·综述·

轴突可塑性在缺血性脑卒中的研究进展

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摘要 缺血性脑卒中是最常见的脑卒中类型。轴突可塑性是脑缺血后神经功能恢复的基础，这一过程受到各种生长因子、抑制因子及周围内环境调节。目前已有多种手段可通过调节轴突可塑性促进脑缺血后的神经功能恢复。本文将对轴突可塑性在缺血性脑卒中的相关研究予以综述。

关键词 缺血性脑卒中；轴突可塑性；抑制因子；生长因子

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Research Progress on Axonal Plasticity in Ischemic Stroke *LI Yan, CHEN Ya-ping, NAN Li-hong. Department of Cardiology, Fujian University of Traditional Chinese Medicine, Fuzhou 350122, China*

Abstract Ischemic stroke is the most common type of stroke. Axonal plasticity is the basis for neurological recovery after ischemia, and this process is regulated by various growth factors, inhibitory factors and the surrounding environment. In this paper, we review the research progress on axonal plasticity in ischemic stroke.

Keywords ischemic stroke; axonal plasticity; inhibitory factors; growth factors

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脑卒中包括缺血性卒中和出血性卒中，其中缺血性脑卒中（ischemic stroke，IS）是占比最高的脑卒中类型，具有致残率高、神经功能恢复困难的特点[1]。近年来研究发现，IS发生后可激活脑组织的自身修复过程，实现大脑功能和组织结构的重组，此被称为神经可塑性[2]。目前认为神经可塑性微观结构上的改变常表现为轴突再塑、树突及树突棘改变、突触数目及受体密度改变，其中脑梗死灶周围的轴突重塑是IS后结构修复及功能恢复的关键因素[3]。但内源性轴突可塑性不足以使得神经功能完全恢复，如何进一步激活轴突修复机制成为目前关注的焦点。

1 轴突可塑性与IS

IS是我国成人致残的主要原因[4]，脑缺血发生后脑组织因缺血缺氧坏死并形成梗死灶，神经网络结构破坏，导致一系列神经功能缺损症状，如运动障碍、感觉异常等。研究发现重建运动功能是卒中患者提高生活质量的决定因素[5]，IS后受损大脑通过轴突可塑性形成新的神经连接对患者运动功能的恢复有较大影响[6,7]。

轴突可传导神经元发出的电脉冲信号，向其他神经元、组织及腺体传递信息。IS发生后锥体神经元轴突发生沃勒变性，轴突的微观结构神经微丝由高度规则排列转为珠装排列，并出现淀粉样前体蛋白的聚集，轴突的基本细胞骨架遭到破坏，内部正常转运被阻断[8,9]，可引发神经功能障碍[10]。研究发现大鼠在脑梗死后轴突发芽率较对照组明显增加，同时新生轴突纤维沿梗死周围皮质发生结构重组，这提示IS后机体可通过轴突可塑性机制发挥神经功能保护作用[11]。但轴突可塑性的发挥、调控受诸多因素的影响[12]。

2 轴突可塑性的影响因素

IS发生后，神经系统轴突可塑能力受限，除了受到组织损伤周围生长因子、抑制因子的影响外，脑微血管生成以及胶质细胞激活能否为轴突可塑创造适宜的内环境也极为重要。

2.1 对轴突可塑性的有利因素

2.1.1 生长因子 在中枢神经系统发育过程中，生长因子发挥着极为重要的作用。研究表明，脑源性神经营养因子（brain derived neurotrophic factor，BDNF）、生长分化因子10（growth differentiation factor 10，GDF10）及胶质源性神经营养因子（glial cell derived neurotrophic factor，GDNF）等均可促进轴突可塑性[13]。

BDNF是脑内含量最多的神经营养因子，也是神经可塑性的关键调节因子。研究表明，当BDNF表达受到抑制时，卒中后发生的轴突重塑程度受限[14]。Charsar等[15]研究发现，BDNF可促进健侧轴突生长和5-羟色胺能纤维的萌芽，并向神经元发出靶向连接以实现轴突重塑。同时BDNF可参与多种下游通路，如可激活cAMP/PKA/p-CREB通路，该通路对于轴突的生长具有强大的调控作用，进一步研究发现α7nAchR通过激活该通路从而增强轴突可塑性并促进神经功能恢复[16]。

GDF10是转化生长因子β（transforming growth factor，TGFβ）超家族的一员，是IS发生后轴突生长和功能恢复重要调节因子[17]。Kingwell等[3]发现GDF10通过调控TGFβRⅠ和TGFβRⅡ信号通路可

促进小鼠、大鼠和人神经元轴突发芽。促红细胞生成素（erythropoietin，EPO）对IS有确切的神经保护作用，EPO能以剂量依赖性的方式促进GDF10表达，从而激活轴突重塑进而发挥神经保护作用[18]。

GDNF是TGFβ超家族成员，主要由胶质细胞和神经元产生。GDNF一方面可促进神经元存活，另一方面对轴突可塑性具有激活作用。Beker等[19]发现GDNF可诱导梗死周围及对侧轴突的可塑性，从而促使神经恢复。还有研究发现GDNF可以阻碍髓鞘相关蛋白对轴突生长的抑制作用，激活轴突可塑性[20]。

2.1.2 血管生成的有利影响 中枢神经系统的轴突可塑性是一个高能量需求的过程[21]。大脑代谢活跃，能量需求高，但脑组织不能贮存能量，需依赖持续的血液供应氧气及营养成分以维持正常的神经功能。所以血管生成可为轴突可塑性提供关键支撑底物。MRI动态监测显示血管生成和轴突可塑过程在空间和时间上呈现显著相关性，同时血管生成可提高局部脑血流量（reginal cerebral blood flow，rCBF）[22]。Liu等[23]通过制备大鼠大脑中动脉阻塞模型发现，莫罗尼昔用药3 d后可增加血管数量，同时改善rCBF，在14 d后可降低梗死面积并显著改善神经功能；当rCBF显著增加时，脑卒中后缺血边界区域的轴突可塑性得到明显改善[24]。此外，血管生成后内皮细胞可释放大量的BDNF，进一步促进轴突重塑[25]。

2.1.3 胶质细胞激活后的有利影响 胶质细胞有多种类型，其中占比最大是星型胶质细胞（astrocytes，AST），约占大脑全部细胞的20%～40%。AST激活后，对IS神经功能的恢复具有双面性。在IS中，AST能通过能量代谢、促进神经再生等途径调控大脑微环境，发挥脑保护作用[26]。脑内毛细血管约有80%的面积与AST相接触，ATS通过终足可从血液中摄取营养物质以供应给神经元；AST终足含有大量葡萄糖转运体，以葡萄糖形式可为轴突的生长和延伸提供能量[27]。AST还能分泌多种神经营养因子包括睫状神经营养因子（ciliary neurotrophic factor，CNTF）、BDNF、GDNF、EPO等，从而刺激轴突可塑能力[26, 28]。

2.2 轴突可塑性的不利因素

近年体内和体外研究都证实髓鞘是损伤后轴突再生的强力抑制剂，卒中后中枢神经系统微环境中存在的髓鞘再生抑制因子和胶质瘢痕则是轴突再塑过程中的重要障碍[29,30]。

2.2.1 髓鞘再生抑制因子 在中枢神经系统中，轴突再生抑制因子也被称为髓鞘相关抑制因子。髓鞘主要成分为髓磷脂，具有保护神经元、维护神经系统保持稳定、增强轴突传导等作用。常见的轴突再生抑制因子包括神经轴突生长抑制因子-A（neurite outgrowth inhibitor A，Nogo-A）、髓鞘相关性糖蛋白（myelin associated glycoprotein，MAG）和少突胶质细胞髓鞘糖蛋白（oligodendrocyte myelin glycoprotein，OMgp）。

在成年中枢神经系统中，当Nogo-A与相应受体结合后，对轴突再塑有极强的抑制作用[31,32]。已有体内实验证明Nogo-A可通过PirB/TrkB途径发挥对轴突的抑制作用[33]。Wang等[34]通过制备局灶性脑缺血大鼠模型，发现丹参酮ⅡA通过抑制Nogo-A/NgR1/RhoA/ROCKII/MLC信号通路，并增强神经丝蛋白200（neurofilament protein 200，NF200）和生长相关蛋白-43（growth associated protein-43，GAP43）的表达，促进轴突可塑性，实现神经功能康复。

MAG是最早被鉴定的中枢神经系统轴突生长髓鞘抑制因子。IS发生后，MAG与受体NgR1结合后可阻止神经元轴突萌芽，继而引发轴突生长锥塌陷，最终抑制神经突起生长[35]。高胤桐[36]研究发现针刺干预后MAG蛋白的表达下调可促进轴突的生长和延伸，从而促使脑缺血大鼠神经功能的恢复。

OMgp是糖基磷脂酰肌醇结合的髓鞘蛋白，在神经元和成熟少突胶质细胞中均有表达。Rosochowicz等[37]通过体外实验进一步证实OMgp可显著抑制大鼠神经元轴突可塑性。研究发现OMgp发挥这一作用是通过与受体NgR结合后改变生长锥形态，从而抑制轴突可塑性的正常发挥[38]。

2.2.2 胶质瘢痕 IS发生后，可引发炎症反应、氧化应激等，诱导星形胶质细胞增殖分化、小胶质细胞极化，并上调胶质纤维酸性蛋白（glial fibrillary，GFAP）和波形蛋白表达，从而进而促进胶质瘢痕形成。损伤区域疤痕组织含有的主要成分为硫酸软骨素蛋白多糖（chondroitin sulphate proteoglycans，CSPGs），它是阻碍轴突可塑的物理与化学屏障，也是阻碍神经功能恢复的重要因素[39]。Xu等[40]发现转录因子SOX9通过阻断来自CSPGs和Nogo的信号途径后，卒中后轴突发芽水平明显提升，同时运动功能得以改善。此外有学者经进一步研究发现CSPGs可与NgR等多种膜受体结合可引起Rho/ROCK信号通路的激活，引发细胞骨架与生长锥的收缩与塌陷，进而导致轴突可塑过程受阻[41]。

3 调节轴突可塑性治疗IS的相关策略

3.1 针刺治疗

针刺是中国传统医学的经典治疗方法，在临床中运用针刺疗法治疗脑缺血、恢复神经功能的作用已得到充分肯定。唐雅妮等[42]研究表明，针刺腧穴能下调急性脑缺血大鼠血清RhoA、ROCKⅡ含量及梗死区脑组织RhoA、ROCKⅡ表达，有效抑制轴突生长抑制因子的表达，从而促进神经功能恢复。此外有研究发现电针百会、足三里能提高损伤周围神经的再生速度和GAP43的水平，显著促进再生轴突和靶细胞的功能联系[43]。Deng B等[44]的研究表明电针组NF200和GAP43表达水平显著高于模型组，提示电针能促进缺血后轴突的出芽和形成。

3.2 中药治疗

中药作为临床常用的治疗手段之一，具有多组分、多层次，多靶点治疗的特点，对于改善IS患者的临床症状具有显著疗效。补阳还五汤是治疗卒中的经典方剂，有研究发现补阳还五汤可上调GAP43和BDNF的蛋白表达，并调控PI3K/Akt和Jak2/Stat3经典信号通路促进突起的增殖和分化以发挥神经保护作用[45,46]。Nan等[47]发现栝楼桂枝汤可调控Nogo-A及NgRl在大脑损伤区域的表达，通过抑制Rho/ROCK信号通路的激活、稳定微管结构发挥神经保护作用。

3.3 康复训练

康复训练作为经典有效的治疗策略之一，可增强IS受损周

围神经元功能重塑。Li C等[48]研究发现通过康复训练后可通过抑制轴突生长抑制因子RhoA、NgR1、ROCK蛋白表达，显著改善神经功能损伤程度。同时康复训练可诱导内环境神经生长因子的表达，参与轴突可塑过程中内环境的调节[49]。

4 小结与展望

轴突可塑性已经成为IS后康复的重要依据和理论基础，与溶栓和神经保护相比，以轴突可塑性为基础的神经恢复治疗具有更长的时间窗。目前已有研究表明针刺治疗、中药治疗、康复训练等治疗途径通过调节轴突可塑性对IS损伤具有良好的治疗前景。深入研究脑缺血后轴突可塑性的影响因素，发现新的积极有效的干预手段，对IS的治疗和康复具有重大意义。

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