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·专题·

电针对脊髓损伤后轴突再生影响的研究进展

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[摘要] 脊髓损伤后运动功能恢复一直是医学界面临的重大难题，而轴突再生是脊髓损伤后运动和神经功能恢复的基础和目标。目前研究认为，电针对脊髓损伤后轴突再生的作用明确。本文主要从胶质瘢痕的形成、轴突生长抑制因子的作用、神经营养因子的分泌以及神经元内在生长状态等方面总结电针对脊髓损伤后轴突再生的作用。

[关键词] 脊髓损伤；轴突再生；电针；胶质瘢痕；综述

Research Progress of Electroacupuncture on Axonal Regeneration after Spinal Cord Injury (review)

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Abstract: The restoration of motor function after spinal cord injury is a major problem in the medical field, in which axonal regeneration is the basis and goal of motor and neurological recovery. Researches showed that electroacupuncture was effective on axonal regeneration after spinal cord injury. In this paper, the mechanisms were summarized from the aspects of the formation of glial scar, the role of axon growth inhibitory factor, the secretion of neurotrophic factor and the growth status of neurons.

Key words: spinal cord injury; axon regeneration; electroacupuncture; glial scar; review

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脊髓损伤(spinal cord injury)是一种严重致残性疾病，给患者心理和身体带来严重伤害。虽然目前临床上不能通过有效治疗使脊髓损伤后功能完全恢复，但是许多动物实验研究表明，脊髓损伤后功能有不同程度的恢复。轴突通过再生的方法，与靶细胞可以形成功能性的突触，这是脊髓损伤后运动和神经功能恢复的基础和目标。特殊情况下，轴突可以发芽、生长和延伸，通过这些方法，与靶细胞重新建立联系，实现神经的再次支配，进而使运动及神经功能恢复。

一般来说，脊髓损伤后，损伤轴突再生或/和芽生并不少见，但由于胶质瘢痕的形成、轴突生长抑制因子的存在、神经营养因子分泌的不足以及神经元内在生长状态等因素的影响，神经损伤后轴突再生比较困难。近年来人们在不断加强脊髓损伤后轴突再生的机制及其修复的实验性治疗的同时，开始注意采用传统中医学的理论和技术方法，探讨其对脊髓损伤后轴突再生可能作用及机制，而其中电针对脊髓损伤的研究备受关注。本文主要就电针对损伤后轴突再生的影响进行综述。

1 电针对胶质瘢痕形成的影响

脊髓损伤后，星形胶质细胞会增生性地生长，使脊髓在结构形态上保持完整性，同时对神经组织也会起到一定的营养和支持作用。后期，星形胶质细胞持续被激活，分泌或合成抑制性的因子；同时胶质细胞过度增生，会在损伤区形成致密的胶质瘢痕。通过干细胞移植等方法，能使轴突有效再生，但是再生的轴突接触到致密的胶质瘢痕时，其轴突的再生就会受到抑制，停止生长[1]。胶质瘢痕通过机械性屏障作用抑制轴突的再生及延长[2]，阻止脊髓损伤后的功能恢复。同时胶质瘢痕也可以通过压迫局部微血管，阻碍损伤部位血液的供应[3]，影响功能恢复。

胶质纤维酸性蛋白(glial fibrillary acidic protein, GFAP)与星

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形胶质细胞的活化程度密切相关，是胶质瘢痕形成的主要标志[4]。当GFAP表达下降，胶质瘢痕的形成会受到明显抑制，轴突的芽生会明显增强[5]，这不仅说明GFAP对胶质瘢痕的重要性，同时也证实通过抑制GFAP的表达能有效缓解胶质瘢痕的形成，对轴突的再生有很好的促进作用。

脊髓损伤后，电针刺激能有效降低损伤部位GFAP含量，阻止轴突变性，改善轴突再生[6]，可能与阻止胶质瘢痕的形成有关。电针刺激足三里和内庭，可使白质中的空洞减少，抑制胶质细胞增生，促进肢体功能的恢复[7]。这些研究提示，电针刺激可以通过有效降低GFAP含量，抑制星形胶质细胞过度增生，从而减少胶质瘢痕对轴突再生的阻碍作用，同时也创造出对轴突再生有利的微环境，促进轴突再生。

2 电针对轴突生长抑制因子的作用

脊髓损伤后会分泌大量抑制因子：GFAP、硫酸软骨素蛋白聚糖(chondroitin sulfate proteoglycans, CSPGs)、硫酸角质素蛋白多糖(keratin sulfate proteoglycan, KSPGs)、腱糖蛋白及斥性轴突导向分子(repulsive axon guidance molecules, RGM)等，阻碍轴突的有效再生。目前研究比较多的是CSPGs。

在中枢神经系统(central nervous system, CNS)中，CSPGs主要参与构成细胞外基质，对轴突的生长和延伸有明显的抑制作用。在CSPGs大量聚集的部位，会形成对轴突的生长有阻碍作用的屏障结构，当使用硫酸软骨素酶消除高表达的CSPGs时，神经轴突会明显生长[8]，同时伴随运动及感觉功能的恢复[9]。

脊髓损伤后，星形胶质细胞分泌的CSPGs大量聚集在损伤部位，参与胶质瘢痕的形成，促使轴突末端生长锥塌陷[10-11]，严重影响轴突的再生及髓鞘化，使轴突和神经功能的再生受到明显抑制[12-13]。Davies等[14]将生长的神经元轴突移植到大鼠脊髓损伤部位，当生长的轴突未与CSPGs接触时，轴突生长未见停止；若轴突与之接触则轴突就会停止生长，这充分表明轴突再生受到CSPGs抑制，同时其神经功能的恢复也受到抑制。而在脊髓损伤后给予电针刺激，会明显降低CSPGs的表达[6]，减弱CSPGs对轴突再生的抑制作用，明显改善轴突再生，促进功能恢复。

3 电针增强神经营养因子的表达

神经营养因子是一种对神经元的存活和生长至关重要的蛋白质分子，通过其受体进入轴突，导致不同的信号通路激活或抑制细胞，调节蛋白表达，发挥其对神经元的保护作用[15]。神经营养因子也可以通过调节突触可塑性[16-17]，促进损伤轴突的有效再生[18]，完成对脊髓损伤后功能恢复的作用。神经营养因子在中枢神经损伤后会反应性增多，能有效改善局部微环境，积极预防继发性损伤。虽然损伤后神经营养因子会明显增高，但仍然不能满足损伤后功能恢复的需要。目前研究较多的有神经生长因子(nerve growth factor, NGF)、脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)和神经营养素-3 (neurotrophin-3, NT-3)。

NGF是一个典型的神经营养因子，在维持神经元的存活及促进轴突延伸方面有显著的效果[19-20]。电针能促使NGF及NGF高亲和力受体TrkA表达增高[21]，通过上调神经营养因子的表达，促进神经元功能的恢复[22]。猫背根神经节受损后，电针刺激可以使受损神经元中NGF含量明显增加，有助于损伤后的功能恢复[23]。电针刺激环跳穴，可以增加NGF的含量，调节Fos的表达，促进神经损伤的修复[24]。

BDNF是一种具有促进神经元存活及分化、诱导轴突再生的神经营养因子[25-26]。Jin等[27]将能表达BDNF的细胞移植到脊髓损伤部位4~5周后发现轴突生长距离较对照组明显增长；通过皮质脊髓束的顺行示踪发现，外源性BDNF可以促进损伤部位轴突的明显再生[28]；BDNF也可以通过介导脊髓的再髓鞘化，对损伤部位轴突有一定的促进作用[29]。督脉电针能诱导BDNF蛋白表达增加，对神经元的存活及皮质脊髓束的修复有积极的治疗作用，促进脊髓损伤后的功能恢复[30]。与非电针组相比，电针组能增加BDNF在小、中神经元中的表达[23]，促进其神经再生。

NT-3对于脊髓灰质神经元，特别是腹侧角运动神经元的存活和正常功能，发挥重要作用[31]，对损伤后的神经元也有积极的治疗作用，促进轴突的有效再生[32-33]。Huang等[34]研究表明，电针通过上调NT-3的表达，促进内源性少突胶质前体细胞(oligodendrocyte precursor cells, OPCs)增殖和分化，抑制损伤脊髓脱髓鞘，促进髓鞘的有效再生。Mo等[35]认为，电针刺激大椎和命门穴能上调NT-3的表达，对神经元的存活及轴突再生有明显的促进作用[15]，可能是通过防止能合成和分泌NT-3的某些细胞的凋亡完成的[35]。电针治疗能增加NT-3的表达，促进NT-3受体基因修饰的间充质干细胞向少突胶质细胞样细胞分化，改善脊髓脱髓鞘病变[36]，对脊髓损伤有神经保护作用[37]。

4 电针改善神经元内在生长状态

CNS损伤后轴突再生和修复困难的主要原因是神经元生长状态不同。与周围神经神经元相比，即使将中枢神经神经元种植在良好的生长底物上，CNS神经元轴突再生能力也相对较弱。在神经元内在生长状态不变的情况下，仅仅通过阻断胶质瘢痕及其他微环境的抑制信号，无法使神经元髓鞘有效再生[38]。提高神经元内在生长状态已成为脊髓损伤后轴突再生的热点，近几年研究比较多的是如何通过提高环磷酸腺苷(cyclic adenosine monophosphate, cAMP)/蛋白激酶A (protein kinase A, PKA)水平、抑制Rho/Rho相关卷曲螺旋形成蛋白激酶(Rho associated coiled-coil forming protein kinase, ROCK)信号传导促进损伤后轴突的再生。

cAMP是对哺乳动物神经元存活和分化、神经突长度及神经导向有调节作用的细胞内信号[39]。cAMP通过激活PKA完成对神经突起和生长锥的调节作用[40-41]。采用cAMP类似物培养神经细胞，能促进神经元存活及神经突起生长[42]。适宜浓度的cAMP可以使生长锥保持运动，并防止崩解[43]，进而对神经突生长有明显的促进作用[44]。神经损害后，当细胞内cAMP水平高表达时，PKA能够被激活，从而抑制各种信号传递，抑制轴突再生[45-46]。有研究表明，电针能通过降低cAMP和PKA活

化[47]，调节cAMP/PKA表达水平[48]，促进损伤后轴突的再生[45]。

Rho/ROCK信号通路在介导神经轴突再生方面有重要作用。由于Ras同源基因A (Ras homolog gene A, RhoA)有控制细胞骨架重组及动力学的能力，所以其在负调控轴突生长方面起关键性作用，被作为众多轴突再生抑制剂的主要靶标[49]。在培养背根神经元过程中，可以通过激活ROCK来抑制神经突的生长[50]。ROCK在轴突生长和微管组装中具有重要作用[51]。CNS损害后所有髓鞘相关抑制因子通过各自相关信号途径，最终都作用于RhoA，激活ROCK，对轴突再生产生抑制性作用[52]。研究表明RhoA/ROCK信号通路既可以通过调节激动蛋白致使生长锥塌陷，也可以调节细胞骨架中的微管及中间丝[53]来发挥其抑制轴突的作用。

脊髓损伤后，电针大椎和命门穴治疗7 d，大鼠运动功能改善，脊髓凋亡细胞量下降，同时伴有RhoA和Nogo-A蛋白及mRNA下降，说明电针通过下调RhoA和Nogo-A的表达促进脊髓损伤的恢复[54]。电针刺激可以增强轴突再生和皮质脊髓束的投射，可能是通过调节RhoA和生长相关蛋白-43 (growth-associated protein-43, GAP-43)的表达[55]，改善神经功能的恢复。

综上所述，电针从胶质瘢痕形成、轴突生长抑制因子、神经营养因子缺乏以及神经元内在生长状态等分子机制方面促进脊髓损伤后轴突的再生，对改善脊髓损伤后功能恢复有一定疗效，可作为脊髓损伤后治疗的一个重要方向，但其临床效果有待进一步研究。

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