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针刺促进神经发生治疗缺血性脑卒中的机制研究进展

张 硕[1]，崔 杨[1]，孙忠人[1,2]，周新宇[1]，曹 宇[1]，王 泽[1]，陈 尧[1]，杨娟弟[1]，代雪缘[1]，尹洪娜[2]✉
（[1]黑龙江中医药大学，哈尔滨 150040；[2]黑龙江中医药大学附属第二医院，哈尔滨 150001）

【摘 要】 针刺在缺血性脑卒中的治疗与康复中展现出显著疗效，能够有效改善患者神经功能及日常生活能力，但其促进神经修复的深层机制尚未完全阐明。本文系统梳理针刺促进缺血性脑卒中后神经发生的研究进展，阐述缺血性脑卒中后神经发生的生物学基础及其在功能恢复中的重要作用，从促进神经干细胞增殖分化、调控神经营养因子表达及激活相关信号通路方面深入剖析针刺促进神经发生的分子机制。同时分析当前研究的局限性并提出未来发展方向，为深入探索针刺促进神经发生的作用机制及开发基于神经再生的卒中治疗新策略提供重要的理论依据。

【关键词】 针刺；缺血性卒中；神经发生

Research progress on the mechanism of acupuncture promoting neurogenesis in the treatment of ischemic stroke

Zhang Shuo[1], Cui Yang[1], Sun Zhong-Ren[1,2], Zhou Xinyu[1], Cao Yu[1], Wang Ze[1], Chen Yao[1], Yang Juandi[1], Dai Xueyuan[1], Yin Hongna[2]✉ ([1]Heilongjiang University of Chinese Medicine, Harbin 150040, China; [2]The Second Affiliated Hospital of Heilongjiang University of Chinese Medicine, Harbin 150001)

【ABSTRACT】 Acupuncture has demonstrated significant therapeutic efficacy in the treatment and rehabilitation of ischemic stroke, effectively improving patients' neurological function and daily living abilities. However, the underlying mechanisms by which it promotes neural repair have not yet been fully elucidated. This article systematically reviews and summarizes the research progress on acupuncture promoting neurogenesis after ischemic stroke. It elaborates on the biological basis of neurogenesis following ischemic stroke and its crucial role in functional recovery. The molecular mechanisms through which acupuncture promotes neurogenesis are deeply analyzed from the aspects of promoting neural stem cell proliferation and differentiation, regulating the expression of neurotrophic factors, and activating related signaling pathways. Additionally, the limitations of current research are analyzed and future directions are proposed, providing an important theoretical basis for further exploring the mechanism of acupuncture in promoting neurogenesis and developing new therapeutic strategies for stroke based on neural regeneration.

【KEYWORDS】 Acupuncture; Ischemic Stroke; Neurogenesis

缺血性脑卒中是一种由脑血管闭塞引起的急性脑血管疾病，主要表现为突发意识障碍、肢体运动功能障碍、感觉异常及认知功能损伤等神经系统症状[1]。据统计，2021年全球脑卒中发病人数达1 190万例，其中缺血性脑卒中约占65.3%，已成为导致成人残疾和死亡的首要原因[2]。在中国，脑卒中发病率呈持续上升趋势，卒中后神经功能缺损的长期存在不仅严重影响患者生活质量，也给家庭和社会带来沉重的经济负担，已成为亟须解决的重大公共卫生问题[3]。

针刺具有安全性高、不良反应少、易于推广等优势，在缺血性脑卒中的治疗与康复中发挥着重要作用[4]。临床研究证实，针刺能有效改善卒中患者的运动功能、认知功能及日常生活能力[5]。针刺能够通过调控多种信号通路促进卒中后神经发生，增加新生神经元数量并促进其功能修复，这可能是针

【DOI】10.13702/j.1000-0607.20251170
引用格式：张硕，崔杨，孙忠人，等.针刺促进神经发生治疗缺血性脑卒中的机制研究进展[J].针刺研究，XXXX，XX(XX)：1-12.
项目来源：国家重点研发计划(No.2022YFC3500403)；黑龙江省自然科学基金(No.PL2024H231)
通信作者：尹洪娜，E-mail：hljucmcy@163.com

刺改善神经功能的重要机制之一[6]。因此，本文系统梳理针刺促进缺血性脑卒中后神经发生的相关研究，深入剖析其涉及的分子机制与信号通路，以期为阐明针刺神经修复作用的生物学基础提供理论依据，并为开发基于神经发生的卒中治疗新策略提供参考。

1 缺血性脑卒中后的神经发生机制

神经发生是指神经干细胞（NSCs）经增殖、分化、迁移等过程，最终生成新的神经元和胶质细胞并整合进神经网络的动态过程[7]。成年人大脑中的神经发生主要发生在侧脑室下区和海马齿状回下区两个特定区域[8]。生理状态下，这些区域的NSCs多处于静止状态，但在缺血性脑卒中等病理条件下，局部脑血流受阻、引起神经细胞死亡，同时也激活了成人脑内源性NSCs的修复机制[9]。卒中后神经发生包括增殖、迁移、分化和突触整合4个关键环节。NSCs的增殖是起始步骤，卒中后成纤维生长因子2、表皮生长因子等生长因子显著上调，促进侧脑室下区和海马齿状回下区的神经前体细胞被迅速激活并大量增殖，为后续修复提供细胞来源[10]。增殖后的神经前体细胞需定向迁移至受损区域，基质细胞衍生因子1与其受体C-X-C趋化因子受体4型构成的趋化因子通路在此过程中发挥关键作用，引导神经母细胞向梗死区域迁移[11]。迁移至目标区域的神经前体细胞随后分化为神经元或胶质细胞，新生神经元需与周围神经元建立突触连接并形成功能性神经环路，最终整合进受损的神经网络[12]。

缺血性卒中后的神经发生受多种因素调控。其中神经炎性反应扮演双重角色：早期适度的炎性反应可促进NSCs的激活和增殖，但慢性炎性反应则通过小胶质细胞和星形胶质细胞的持续激活形成胶质瘢痕，阻碍神经前体细胞的迁移和轴突再生，限制了神经发生的效率[13-14]。此外，胶质淋巴系统功能障碍影响脑内代谢废物清除，进而加重神经损伤并限制神经发生[15]。而脉络丛通过分泌脑脊液和释放生长因子，在调节神经炎性反应和支持神经修复方面发挥重要作用[16]。缺血性脑卒中后的神经发生为脑功能恢复提供了重要的生物学基础。新生神经元整合进受损神经网络后，可在一定程度上替代死亡神经元，恢复受损的神经环路功能，显著改善运动功能和认知功能[17]。

2 针刺调控神经发生的分子机制

2.1 针刺促进内源性NSCs增殖与分化

NSCs是一类具有自我更新和多向分化潜能的原始细胞，可分化为神经元、星形胶质细胞和少突胶质细胞[18]。在成年哺乳动物脑内，NSCs主要分布于侧脑室下区和海马齿状回下区两个神经源性区域，在生理状态下处于相对静息状态[19]。脑缺血损伤发生后，神经源性区域的NSCs被自发激活，增殖水平显著上升，表明机体存在一定的“自我修复”能力[20]。然而，大部分新生细胞未能存活或成功分化为功能性神经元，因此需要外部干预手段增强NSCs的修复能力[12]。

针刺通过促进NSCs增殖、迁移和定向分化发挥神经修复作用。在增殖方面，针刺治疗后，巢蛋白（Nestin）和5-溴脱氧尿嘧啶核苷（BrdU）双阳性再生细胞数量明显增加，皮层区Nestin mRNA表达水平升高，海马区表达略有增加而纹状体区有所下降，海马齿状回下区BrdU/胶质纤维酸性蛋白（GFAP）双阳性细胞及纹状体区BrdU/神经元核抗原（NeuN）双阳性细胞数量均增加[21-23]。在迁移方面，电针促进内源性NSCs从侧脑室下区向受损皮层区和纹状体区迁移，室管膜下区双皮质素阳性神经前体细胞减少，而缺血周围皮层区NeuN阳性成熟神经元增加，表明新生细胞成功迁移至损伤区域[24]。在分化调控方面，针刺发挥双向调节作用：一方面抑制NSCs过度分化为病理性星形胶质细胞，减少瘢痕形成[21]；另一方面促进GFAP、波形蛋白和Nestin阳性反应性星形胶质细胞增殖，通过分泌神经营养因子发挥保护效应，同时长时程促进NSCs优先向神经元分化[25]。

2.2 针刺调节神经营养因子表达

2.1.1 脑源性神经营养因子（BDNF）

BDNF是神经营养素家族的核心成员，通过与原肌球蛋白受体激酶B（TrkB）结合，激活丝裂原活化蛋白激酶（MAPK）、磷脂酰肌醇3-激酶（PI3K）等信号通路[26]。BDNF表达水平与齿状回颗粒细胞增殖密切相关，直接影响新生神经元的数量与功能整合[26]。研究表明，BDNF对缺氧缺糖条件下的海马神经元具有保护作用，并能在缺血性脑卒中后促进神经发生[27]。针刺通过多层次机制调控BDNF表达。在转录水平，针刺通过下调miR-191a-5p表达解除对BDNF基因的抑制[28]；在蛋白加工层面，针刺促进前体BDNF向成熟BDNF转化，优化受体表达模式，增强神经保护效应[29]；在信号转导层面，针刺

激活BDNF/TrkB/PI3K/蛋白激酶B(Akt)通路,促进海马和室下区NSCs增殖分化,同时促进梗死周围皮层胶质细胞增殖和祖细胞存活分化[30]。此外,针刺对BDNF的调控具有时间依赖性,单纯针刺治疗1周后即可显著上调海马BDNF及TrkB蛋白表达[31],联合康复训练、干细胞移植或药物治疗可产生更显著的协同效应[32-33]。临床研究证实,针刺可有效提高患者血清BDNF水平,神经功能和日常生活能力显著改善[34]。

2.1.2 神经生长因子(NGF)

NGF是最早发现的神经营养因子,主要通过高亲和力受体原肌球蛋白受体激酶A(TrkA)激活MAPK和PI3K通路[35]。NGF通过激活TrkA增加神经前体细胞存活并诱导轴突生长,包括轴突分支形成及髓鞘化,还参与脑卒中后的血管新生过程[36]。研究证实,持续给予NGF可通过增强胆碱能活性促进海马新生神经元存活[37]。针刺能够上调脑缺血模型海马区NGF阳性细胞数量[38]。针刺预处理可提高梗死侧海马NGF表达水平,减轻早期脑损伤[39]。此外,针刺联合运动疗法通过上调NGF表达、下调神经再生抑制因子Nogo-A和p75神经营养因子受体(p75NTR)表达,减小脑梗死体积,协同促进运动功能恢复[33]。临床研究[40-42]显示,针刺联合认知训练或康复训练可显著提高脑卒中患者血浆NGF水平,治疗数周后认知和运动功能明显改善,联合治疗组疗效优于单独治疗组。

2.1.3 胶质细胞源性神经营养因子(GDNF)

GDNF属于转化生长因子-β超家族,主要由星形胶质细胞和神经元分泌[43]。GDNF与GDNF家族受体α结合后,募集重排转染受体酪氨酸激酶形成信号复合体,激活下游磷脂酶Cγ(PLC-γ)、MAPK和PI3K/Akt信号通路,调控神经前体细胞迁移[44]。研究显示,GDNF可显著减少脑卒中梗死面积,促进海马齿状回细胞增殖和分化,诱导长期神经恢复和脑重塑[45]。针刺可通过多种信号通路上调GDNF表达并发挥神经保护作用,上调黑质和纹状体GDNF表达,增强神经元保护性蛋白表达,减少神经元丢失,改善运动功能障碍[46]。在缺血性脑卒中模型中,针刺可上调海马GDNF水平,减轻细胞凋亡,改善神经行为功能和学习记忆能力[47],且缺血半暗带GDNF表达在治疗后持续上调[48]。针刺对GDNF的调控与PI3K/Akt和核因子κB(NF-κB)信号通路密切相关,可激活相关通路上调GDNF表达,增加抗凋亡蛋白比值[49]。此外,针刺联合肉毒素治疗缺血性脑卒中可激活GDNF/TrkB信号通路,促进轴突和髓鞘再生[50]。

2.1.4 生长相关蛋白-43(GAP-43)

GAP-43是膜结合磷蛋白,主要定位于生长锥膜和突触前膜[51]。GAP-43在神经发育和轴突再生过程中高表达,通过调节肌动蛋白细胞骨架动力学介导生长锥运动与导向[52]。在成年神经发生中,GAP-43是新生神经元未成熟阶段的特征性标志物,其表达水平反映神经元的分化状态与突触形成能力。GAP-43通过与钙调蛋白相互作用,参与调控神经递质释放和突触可塑性,促进新生神经元整合入既有神经环路[53]。针刺可通过多种途径上调GAP-43表达。在分子层面,针刺通过下调miR-191a-5p解除对GAP-43基因的抑制,减轻缺血再灌注损伤后神经元损伤,缩小脑梗死体积[28]。针刺还可激活哺乳动物雷帕霉素靶蛋白(mTOR)信号通路,上调GAP-43和突触蛋白表达,促进皮层和皮质脊髓束轴突再生,增加脊髓轴突芽生[54]。在时空分布特征上,针刺联合康复训练可显著增加梗死周围皮层GAP-43阳性细胞数量,在治疗后不同时间点GAP-43表达水平均显著提高[55-56]。针刺还能加快启动梗死对侧皮层的保护机制,对侧皮层GAP-43阳性细胞在术后早期显著增加并长期维持较高水平,同步增加树突蛋白表达,减少远隔继发性损害[57]。

2.1.5 胰岛素样生长因子-1(IGF-1)

IGF-1是多肽类生长因子,通过与IGF-1受体结合激活PI3K-Akt-mTOR和MAPK/细胞外信号调节激酶(ERK)信号通路[58]。IGF-1促进NSCs增殖,上调细胞周期蛋白表达,加速细胞周期进程;同时抑制糖原合成酶激酶-3β活性,促进神经元分化并增强突触发生[59]。在脑卒中后,IGF-1水平升高可减轻神经元凋亡,促进神经前体细胞增殖和向神经元分化,还具有抗炎和抗氧化作用[60]。针刺对IGF-1的调控呈现时间依赖性特征。针刺治疗局灶性脑缺血大鼠时,皮层IGF-1蛋白和mRNA表达呈现动态变化,在治疗早期迅速升高,随后经历调整期,后期再次升高,且梗死侧与非梗死侧的表达模式存在时间差异,提示针刺可能通过调控IGF-1的时空表达增强早期神经保护并促进功能恢复[61]。临床研究显示,针刺治疗可显著提高患者血清IGF-1水平,改善脑血流动力学指标,促进神经功能和运动功能恢复[62-63]。

2.1.6 碱性成纤维细胞生长因子(bFGF)

bFGF通过与成纤维细胞生长因子受体结合激活Ras-MAPK和PLC-γ信号通路[64]。在神经发生中,bFGF维持NSCs的自我更新能力,促进NSCs向神经元分化,并诱导血管生成为新生神经元提供代谢支持[65]。bFGF与其他神经营养因子联合使用时产生协同效应,还具有调节胶质细胞功能、减轻神经炎性反应的作用[66]。针刺可通过多种机制上调bFGF表达并促进血管新生。针刺联合运动训练能够显著增加缺血侧脑组织NSCs标志物、bFGF及血管标志物表达,减小脑梗死面积,提高局部脑血流量[67]。此外,针刺可显著上调纹状体和皮层bFGF水平,增加脑血管开放,发挥神经保护作用[68]。在延长溶栓时间窗方面,针刺早期介入可显著提高缺血区bFGF及促血管生成因子表达,降低血管生成抑制因子内皮抑素表达,增强溶栓治疗效果[69]。临床研究证实,针刺配合药物治疗可有效提高患者血清bFGF水平,改善脑血流动力学和神经功能[62]。

2.1.7 血管内皮生长因子(VEGF)

VEGF主要通过血管内皮生长因子受体2激活PI3K/Akt和MAPK/ERK信号通路[70]。除促血管生成作用外,VEGF在神经发生中具有直接的神经营养效应,促进NSCs增殖、迁移和存活,并诱导神经元分化[71]。VEGF可增强神经前体细胞增殖和向神经元分化,促进新生神经元迁移至损伤区域并支持其存活和成熟。在血管-神经发生偶联过程中,VEGF协调新生血管与新生神经元的时空分布,构建功能性的神经血管单元[72]。针刺通过多重机制调控VEGF表达并促进血管-神经重塑。在血脑屏障调节方面,针刺可通过激活相关信号通路调控VEGF及紧密连接蛋白表达,实现血脑屏障的动态调节,既可在需要时促进治疗因子进入脑组织,又能在恢复期降低血脑屏障通透性,减轻再灌注损伤[73-74]。在血管生成调控方面,针刺激活血管生成素-酪氨酸激酶受体2通路,上调VEGF及其受体表达,优化血管生成调节因子平衡,增加脑皮层微血管密度[75]。针刺治疗还可上调脑组织缺氧诱导因子表达,增强神经血管再生,改善神经行为学表现[74, 76-77]。

2.3 针刺调控信号通路促进神经发生

2.3.1 Wnt/β-catenin信号通路

Wnt/β-catenin信号通路是调控NSCs增殖与分化的关键通路。在无Wnt信号时,胞质内由糖原合酶激酶3β(GSK3β)、酪蛋白激酶1等激酶组成的破坏复合体催化β-catenin磷酸化并标记其降解[78]。当Wnt配体与Frizzled受体及共受体低密度脂蛋白受体相关蛋白5/6结合后,该复合体被抑制,β-catenin在胞质内累积并进入细胞核,与T细胞因子/淋巴增强因子转录因子结合激活CyclinD1、NeuroD1等靶基因转录[79]。在缺血性脑卒中后,低氧环境可自发上调Wnt3a表达并下调抑制因子Dickkopf-1,激活Wnt通路促进NSCs增殖与存活,但这种自发激活的强度和持续时间有限[80]。针刺可增强Wnt/β-catenin通路活性,促进内源性神经修复。电针能够显著上调Wnt1、Wnt3a和β-catenin表达,下调Axin2表达,抑制GSK3β转录和蛋白活性[81-83],促进梗死周围皮层NSCs增殖,增加Nestin阳性NSCs及Nestin/GFAP双阳性反应性星形胶质细胞数量[81]。针刺上调叉头框蛋白G1、核受体亚家族4成员3和锌指蛋白423等神经发生相关转录因子表达,促进NSCs向神经元分化,同时抑制向星形胶质细胞的过度分化,减少胶质瘢痕形成[84-85]。针刺对该通路的调控呈现时间依赖性,β-catenin表达随治疗时间延长逐渐增加并在21 d时达到峰值,而Axin2表达持续下降[82-83]。此外,针刺预处理可通过增加磷酸化GSK3β和β-catenin水平抑制过度自噬,减小脑梗死体积,改善神经功能缺损[86]。

2.3.2 Notch信号通路

Notch信号通路在NSCs命运决定中具有关键作用。当配体与相邻细胞的Notch受体结合后,受体经γ-分泌酶切割释放Notch胞内段(NICD),进入细胞核与C启动子结合因子/重组信号结合蛋白Jκ转录因子结合,激活毛状增强子分裂(Hes)/毛状增强子分裂相关家族基因表达[87]。Hes基因编码的转录抑制因子抑制促神经基因如Mash1和Neurogenin表达,从而维持NSCs的未分化状态[88]。在缺血性脑卒中后,脑损伤诱导Notch1、Hes1和Jagged1表达上调,增加NSCs数量。Notch信号适度激活可维持NSCs的自我更新和增殖能力,促进新生神经元生成;而过度激活则可能阻碍分化或误导NSCs向反应性星形胶质细胞分化形成瘢痕[89]。针刺通过精细调控Notch通路平衡NSCs的自我更新与分化。电针治疗显著上调Notch1、NICD、Jagged1、Hes1和Hes5 mRNA及蛋白表达,促进缺血周围皮层和侧脑室下区NSCs增殖,增加Nestin/GFAP和Nestin/Vimentin阳性细胞数量,同时促进NSCs向神经元分化,增加$BrdU^+/NeuN^+$细胞数量[25, 90]。针刺通过

VEGF/Notch信号通路促进血管内皮细胞存活和血管新生[91-92]。此外,针刺预处理可通过Notch通路介导的低氧诱导因子1α(HIF-1α)上调发挥神经保护作用,抑制神经元凋亡,上调抗凋亡蛋白B细胞淋巴瘤2(Bcl-2)表达并下调促凋亡蛋白Bcl-2相关X蛋白(Bax)表达,减小脑梗死体积[93]。电针还可通过上调外泌体miR-210表达激活HIF-1α/VEGF/Notch1信号通路,促进缺氧诱导的血管内皮细胞增殖、迁移并抑制凋亡[94]。

2.3.3 PI3K/Akt信号通路

PI3K/Akt信号通路是调控NSCs存活的核心通路。当神经营养因子如BDNF、NGF或IGF-1与受体结合后,受体酪氨酸激酶募集并激活PI3K,催化磷脂酰肌醇4,5-二磷酸转化为磷脂酰肌醇3,4,5-三磷酸,进而激活Akt[95]。磷酸化的Akt激活mTOR促进蛋白质合成和细胞增殖;磷酸化促凋亡蛋白Bcl-2相关死亡促进因子和叉头框转录因子O使其失活[96];抑制Caspase-9并激活NF-κB,发挥抗凋亡效应。该通路还通过磷酸化GSK3β使其失活,稳定β-catenin并激活Wnt通路,促进NSCs增殖、迁移、分化及轴突生长[97]。

针刺通过激活PI3K/Akt通路促进缺血后神经发生。电针显著上调PI3K表达并增强Akt磷酸化水平,提高新生神经母细胞中磷酸化PI3K含量,促进NSCs增殖和分化[30, 98]。磷酸化Akt激活下游mTOR,调控自噬相关蛋白Beclin-1表达,同时下调p53表达[98]。PI3K/Akt通路通过上调BDNF/TrkB信号通路发挥神经保护作用,减轻神经功能缺损症状[30]。此外,针刺通过激活PI3K/Akt通路促进血管新生,为神经发生提供血供支持:一方面通过上调miR-142-5p抑制整合素-金属蛋白酶与血小板反应蛋白基序1表达,介导VEGF上调,激活PI3K/Akt通路并促进内皮型一氧化氮合酶释放,参与促进缺血后血管新生[99];另一方面通过上调钠钙交换体1表达,增强钙外排能力,维持钙稳态发挥神经保护作用[100]。针刺还通过调节PI3K/Akt/NF-κB通路抑制炎性反应,促进小胶质细胞从M1向M2极化,优化神经发生微环境[101]。

2.3.4 Nogo-A/Nogo受体(NgR)信号通路

Nogo-A/NgR信号通路是中枢神经系统轴突再生的主要抑制通路。Nogo-A属于髓鞘相关抑制蛋白家族,主要由少突胶质细胞产生,其Nogo-66功能区与神经元表面的NgR1受体及共受体p75NTR/富含亮氨酸重复序列和免疫球蛋白结构域的Nogo受体作用蛋白-1(LINGO-1)形成复合物,激活下游Ras同源基因家族成员A(RhoA)/Rho相关卷曲螺旋蛋白激酶(ROCK)信号级联反应,导致生长锥细胞骨架崩解和轴突生长停止[102]。在缺血性脑卒中后,Nogo-A和NgR1表达显著上调并持续数周至数月,形成抑制性微环境,阻止受损轴突再生和侧支形成,限制神经可塑性和功能代偿性重组[103]。针刺通过抑制Nogo-A/NgR信号通路促进缺血后神经发生。电针治疗显著下调脑组织和海马区Nogo-A和NgR的蛋白及mRNA表达水平,减轻髓鞘生长抑制因子对NSCs增殖分化的负性调控[104]。Nogo-A/NgR信号抑制解除为新生神经元提供了更有利的微环境,促进轴突延伸、神经元迁移和突起形成[105]。此外,针刺同步上调髓鞘碱性蛋白表达,促进新生神经元轴突再生和髓鞘形成[106]。

2.3.5 RhoA/ROCK信号通路

RhoA/ROCK信号通路是整合多种轴突生长抑制信号的关键汇聚点。当Nogo-A、硫酸软骨素蛋白聚糖或Semaphorin 3A等抑制性配体与相应受体结合后,激活鸟嘌呤核苷酸交换因子催化RhoA-GDP向RhoA-GTP转换,活化的RhoA-GTP进而激活下游效应激酶ROCK。ROCK通过磷酸化肌球蛋白轻链、LIM结构域激酶和塌陷反应中介蛋白2等底物,导致肌动球蛋白收缩、F-肌动蛋白解聚和微管不稳定,最终引起生长锥塌陷和轴突生长停止[107]。在缺血性脑卒中后,RhoA和ROCK活性显著上调,抑制轴突再生和树突发育,限制突触重塑和神经可塑性[108]。

针刺通过抑制RhoA/ROCK信号通路促进缺血后神经再生与重塑。电针治疗可下调RhoA、ROCK2及其下游效应分子肌球蛋白轻链和肌球蛋白磷酸酶靶亚基1的表达水平,解除对新生神经元轴突延伸和神经元迁移的抑制作用[109]。RhoA/ROCK通路受抑制后,肌球蛋白轻链磷酸化减少,稳定生长锥细胞骨架结构,为新生神经元提供更有利的迁移与分化微环境[110]。针刺同步上调轴突生长相关蛋白GAP-43表达,促进新生神经元突起延伸和神经网络重建[111-112]。

2.3.6 AMP活化蛋白激酶(AMPK)/PGC-1α信号通路

AMPK/PGC-1α信号通路是调控线粒体生物发生和能量代谢的关键途径。AMPK作为细胞能量感受器,通过与三磷酸腺苷(ATP)、二磷酸腺苷和单磷酸腺苷直接相互作用感知细胞能量状态。

过氧化物酶体增殖物激活受体γ辅激活因子1α(PGC-1α)是线粒体基因转录的强大调控因子,激活核呼吸因子1/2(NRF1/NRF2)和线粒体转录因子A(TFAM)等核受体,参与线粒体生物发生、糖脂代谢和氧化应激调控[113]。在缺血性脑卒中后,线粒体功能障碍和能量代谢紊乱加剧神经元死亡。AMPK激活后磷酸化PGC-1α,促进其向核内转位并与转录因子结合,上调线粒体呼吸链复合物和线粒体转录因子表达,增强线粒体生物发生和氧化磷酸化能力,为新生神经元提供能量供应[114]。针刺通过激活AMPK/PGC-1α信号通路促进线粒体生物合成,为神经发生提供能量代谢支持。电针治疗可增加AMPK磷酸化水平,上调PGC-1α表达,进而激活下游转录因子NRF1和TFAM,启动线粒体生物合成程序[115]。线粒体生物合成增强后,线粒体呼吸链复合物I活性提高,ATP生成增加,改善缺血区脑组织能量代谢障碍[116]。AMPK拮抗剂和PGC-1α抑制剂实验证实,阻断该通路可逆转针刺的神经保护效应,表明AMPK/PGC-1α是针刺作用的关键分子靶点[117]。此外,针刺通过该通路调节偶联蛋白2表达,减少线粒体氧化应激损伤,降低海马神经元凋亡[115]。

3 小结与展望

缺血性脑卒中后的神经功能恢复依赖于内源性神经发生的启动与维持。针刺作为传统中医特色疗法,通过多层次、多靶点调控神经发生过程,在卒中后神经修复中展现出独特优势。本文系统梳理了针刺促进神经发生的分子机制,揭示了针刺通过上调BDNF、NGF、GDNF等神经营养因子表达,激活Wnt/β-catenin、Notch、PI3K/Akt等关键信号通路,抑制Nogo-A/NgR和RhoA/ROCK等轴突再生抑制通路,以及调控AMPK/PGC-1α通路改善能量代谢,协同促进NSCs增殖、迁移、分化及新生神经元的轴突再生与突触整合。尽管针刺促进神经发生的研究取得显著进展,但仍面临诸多挑战。

3.1 现有研究的关键局限

首先,神经发生的功能性整合评价不足。现有研究多通过BrdU/NeuN、DCX、Nestin等标志物证实针刺可增加新生神经元数量,但缺乏对这些新生神经元功能整合的验证,其电生理特性、突触连接模式及在神经环路中的功能贡献尚不明确。其次,信号通路间的交互调控机制不明。针刺涉及的Wnt/β-catenin、Notch、PI3K/Akt等通路在神经发生中形成复杂的调控网络,但现有研究多采用单通路分析,缺乏系统性研究。针刺激活通路的优先级、激活时序以及通路间信号整合的分子机制尚不清楚,针刺同时激活多条通路时NSCs如何实现增殖-分化平衡的精确调控缺乏阐释。再次,针刺参数与神经发生特定阶段的匹配关系缺失。神经发生包括增殖、迁移、分化和整合4个连续但机制各异的阶段。不同频率、强度及穴位组合对神经发生各阶段的差异化影响缺乏系统性研究,针刺参数与神经发生时空动态的匹配关系不明,限制了精准化治疗方案的建立。

3.2 未来研究方向

第一,建立神经发生功能性评价体系。整合电生理记录、神经示踪及行为学测试等技术手段,系统评估新生神经元的电生理特性、环路连接模式及其在运动或认知功能中的作用,明确针刺诱导的新生神经元对神经环路重建的实际贡献。第二,采用多组学技术分析针刺后不同时间点的通路激活时序和强度,结合条件性基因敲除和药理学干预手段,明确各通路在针刺效应中的必要性及上下游关系,识别通路交互作用的关键节点和信号整合模式,阐明针刺如何通过多通路协同调控实现NSCs增殖与分化的动态平衡。第三,建立针刺参数优化的时空匹配模型。针对增殖、迁移、分化和整合4个阶段,系统比较不同针刺频率、强度和穴位组合的差异化效应,建立针刺参数-神经发生效率的量效关系模型,构建基于神经发生时空动态的精准针刺治疗方案。通过上述研究方向的系统推进,有望全面阐明针刺促进神经发生的作用机制和调控规律,为缺血性脑卒中的精准康复治疗提供科学依据。

利益冲突 所有作者声明不存在利益冲突。

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收稿日期:2025-10-29 修回日期:2025-12-25