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组蛋白去乙酰化酶抑制剂调控缺血性脑卒中的分子机制*

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摘要 缺血性脑卒中（ischemic stroke，IS）约占所有卒中病例的80%，是全球范围内导致死亡和长期残疾的主要神经系统疾病，其核心病理机制为脑血流中断导致的神经细胞坏死和脑组织缺血性损伤，涉及细胞凋亡、炎症反应及氧化应激等多重分子过程。组蛋白去乙酰化酶（histone deacetylase，HDAC）通过去除组蛋白上的乙酰基团（acetyl group，Ac）调控染色质构象与基因表达，在神经细胞存活、炎症反应调控及血脑屏障稳态调节中发挥重要的作用。组蛋白去乙酰化酶抑制剂（HDAC inhibitor，HDACi）可抑制HDAC的活性，HDACi不仅作用于组蛋白，还可作用于热休克转录因子1（HSF1）、分子伴侣热休克蛋白90（HSP90）及细胞骨架蛋白α微管蛋白（α-tubulin）在内的多种非组蛋白，进而调控下游基因转录及相关信号通路，在IS模型中表现出显著神经保护作用。本文系统综述HDACs的分类、HDACi的作用机制，及其在IS后细胞凋亡抑制、神经炎症调控、血脑屏障修复及认知功能改善中的多重效应，同时探讨HDACi的靶向策略与临床应用前景，为HDACi治疗IS提供了新的理论依据与科学的研究方向。

关键词 组蛋白去乙酰化酶，组蛋白去乙酰化酶抑制剂，缺血性脑卒中，神经保护
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缺血性脑卒中（ischemic stroke，IS），又称脑梗死，是最常见的卒中类型，占所有卒中病例的80%以上[1]，其核心病理机制始于脑血流中断，引发脑组织缺氧及能量代谢障碍，进而诱发神经元兴奋性毒性与钙离子超载，导致线粒体损伤，最终造成细胞凋亡与坏死。缺氧状态下，自由基大量积累引发氧化应激与炎症反应，炎症激活后破坏血脑屏障（blood-brain barrier，BBB），进一步诱发脑水肿并扩大缺血区域。从分子层面而言，IS的发生与发展，主要是细胞凋亡、神经炎症与氧化应激等多重损伤途径共同作用的结果[2]。

组蛋白去乙酰化酶（histone deacetylase，HDAC）可特异性去除组蛋白上的乙酰基团，使染色质结构趋于紧密，阻碍转录因子与RNA聚合酶的结合，最终实现基因沉默[3]（图1）。HDACs在多种疾病的发生发展中发挥关键作用，尤其在癌症、神经退行性疾病及心血管疾病中，其异常表达或活性改变会导致基因表达失调，进而引发病理性变化，因此抑制HDACs活性已成为重要的治疗策略[4]。在神经科学领域，抑制HDACs的作用已被证实具有神经保护效应，HDAC抑制剂（HDAC inhibitor，HDACi）可阻断HDACs的去乙酰化功能，维持或升高组蛋白乙酰化水平，使染色质保持松散构象，从而促进转录因子结合和基因转录激活[5]。已经有研究证实HDACi对脑损伤具有显著神经保护作用[6]，近年来相关研究证据表明HDACi可通过抑制卒中后神经细胞凋亡、缓解神经炎症、修复血脑屏障损伤及改善卒中后认知障碍（post-stroke cognitive impairment，PSCI），发挥IS治疗作用，本文将系统综述HDACi调控IS的分子机制以及相关治疗研究进展。

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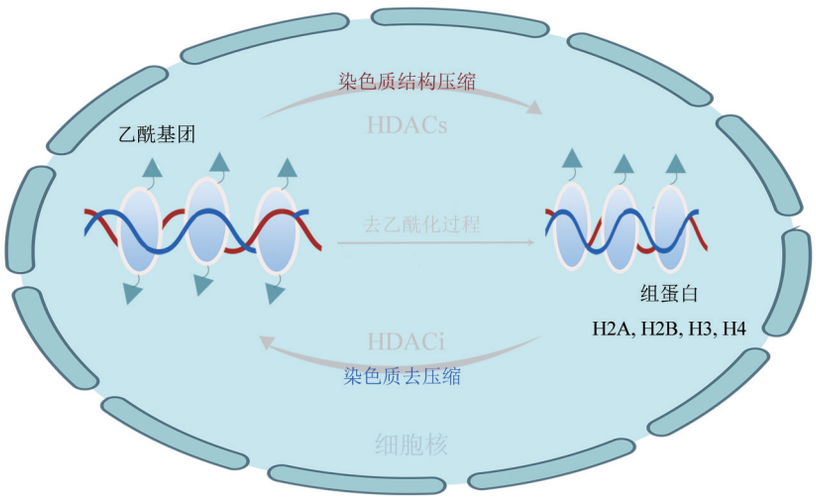

Fig. 1　Histone deacetylase and histone deacetylase inhibitors

图1　HDAC和HDAC抑制剂

1　HDAC的分类与结构

1.1　HDAC的分类

迄今为止，HDACs家族已鉴定出18个成员。根据进化起源差异，HDACs可大致分为Ⅰ、Ⅱ、Ⅲ、Ⅳ四大类[7]；而依据催化方式不同，其可分为两大类[8]：一类是锌离子（Zn^{2+}）依赖型经典HDACs，包括Ⅰ类（HDAC1~3、HDAC8）、Ⅱa类（HDAC4、5、7、9）、Ⅱb类（HDAC6、10）和Ⅳ类（HDAC11）；另一类是烟酰胺腺嘌呤二核苷酸（NAD^+）依赖型Ⅲ类去乙酰化酶，通常称为沉默信息调节因子（sirtuins，SIRTs）。该分类既明确了各类HDACs在催化机制上的显著差异，也暗示了它们在细胞代谢过程和表观遗传调控中具有不同的生物学功能。

1.2　HDAC的结构

在神经科学领域，Ⅰ类和Ⅱ类HDACs因在中枢神经系统发育和功能中扮演关键角色，成为研究最为广泛的亚型[9]。Ⅰ类HDACs定位于细胞核，属于广泛表达的核酶[10]；Ⅱ类HDACs可在细胞质和细胞核之间作为信号转运蛋白，通过调控基因表达、细胞周期、细胞分化等多个生理过程，影响神经系统与免疫系统的功能[11]。Ⅱa类HDACs作为信号转导因子，其N端调控结构域包含2或3个保守丝氨酸残基，这些残基能进行可逆性磷酸化修饰；磷酸化可促进14-3-3蛋白结合，进而介导HDACs的核出口并解除对其靶基因的抑制[12]。Ⅲ类HDACs是区别于Ⅰ类和Ⅱ类的独立家族，主要包括SIRTs，其家族成员SIRT1~7广泛参与调控DNA修复、细胞凋亡、抗氧化反应以及代谢稳态等过程，该类HDACs的活性依赖NAD^+，其中SIRT1作为最具代表性的成员，在神经退行性疾病和心血管疾病领域已有广泛研究[13-14]。Ⅳ类HDAC与Ⅱ类在序列上有一定相似性，目前仅发现HDAC11，相关研究仍较为匮乏。

2　HDAC抑制剂（HDACi）分类与功能

2.1　HDACi的分类

按化学结构分类，HDACi大致可分为异羟肟酸类、短链脂肪酸类、苯甲酰胺类及其他类型[15]。异羟肟酸类为广谱抑制剂[16]，分子质量<500 u，易穿过BBB，其含有的异羟肟酸基团（–CONHOH）可强效螯合锌离子，竞争性占据HDAC催化活性中心，抑制Ⅰ类HDACs（1/2/3/8）、Ⅱb类HADCs（6/10）和Ⅳ类HDACs（11）的活性[17]。曲古抑菌素A（Trichostatin A，TSA）属于异羟肟酸类HDACi，对7日龄大鼠缺氧缺血模型，损伤后给予TSA治疗，可减少大鼠神经元及少突胶质细胞祖细胞丢失，同时促进脑源性神经营养因子（brain-derived neurotrophic factor，BDNF）表达并激活TrkB受体[18]；Tubacin能减少促炎细胞因子介导的内皮一氧化氮合酶（endothelial nitric oxide synthase，eNOS）降解，改善小鼠心血管内皮功能，其通过上调eNOS表达可能对内皮功能障碍相关的心血管疾病具有治疗潜力[19]；伏立诺他（Vorinostat Zolinza，SAHA）属于广谱抑制剂，能

够降低白介素（interleukin，IL）-1β、IL-6、肿瘤坏死因子α（tumor necrosis factor-α，TNF-α）等促炎因子的水平[20]。短链脂肪酸类主要抑制I类HDACs（1/2/3）和IIa类HDACs（4/5/7/9），具有一定靶向选择性，主要由肠道产生[21]，代表药物为丙戊酸钠（sodium valproate，VPA）和丁酸钠（sodium butyrate，SB）。研究发现，在小鼠大脑中动脉闭塞（MCAO）模型中，SB可下调TNF-α和一氧化氮合酶（nitric oxide synthase 2，NOS2）、上调IL-10，通过小胶质细胞介导的表观遗传调节发挥神经保护作用并缓解炎症反应[22]。苯甲酰胺类HDACi的代表药物包括恩替诺特（Entinostat）和恩替司他（MS-275），常作为I类HDACi，靶向作用于HDAC1~3和HDAC11[23]，研究显示，MS-275在缺血再灌注模型中可有效缩小脑梗死面积，改善神经功能评估结果[24]。其他类型中，β萘酚衍生物类、噻吩并嘧啶酮衍生物类主要抑制III类去乙酰化酶[25-26]，HDAC11特异性抑制剂PB94包含苯乙烯基（styryl）和苯甲酰胺（Benzamide）两大核心基团，通过特定连接形成独特的三环骨架[27]（表1）。

Table 1　Classification, representative drugs and mechanisms of HDAC inhibitors

表1　HDACi的分类、代表药物以及作用机制

化学类别	代表药物	作用机制
异羟肟酸类	TSA	抑制I类、II类、IV类HDAC[18]
	Tubacin	高度选择性抑制HDAC6[19]
	SAHA	抑制I类、II类、IV类HDAC[20]
短链脂肪酸类	SB	抑制I类和IIa类HDAC[21]
	VPA	
苯甲酰胺类	Entinostat	抑制I类HDAC[23-24]
	MS-275	
	RGFP966	主要抑制HDAC1/2/3[28]
β萘酚衍生物	Sirtinol	选择性抑制SIRT1和SIRT2[25]
噻吩并嘧啶酮衍生物	AGK2	选择性抑制SIRT2[26]
苯乙烯基苯甲酰胺	PB94	选择性抑制IV类HDAC[27]

TSA：曲古抑菌素A（Trichostatin A）；SAHA：伏立诺他（Vorinostat Zolinza）；SB：丁酸钠（sodium butyrate）；VPA：丙戊酸钠（sodium valproate）；Entinostat：恩替诺特；MS-275：恩替司他；Sirtinol：西尔替诺；AGK2：SIRT2抑制剂；SIRT1：沉默信息调节因子1（sirtuin1）；SIRT2：沉默信息调节因子2（sirtuin2）。

2.2　HDACi的功能

HDACi作为一类重要的表观遗传修饰剂，其经典机制是通过抑制HDACs活性升高组蛋白乙酰化水平，进而松弛染色质并激活*p21*等基因转录进程[29]，此外，HDACi的作用范畴不限于组蛋白，还可广泛作用于转录因子热休克因子1（heat shock factor 1，HSF1）、分子伴侣HSP90及细胞骨架蛋白α微管蛋白（α-tubulin）在内的多种非组蛋白底物[30]，通过调控这些底物的乙酰化状态影响细胞功能，同时激活抑癌基因、神经营养因子等相关基因转录[31]。不仅如此，HDACi还能调控p53、核因子κB（nuclear factor κB，NF-κB）等50余种非组蛋白底物的乙酰化修饰，对细胞凋亡、炎症反应、代谢调控及细胞骨架稳定性等关键通路进行重编程[32-33]。

在神经疾病领域，HDACi可通过抑制神经炎症、抵抗氧化应激、抑制细胞凋亡和促进突触可塑性等途径发挥神经保护作用。HDAC2抑制剂CAY10683能够有效抑制脂多糖（lipopolysaccharide，LPS）激活的BV2小胶质细胞，以及LPS诱导的小鼠神经炎症模型中炎症细胞因子TNF-α和IL-1β的表达[34]；研究发现[35]，IS后，HDAC2与凋亡神经元存在共定位关系；另有研究证实[36]，HDACi可通过抑制NF-κB通路减少促炎因子分泌，从而减轻BBB的炎症损伤。

IS的传统治疗手段（如溶栓、取栓等）虽能在短时间内恢复脑部供血，但易引发脑缺血再灌注损伤，且存在出血风险高、救治时效性要求严苛等弊端[37]。相比之下，HDACi具备多靶点神经保护特性，不仅能保护神经元，还可维护BBB完整性，降低出血风险[6]。

3　HDACi调控IS的效应

3.1　HDACi调控IS后的细胞凋亡过程

IS会诱导细胞凋亡，而激活内源性抗凋亡通路是保护神经元免受损伤的关键机制。HDACi可通过多途径干预这一过程，进而激活抗凋亡通路发挥神经保护作用[5]。有研究表明，HDACi能显著改善脑缺血后神经功能损伤，减小脑梗死体积，并且延缓神经细胞凋亡进程[38]。

HDACi能促进组蛋白乙酰化，使该基因启动子区域开放（如p21/CIP1），引发细胞周期阻滞，从而阻止受损神经元启动凋亡程序[39]；HDACi如VPA和SAHA通过增加组蛋白乙酰化水平，下调促凋亡蛋白，如caspase-3等，同时上调抗凋亡蛋白，如Bcl-2等，从而抑制神经元凋亡[40]。此外，丁酸盐通过乙酰化HSF1促进热休克蛋白70（heat shock protein 70，Hsp70）表达，维持细胞内蛋白质稳态，抵抗内质网应激诱发的细胞凋亡[41]。在促凋亡信号抑制方面，HDACi同样发挥重要作用。在p53通路中，抑制HDAC1可诱导p53乙酰化，阻断其与DNA的结合能力，减少促凋亡基因的转录；在JNK通路中，抑制HDAC3能阻断Jun激酶（Jun kinase，JNK）磷酸化级联反应，降低减少c-Jun氨基端激酶（c-Jun N-terminal kinase，c-Jun）的激活水平，抑制应激诱导的神经元凋亡[42]；HDAC6抑制剂（如Tubastatin A）可恢复α-tubulin功能，促进自噬清除受损线粒体，同时阻断caspase-3激活，进一步抑制凋亡进程[43]。通过上述机制的协同作用，HDACi能有效调节细胞周期，抑制神经元凋亡，发挥神经保护作用。

3.2　HDACi调控IS后的神经炎症

IS会诱发神经炎症反应，而HDACi通过表观遗传调控与信号通路干预双重作用，在抑制该炎症进程中发挥关键作用，核心机制包括沉默促炎基因、促进抗炎表型转换及调控炎症相关通路。在沉默促炎基因与抑制炎性体激活方面，HDAC3抑制剂RGFP966可激活Nrf2通路，促进其核转位并激活下游交替氧化酶（alternative oxidase，AO）表达，进而显著抑制高迁移率族蛋白B1（high mobility group box 1，HMGB1）/Toll样受体4（Toll-like receptor 4，TLR4）介导的NOD样受体家族Pyrin域包含蛋白3（NOD-like receptor protein 3）炎性体激活[44]；在缺血再灌注损伤中，SAHA通过抑制NF-κB通路减少促炎因子（如IL-1β、IL-6、TNF-α）释放，并激活核因子E2相关因子2（nuclear factor erythroid-2-related factor 2）/血红素加氧酶1信号轴（heme oxygenase-1）抗氧化通路[45]；IS还会诱导小胶质细胞中HDAC3过表达，后者通过去乙酰化作用促进P65核易位，诱导环磷酸鸟苷-磷酸腺苷合成酶（cyclic GMP-AMP synthase，cGAS）表达，最终激活干扰素基因刺激蛋白（stimulator of interferon genes，STING）/干扰素调节因子（interferon regulatory factor，IRF）通路，反之，敲除HDAC3可阻断该通路激活，从而下调缺血诱导的脑组织损伤和神经炎症[46]。此外，IV类HDACs（HDAC11）通过抑制抗炎因子IL-10维持促炎微环境，其选择性抑制剂PB94已被证实能有效阻断其促炎作用，不过其具体抗炎机制仍有待进一步明确[47]。在促进抗炎表型转换与调控细胞极化方面，HDAC3在巨噬细胞中可通过非去乙酰化依赖性机制激活*TNF-α*、*IL-6*等促炎基因表达，基于蛋白质靶向降解嵌合体（proteolysis targeting chimera，PROTAC）技术开发的HDAC3降解剂P7，能有效阻断M0型巨噬细胞向促炎表型M1极化，显著减少促炎因子分泌并增加IL-10等抗炎因子释放[48]。

HDAC2通过调控促炎基因的染色质重塑参与炎症调控，其失活会导致促炎基因表达升高[49]；IIa类HDACs（HDAC4/5）主要促进脑卒中后星形胶质细胞活化及瘢痕形成[50]，而抑制HDAC4/5可降低STAT3磷酸化水平，抑制星形胶质细胞的反应性胶质增生[51]，因此IIa类HDACi更适合在卒中修复期使用。综上，HDACi通过表观遗传调控和信号通路干预双重作用，发挥对神经炎症的抑制作用，尤其是针对HDAC3的靶向抑制或降解，揭示了精准调控神经炎症的新方向，为IS的治疗提供了新思路。

3.3　HDACi调控IS后的BBB损伤

IS后，BBB会发生多阶段损伤，其破坏过程分为急性期、亚急性期和慢性期[52]。急性期时，缺氧导致ATP耗竭，使Na^+/K^+-ATP酶功能失效，引发细胞毒性水肿，同时闭合蛋白（occludin）、密封蛋白5（claudin-5）等紧密连接蛋白被降解，微血管通透性增加，进而导致血管源性水肿。亚急性期伴随炎症反应级联激活，小胶质细胞释放TNF-α、IL-1β等炎性因子损伤内皮细胞，加之白细胞浸润和活性氧类（reactive oxygen species，ROS）大量释放，进一步破坏BBB完整性，增加出血转化风

险[53]。慢性期则以周细胞凋亡、基底膜降解为主要特征，导致微血管稳定性丧失、血管再生受阻，最终延迟脑组织修复进程[54]。

HDACi通过多种机制保护或修复BBB，包括抗炎抗氧化、调控紧密连接蛋白表达、抑制异常通路激活及促进修复相关基因表达。HDAC3抑制剂可通过抑制炎症和氧化应激减轻BBB损伤，这一作用在缺血性脑损伤、阿尔茨海默病等疾病模型中已得到验证[55]。在脑梗死缺血再灌注模型中，VPA通过抑制NF-κB核转位和基质金属蛋白酶9（matrix metallopeptidase 9，MMP-9）表达，能够保护BBB完整性[56]。有研究表明，益母草碱（leonurine，SCM-198）在氧糖剥夺/再灌注（OGD/R）模型中，通过抑制HDAC2加速occludin和claudin-5的恢复，降低内皮细胞单层通透性[57]；W2A-16通过激活Wnt/β-catenin信号通路和抑制I类HDACs，增强跨内皮电阻（transendothelial electrical resistance，TEER），并上调BBB相关蛋白（如P-糖蛋白）的表达[58]。

需要注意的是，HDACi作用于BBB的具体效应取决于疾病类型和使用时机。例如，在脑肿瘤治疗中，HDACi可能通过暂时性开放BBB促进药物输送[59]，而在脑缺血治疗中则以保护BBB完整性为主要作用。

3.4 HDACi调控IS后的认知障碍

IS后，PSCI是临床常见后遗症[60]，但目前针对性治疗手段仍较为有限。HDACs在PSCI的病理进程中发挥关键调控作用，不同亚型的功能具有显著特异性，为HDACi的干预提供了明确靶点。I类HDACs主要定位于细胞核[61]，研究证实其在卒中后表达显著上调，是加剧神经元损伤、抑制神经可塑性及损害认知功能的核心因素[62]，因此成为HDACi治疗PSCI的主要靶点。IIa类HDACs可在核质间穿梭，其中HDAC4常被用作PSCI的潜在标志物[63]，主要参与记忆功能与认知障碍的调控。研究发现[64]，IS后PSCI患者的HDAC4表达水平低于仅发生卒中而无认知障碍的患者，这一特征可作为PSCI早期筛查的参考标准。动物实验显示，IS 4周后，大鼠海马区HDACs活性增强，导致认知功能受损，而应用I类HDACi SB可有效降低海马区HDACs活性，提高组蛋白乙酰化水平，促进神经可塑性相关基因表达，进而改善认知功能障碍[65]。

HDACi通过多种机制协同改善PSCI的病理过程。其一，促进组蛋白乙酰化，解除神经营养因子（如BDNF）和突触相关基因的转录抑制，激活TrkB受体及其下游信号通路，改善神经元存活与突触功能，提升学习记忆能力[66-67]；其二，抑制NF-κB、转录激活因子1（activator protein-1，AP-1）等炎症通路，减少促炎因子表达[68]，改善炎症微环境，发挥神经保护作用[69]；其三，增强抗氧化防御能力，清除ROS，减轻氧化应激对神经元的损伤[70]，通过调节线粒体相关蛋白的乙酰化状态，促进线粒体生物发生，提升电子传递链效率，减轻氧化应激并优化脑内能量供应[71]；其四，通过激活磷脂酰肌醇3激酶（phosphatidylin ositol 3 kinase）/蛋白激酶B（protein kinase B）/糖原合成酶激酶3β（glycogen synthase kinase 3 beta）通路发挥抗凋亡作用，保护海马和皮层等认知关键脑区的神经元[72]；其五，促进海马齿状回神经发生，修复损伤的神经元网络，改善空间学习和记忆能力[73]；其六，针对HDAC6的特异性抑制可增加α-tubulin乙酰化水平，改善轴突运输效率，减少tau蛋白异常聚集，同时增强热休克蛋白功能，保护神经元结构和功能完整性[74]。综上，HDACs在IS后认知障碍的发生发展中发挥关键调控作用。当前，HDACi治疗PSCI的相关研究持续深入，其多机制协同的干预特性，为PSCI的临床治疗开辟了新路径，展现出广阔的应用前景。

4 总结与展望

HDACi可通过调节组蛋白乙酰化水平，改善神经细胞功能及生存微环境，减轻缺血性脑卒中后的脑损伤，推动神经功能恢复[75]。作为极具潜力的神经保护治疗手段，HDACi已在多项研究中证实对神经系统疾病的干预价值，其机制主要涉及乙酰化修饰调控。一方面通过增强组蛋白乙酰化，激活神经营养因子、*Hsp70*、*Bcl-2*等促存活、修复相关基因表达，同时抑制NLRP3等促炎相关基因活性；另一方面通过上调细胞内乙酰化水平，调控Nrf2、NF-κB、BDNF/TrkB等信号通路，实现抑制细胞凋亡、减少炎症反应、修复BBB损伤、缓解PSCI等协同效应，最终促进神经细胞存活与损伤修复（图2）。目前，临床常用的HDACi包括VPA、SB、TSA、Entinostat、SAHA等，其中VPA是最具代表性的药物之一，已应用于多种神经系统疾病的临床治疗。临床数据显示，VPA具有脂溶性，能够穿透BBB进入脑组织，在卒中治疗中，

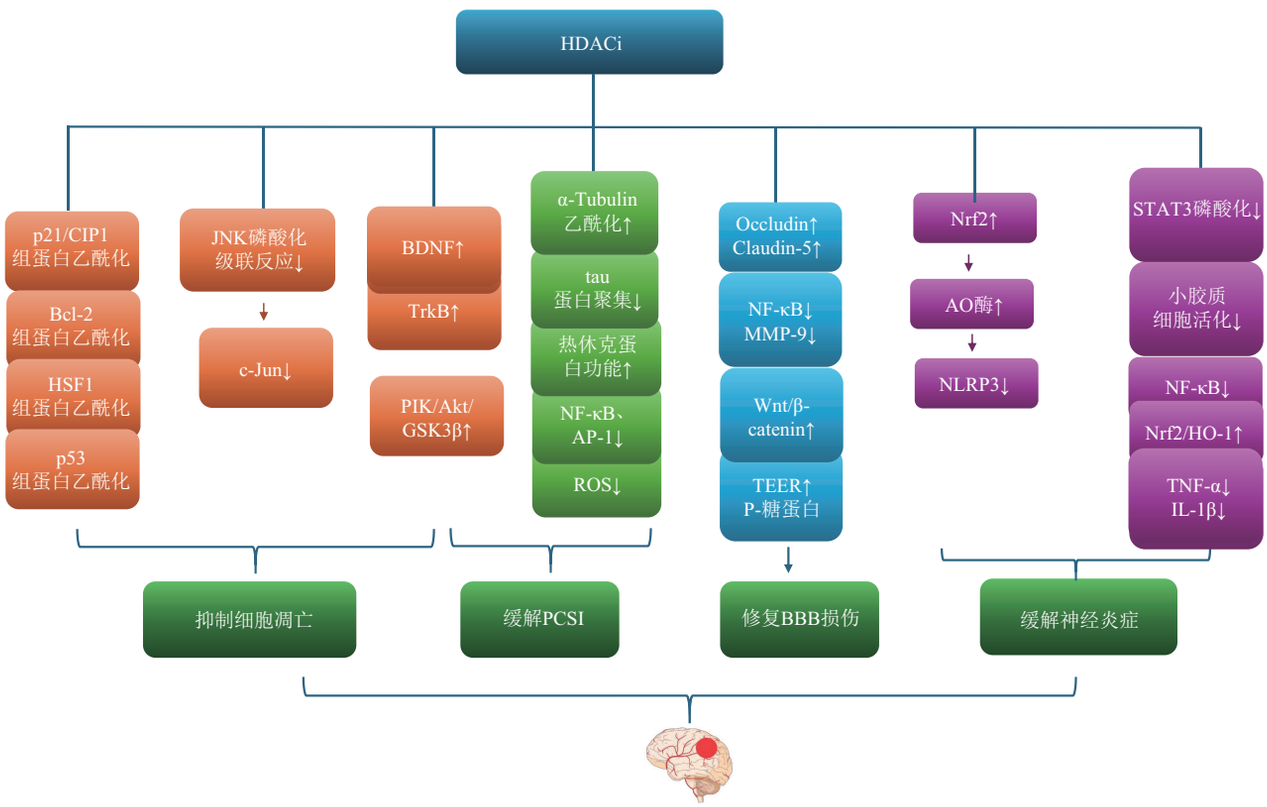

Fig. 2　The mechanism of HDACi in treating ischemic stroke

图2　HDACi治疗缺血性脑卒中的机制

HDACi：组蛋白去乙酰化酶抑制剂（histone deacetylases inhibitors）；p21：细胞周期依赖性蛋白激酶抑制因子1A（cyclin-dependent kinase inhibitor 1A）；CIP1：周期素依赖激酶相互作用蛋白1（cyclin-dependent kinase interacting protein 1）；Bcl-2：B细胞淋巴瘤/白血病-2基因（B-cell lymphoma-2）；HSF1：热休克转录因子1（heat shock transcription factor 1）；p53：磷酸化蛋白53（phosphorylated protein 53）；JNK：Jun激酶（Jun kinase）；c-Jun：c-Jun氨基端激酶（c-Jun N-terminal kinase）；BDNF：脑源性神经营养因子（brain-derived neurotrophic factor）；TrkB：神经营养酪氨酸激酶受体2型（neurotrophic tyrosine kinase receptor，type 2）；PIK：磷酸肌醇3激酶（phosphoinositide-3-kinase）；Akt：蛋白激酶B（protein kinase B）；GSK3β：糖原合成酶激酶3β（recombinant glycogen synthase kinase 3 beta）；α-tubulin：α微管蛋白；tau：微管相关蛋白（microtubule-associated protein tau）；NF-κB：核因子κB（nuclear factor κB）；AP-1：活化蛋白1（activator protein-1）；ROS：活性氧类（reactive oxygen species）；occludin：闭合蛋白；claudin-5：密封蛋白5；MMP-9：基质金属蛋白酶9（matrix metallopeptidase 9）；β-catenin：β连环蛋白；TEER：跨内皮电阻（transendothelial electrical resistance）；Nrf2：核因子E2相关因子2（nuclear factor erythroid-derived 2-related factor 2）；AO：下游交替氧化酶（alternative oxidase）；NLRP3：核苷酸结合寡聚化结构域样受体蛋白3（NOD-like receptor protein 3）；STAT3：信号转导与转录激活因子3（signal transducer and activator of transcription 3）；HO-1：血红素氧合酶1（heme oxygenase-1）；TNF-α：肿瘤坏死因子α（tumor necrosis factor-α）；IL-1β：白介素-1β（interleukin-1β）。

剂量100~250 mg/kg的短期应用（如7~28 d）的耐受性良好[76]。

尽管HDACi在神经损伤及神经退行性疾病治疗中表现出显著潜力，但临床转化过程中仍面临关键挑战，长时间使用HDACi易引发毒副作用，且可能影响正常细胞功能，这在一定程度上限制了其广泛应用。以临床已应用的VPA为例，其常见副作用包括胃肠道反应、头晕、恶心等，严重时还可导致肝毒性，需重点关注用药安全性[76]。因此，研发高选择性、低毒性的新型HDACi药物成为未来研究的关键要点。此外，VPA的临床潜力需进一步通过随机对照试验验证，尤其是针对复发性卒中预防和神经修复的优化方案，如联合细胞疗法或靶向HDACi[77]。

HDACi在神经系统疾病治疗领域具有广阔的应用潜力，尤其在IS的防治中已表现出良好的临床转化前景。未来研究需进一步探讨HDACi的作用机制，同时基于精准靶向理论与技术筛选最优治疗方案。针对HDACi临床应用中面临的不良反应控制、给药剂量优化等核心问题，进一步提升其靶

向选择性、优化药物递送系统是关键研究方向。随着表观遗传调控技术、药物研发技术及递送系统的创新突破，HDACi有望发展为治疗神经损伤及神经退行性疾病的高效、安全干预手段，为相关疾病的临床诊疗提供新的思路。

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The Molecular Mechanisms of HDACi in Regulating Ischemic Stroke*

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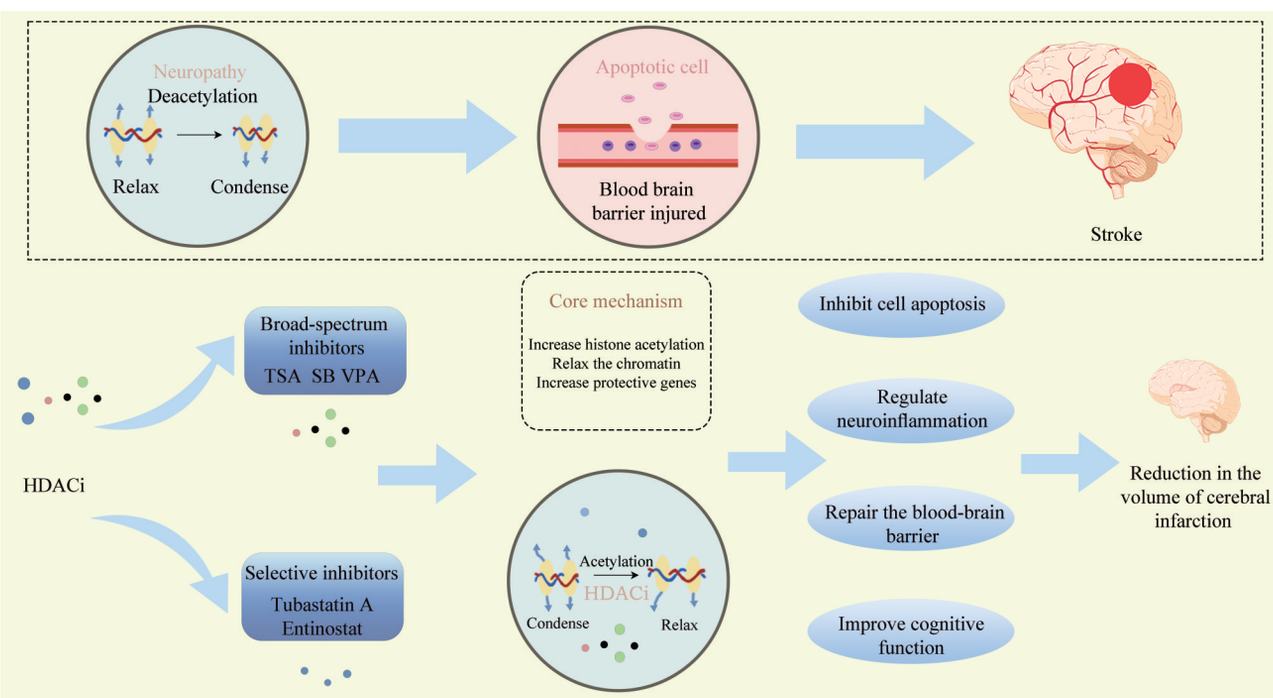
Graphical abstract



Abstract　Ischemic stroke (IS) accounts for approximately 80% of all stroke cases and is a leading cause of death and long-term disability worldwide. Its core pathological mechanism involves the interruption of cerebral blood flow, leading to neuronal cell death and ischemic tissue necrosis in the brain, which is associated with multiple molecular processes including apoptosis, inflammation, and oxidative stress. This review systematically discusses the classification of HDACs, the mechanisms of action of HDAC inhibitors, and their multiple effects in inhibiting cell apoptosis, regulating neuroinflammation, repairing the blood-brain barrier, and improving cognitive function following IS. HDACs function by removing acetyl groups from histone lysine residues, leading to chromatin condensation and gene silencing. The HDAC family is classified into four classes: class I (HDAC1, 2,

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3, 8), class IIa (HDAC4, 5, 7, 9), class IIb (HDAC6, 10), and class IV (HDAC11), with class III being the NAD^+-dependent sirtuins. Histone deacetylase inhibitors (HDACi) exert significant neuroprotective effects following ischemic stroke through a multi-target, multi-pathway synergistic mechanism. The core mechanisms include inhibition of neuronal apoptosis, regulation of neuroinflammation, protection of the blood-brain barrier (BBB), and improvement of cognitive impairments (PSCI). HDACi regulate gene expression epigenetically by upregulating genes such as *p21*/*CIP1*, leading to cell cycle arrest, while also modulating apoptosis-related proteins by inhibiting pro-apoptotic signaling pathways, thereby reducing neuronal cell death. In terms of neuroinflammation, HDACi suppress NF-κB and activate Nrf2 pathways, decreasing the release of pro-inflammatory cytokines and preventing the pro-inflammatory polarization of microglia and macrophages, thus modulating the inflammatory response. Regarding BBB protection, HDACi regulate the expression and restoration of tight junction proteins such as occludin and claudin-5, while inhibiting the release of destructive factors like MMP-9, alleviating vasogenic edema, and maintaining BBB integrity. Furthermore, HDACi promote the transcription of neurotrophic factors and synaptic-associated genes, enhancing neuroplasticity and repairing neuronal networks, ultimately improving cognitive functions. Therefore, HDACi demonstrate great potential as a multifaceted therapeutic strategy for ischemic stroke. HDACis represent a powerful multi-target therapeutic approach that transcends the limitations of traditional thrombolytic therapies. HDACis represent a powerful multi-target therapeutic approach that transcends the limitations of traditional thrombolytic therapies, which are hampered by a narrow time window and risks of reperfusion injury. Histone acetylation is increased by HDACis, which relaxes chromatin and reactivates protective gene transcription. Their selectivity and chemical structure are used to classify them. Trichostatin A (TSA) and sodium butyrate (SB), a short-chain fatty acid, are examples of broad-spectrum inhibitors that are effective in lowering infarct volume and reducing neuroinflammation. More selective inhibitors, including Tubastatin A (HDAC6-selective) and Entinostat (class I-selective), may have fewer adverse effects while increasing efficacy. By suppressing apoptosis by modifying the p53, Bcl-2, and JNK pathways, reducing neuroinflammation by blocking NF-κB and NLRP3 activation, preserving the integrity of the blood-brain barrier by strengthening tight junction proteins, and promoting synaptic plasticity, neurogenesis, and the expression of neurotrophic factors like BDNF, these inhibitors provide neuroprotection through a variety of interrelated mechanisms. Despite their great potential, HDACis' clinical translation is fraught with difficulties, mostly because of non-selective inhibition-related adverse effects such as hepatotoxicity and gastrointestinal problems with valproic acid (VPA). In order to accomplish targeted delivery to the brain, future research is consequently shifting toward the development of highly selective inhibitors, refining dosing regimes, and utilizing cutting-edge drug delivery technologies like nanoparticles. In summary, the development of effective neuroprotective and neurorestorative treatments for IS may be greatly aided by a nuanced, spatiotemporally accurate understanding of HDAC activities and the judicious use of subtype-selective HDACis.

Key words histone deacetylase, histone deacetylase inhibitor, ischemic stroke, neurological protection
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