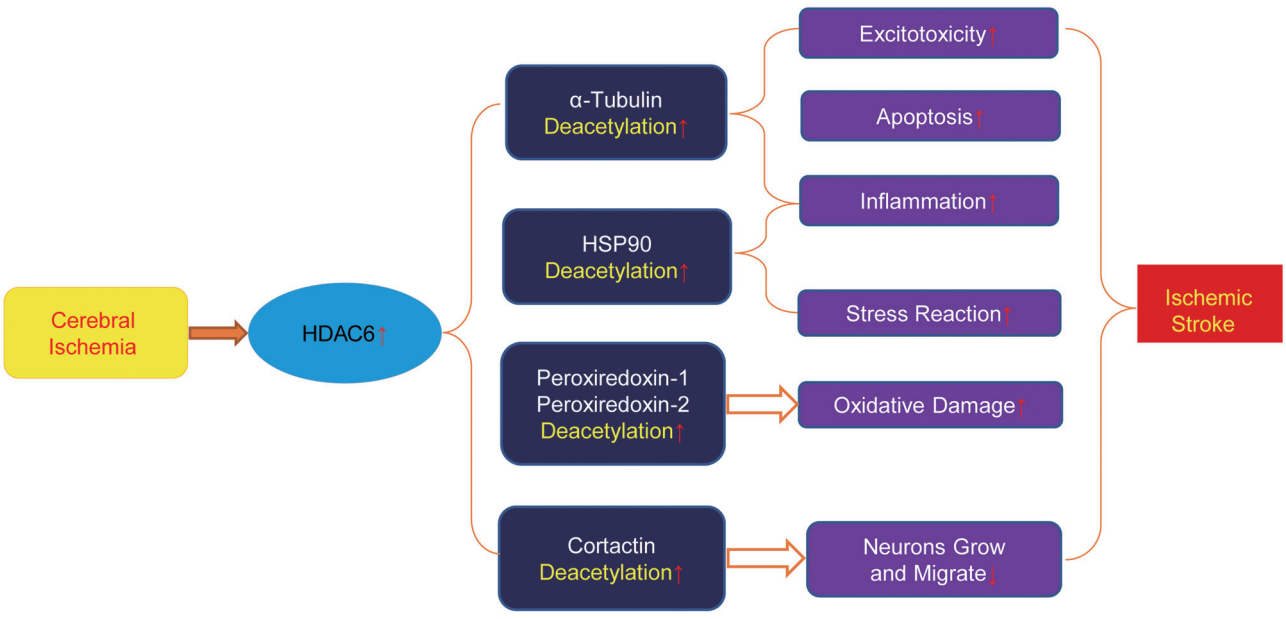


图 1. HDAC6与缺血性脑卒中的关系示意图

Fig. 1. Relationship between HDAC6 and ischemic stroke.

表1. HDACs抑制剂治疗缺血性脑卒中的机制

Table 1. Mechanism of HDACs inhibitors for ischemic stroke

| Classification | Name | Mechanism | Effect |
|---|---|---|---|
| Broad spectrum HDACs inhibitors | VPA | GLT↑ | Reduce excitotoxicity[82] |
| | | NOS, COX-2↓ | Anti-inflammation[87] |
| | | TFs, HIF-1α, VEGF, MMP ↑ | Angiogenesis[92] |
| | Sodium butyrate | NOS, COX-2 ↓ | Anti-inflammation[87] |
| | Trichostatin A | NOS, COX-2↓ | Anti-inflammation[87] |
| | | GLT1↑ | Reduce excitotoxicity[83] |
| | SAHA | Inhibit p53 | Inhibit neuronal apoptosis[90] |
| | LB-205 | NGF↑, Activate TrkA pathway | Nerve nutrition[93] |
| Selective HDAC6 inhibitors | Tubastatin A | α-Tubulin acetylation↑, FGF-21 ↑ | Inhibit neuronal apoptosis[19] |
| | | α-Tubulin acetylation↑, IL-10↑ | Anti-inflammation[88] |
| | Tubacin | α-Tubulin acetylation↑, ROS ↓ | Inhibit neuronal necrosis[68] |
| | | Prx-1 and -2 acetylation↑ | Reduce oxidative stress damage[73,74] |
| | | Cortactin acetylation↑ | Promote nerve cell growth[57] |

VPA: valproic acid; SAHA: suberoylanilide hydroxamic acid; GLT: glutamate transporter; NOS: nitric oxide synthase; COX-2: cyclooxygenase-2; TFs: transcription factors; HIF-1α: hypoxia inducible factor-1α; VEGF: vascular endothelial growth factor; MPP: 1-methyl-4-phenylpyridine; NGF: nerve growth factor; FGF-21: fibroblast growth factor-21; IL-10: interleukin-10; ROS: reactive oxygen species; TrkA: tyrosine kinase receptor type 1; Prx-1: peroxiredoxin-1; Prx-2: peroxiredoxin-2.

酸转运蛋白1 (glutamate transporter 1, GLT1)的表达，增强星形胶质细胞对谷氨酸的摄取，降低脑缺血后的兴奋性毒性作用[83]。

### 2.2 减轻氧化应激损伤

脑缺血发生后，受损部位分泌大量过氧化物和自由基等高活性物质，引起核酸主链断裂和蛋白降解，严重破坏细胞膜结构，最终导致神经细胞的功能紊乱甚至死亡。这种氧化应激损伤是缺血后脑神经损伤的重要因素。HDAC6表达的上调使得过氧化物酶Prx-1和Prx-2去乙酰化，加剧氧化应激损伤。研究显示MCAO大鼠脑组织的丙二醛 (malondialdehyde, MDA)含量显著增加，而过氧化物歧化酶 (superoxide dismutase, SOD)的水平则明显下降，说明过氧化应激损伤是脑缺血发生和发展的重要因素[84]。对缺血缺氧的小鼠模型给予HDACs抑制剂处理，可抑制真核翻译起始因子2 (eukaryotic initiation factor 2, eIF2)的磷酸化从而降低elF-2α介导的凋亡前体C/EBP同源蛋白的表达，减轻内质网的氧化应激损伤[85]。

### 2.3 抑制炎症介质的释放

脑缺血发生后，损伤的神经元可释放白细胞介素-1β (interleukin-1β, IL-1β)、肿瘤坏死因子-α (tumor necrosis factor-α, TNF-α)等炎症介质，以及血管细胞黏附分子-1 (vascular cell adhesion molecule-1, VCAM-1)、细胞间黏附分子-1 (intercellular adhesion molecule-1, ICAM-1)、内皮细胞黏附分子 (endothelial cell adhesion molecules, ECAM)、单核细胞趋化蛋白-1 (monocyte chemotactic protein, MCP-1)、环氧合酶-2 (cyclooxygenase-2, COX-2)等。这些炎症介质及细胞因子的表达上调使得血管壁通透性增加，并诱导外周中性粒细胞、淋巴细胞等穿透血管壁浸润脑实质，进一步激发炎症反应。研究显示，艰难梭菌毒素A可激活HDAC6，降低α-tubulin的乙酰化程度而加速微管解聚，介导急性炎症的发生[86]。在大鼠MCAO模型中应用广谱HDACs抑制剂丁酸钠 (sodium butyrate, SB)、VPA和曲古抑菌素A (Trichostatin A, TSA)均可下调炎症介质一氧化氮合酶 (nitric oxide synthase, NOS)和COX-2的表达，从而发挥其神经保护作用[87]。HDAC6抑制剂Tubastatin A可乙酰化α-tubulin，激活脂多糖 (lipopolysaccharide, LPS)诱导的p38激酶信号通路，刺激抗炎介质IL-10的分泌而发挥抗炎作用[88]。此外，HDAC6抑制剂还

可能通过抑制 Caspase-3、上调热休克蛋白 70 (heat shock protein, HSP70) 的表达而减少炎症反应，发挥神经保护作用 [89]。

### 2.4 抑制神经细胞凋亡

脑缺血损伤后，兴奋性毒性、$Ca^{2+}$ 超载、线粒体功能障碍、自由基的产生以及炎症反应等都可对细胞造成严重损伤。Caspases、p53、Bcl-2、Bax 等基因被激活，在缺血梗死区引起细胞坏死，而在缺血半暗带区则引发细胞凋亡。研究显示，在大鼠 MCAO 模型脑缺血损伤 24 h 后给予 HDAC6 抑制剂处理，可上调具有神经保护作用的蛋白 HSP70 和 Bcl-2 的表达，抑制神经细胞凋亡 [90]。而在大鼠短暂性 MCAO 模型中应用 HDAC6 抑制剂，则可下调促凋亡因子 Caspase-3 的表达，增加凋亡蛋白 Bcl-2/Bax 的比值，减轻脑损伤 [89]。另有研究表明，神经细胞凋亡可能与核内 p53 过表达有关，HDACs 抑制剂 SAHA 可抑制 p53，同时增加磷酸化 PKB 的表达，发挥神经保护作用。而在小鼠 MCAO 模型中应用 HDAC6 抑制剂 Tubastatin A 抑制 HDAC6 的去乙酰化活性，可增加 α-tubulin 乙酰化水平，上调成纤维细胞生长因子 -21 (fibroblast growth factor-21, FGF-21) 的表达，从而减少细胞死亡，改善神经功能 [19]。在大鼠 OGD 模型中应用 HDAC6 抑制剂 Tubacin 抑制 HDAC6 活性，可以降低 ROS 的水平从而提高神经元的存活率 [68]。

### 2.5 促进神经细胞再生与血管新生

脑缺血损伤后，位于纹状体室管膜下层 (subventricular zone, SVZ) 和海马颗粒下层 (subgranular zone, SGZ) 的神经干细胞被激活并增殖，随后迁移至颗粒细胞层分化为神经元，促进神经再生。抑制 HDAC6 可增加脑源性神经营养因子 (brain derived neurotrophic factor, BDNF) 的释放和运输，激活 BDNF-TrkB 信号通路，促进神经干细胞的增殖和分化，帮助修复受损脑组织 [91]。广谱 HDACs 抑制剂 VPA 可上调转录因子 (transcription factors, TFs)、低氧诱导因子 1α (hypoxia-inducible factor-1α, HIF-1α)、血管内皮生长因子 (vascular endothelial growth factor, VEGF) 和基质金属蛋白酶 (matrix metalloprotein, MMP) 的表达，刺激血管内皮细胞增生，改善局部血液供应，促进神经功能修复 [92]。小分子 HDACs 抑制剂 LB-205 具有锌结合部分，可抑制依赖于锌的 I 类和 II 类 HDACs，促进神经生长因子 (nerve growth factor, NGF) 分泌，激活酪氨酸激酶受体 (tyrosine kinase receptor type 1, TrkA) 通路，发挥营养神经的作用 [93]。此外，HDAC6 抑制剂可增加 cortactin 的乙酰化，促进轴突生长，增强皮层神经元的迁移，促进神经细胞的功能恢复 [57]。

## 3 总结与展望

HDAC6 在神经系统发育中具有重要作用，是神经细胞存活、分化、成熟的重要调节者，参与缺血性脑卒中的病理过程，是脑损伤发生和发展的一个重要蛋白。随着脑缺血损伤引起的神经化学级联反应机制被逐渐阐明，HDAC6 作为一个极具潜力的药物靶点引起广泛关注。以 HDAC6 为作用靶点的抑制剂可以作用于缺血性脑卒中多个病理环节，如兴奋性毒性、氧化应激损伤、炎症反应、细胞凋亡、神经细胞再生及血管新生等，发挥多靶点抗缺血性脑损伤的作用。作为一类新兴的药物，选择性 HDAC6 抑制剂已被广泛研究用于各种临床治疗目的，包括癌症、神经退行性疾病和自身免疫疾病等 [94]。目前，有效的 HDAC6 抑制剂很少，新发现的 HDAC6 抑制剂还处于试验阶段。现有的 HDAC6 抑制剂也存在着一定的不足，比如 Tubacin，作为一种研究工具很有用，但由于其亲脂性高，在体内代谢快，合成繁琐，并不适合作为药物用于临床治疗 [95]。未来对选择性 HDAC6 抑制剂的研究应该更加关注体内生物学、药代动力学和药物性质的评估。我们期望安全低毒且具有良好血脑屏障通透性的选择性 HDAC6 抑制剂被开发出来，用于治疗缺血性脑卒中、癌症、神经退行性疾病等。

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