

# 电针治疗神经病理痛机制的研究进展

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**【摘要】** 神经病理痛严重影响患者的生存质量,目前的治疗手段面临镇痛效果不佳、副作用大的难题。近年来,基于电针能缓解神经病理痛的临床证据,对于电针在神经系统不同水平的调节机制进行了广泛的探索,其中包括对离子通道活性、促炎/抑炎因子平衡、胶质细胞激活及痛相关脑环路等的调节。本文总结了近期对于电针镇痛的外周、脊髓及脑各个层面机制的研究,为进一步探究电针镇痛的原理提供线索。

**【关键词】** 神经病理痛; 电针; 细胞因子; 信号通路; 脑环路

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## Research progress on the mechanisms of electroacupuncture analgesia in neuropathic pain

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**【Abstract】** Neuropathic pain seriously affects the quality of patients' life. Current treatments are challenged by limited analgesic effect and great side-effect. In recent years, based on clinical evidence that electroacupuncture (EA) could ameliorate neuropathic pain, the mechanisms of EA analgesia at different levels of the nervous system have been extensively investigated, including the regulation of ion channel, the balance of pro-inflammatory and anti-inflammatory cytokines, the activation of glia and the pain-related brain circuitry. This review summarized recent studies on the mechanisms of EA analgesia at peripheral, spinal and brain levels, hoping to provide clues for further investigation of the theory on EA analgesia.

**【Key words】** neuropathic pain; electroacupuncture; cytokine; signal pathway; brain circuitry

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据最近统计,慢性神经病理痛在全球人口中的发生率达到6.9%~10%,对患者生活和社会经济造成重大负担<sup>[1]</sup>,而目前临床上尚无很好的治疗手段,现常用的治疗药物仍以阿片类、抗抑郁类、抗癫痫类等药物为主<sup>[2]</sup>,这些药物常常效果不佳、针对少部分患者有效且伴有副作用<sup>[3]</sup>。不同诱因可导致神经病理痛,如切断或损伤神经、代谢综合征、病毒感染、自体免疫反应等,表现症状包括阵发性或持续性自发痛,触、冷、热痛觉超敏(allodynia)及痛觉过

敏(hyperalgesia)<sup>[3-5]</sup>,并且很多转为慢性疼痛,在许多患者中还会引发焦虑、抑郁等情绪障碍的共病<sup>[6-7]</sup>,给患者带来巨大的痛苦。

针刺疗法起源于中国,在亚洲国家有悠久的临床应用基础,对于多种疾病被证实有较好的疗效,其中包括对慢性疼痛的治疗。在基础研究中,大量证据表明电针可以有效缓解多种神经病理痛动物模型中的触诱发痛及冷、热痛敏,包括模拟外周神经压迫或切断损伤的结扎或切断类模型、紫杉醇化

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疗痛、糖尿病神经病理痛、疱疹后遗神经病理痛等模型<sup>[8-13]</sup>。

由于近年来电针治疗神经病理痛的机制研究积累了大量重要的进展,但尚未见有文献对其归纳总结,本文对多种神经损伤模型中电针镇痛的机制研究进行总结,并对存在于外周、脊髓至高级中枢各个层面的镇痛机制进行综述。

### 外周机制

**调节离子通道的表达与活性** 神经病理痛的发病机制之一是外周神经的病变,其中初级传入神经上离子通道的活性和表达量的改变可导致异位放电,进而产生痛觉敏化。已知瞬时感受器电位香草酸受体(transient receptor potential vanilloid, TRPV)家族离子通道参与介导各种疼痛,包括神经病理痛。一项最近的研究中发现电针可以下调紫杉醇化疗痛模型中背根神经节(dorsal root ganglion, DRG)过表达的TRPV1通道,并可抑制其功能活性<sup>[14]</sup>。在另一项研究中曾观察到类似的现象:对脊神经结扎模型(spinal nerve ligation, SNL)大鼠进行电针治疗,在结扎神经前后的未受损DRG中TRPV1的过表达均受到抑制<sup>[15]</sup>。

在三叉神经病理痛模型中,连续电针14天可显著减少半月神经节中超极化激活的环核苷酸门控阳离子通道(hyperpolarization-activated cyclic nucleotide-gated channel, HCN)家族通道的表达,而该通道可通过内向电流诱发神经病理痛的异位放电<sup>[11]</sup>。

**调节外周促炎/抑炎细胞因子的平衡** 不同的神经损伤模型中,在mRNA和蛋白水平均观察到电针对DRG中促炎细胞因子IL-1 $\beta$ 和IL-6的抑制效果,而2 Hz低频电针可以上调神经损伤后表达降低的IL-10<sup>[16-18]</sup>,这种对于DRG促炎/抑炎细胞因子平衡的调节可有效缓解疼痛。

**对外周其他通路的调节** 由既往研究已知DRG中ATP门控的P2X3型受体(ATP-gated P2X3 receptor, P2X3R)在慢性压迫性损伤模型(chronic constriction injury, CCI)、SNL、糖尿病神经病理痛等模型中表达增加,并促进痛觉信号向中枢的传递,而对于这些模型给予电针均可部分甚至完全反转P2X3R的上调,进而发挥镇痛功效<sup>[19-20]</sup>。

在化疗痛的发展中观察到核因子E2相关因子2(nuclear factor erythroid 2-related factor 2, Nrf2)/

抗氧化反应序列元件(antioxidant response element, ARE)抗氧化通路受到破坏,外周氧化应激产物堆积引发痛敏;而电针可以修复Nrf2/ARE的活性,从而抑制超氧化物歧化酶(superoxide dismutase, SOD)等氧化产物的上调,缓解神经病理痛<sup>[13]</sup>。

在糖尿病神经病理痛模型中,电针能下调坐骨神经中葡萄糖调节蛋白78(glucose-regulated protein 78, GRP78)和caspase-12,显著抑制外周神经细胞的凋亡,表现出神经保护作用<sup>[12]</sup>。

### 中枢机制

**抑制脊髓胶质细胞激活** 近些年来,大量对于电针镇痛机制的研究涉及脊髓胶质细胞活性的调节,其中通过多种手段检测到电针后星形胶质细胞的特异性标记物胶质纤维酸性蛋白(glial fibrillary acidic protein, GFAP)和小胶质细胞标记物离子钙接头蛋白抗原(ionized calcium-binding adaptor molecule 1, Iba-1)、分化抗原簇分子11b(cluster of differentiation molecule 11b, CD-11, 又名OX-42)、跨膜蛋白119(transmembrane protein 119, TMEM119)等在mRNA及蛋白水平的下调<sup>[8-9, 21-24]</sup>。在各种模型上均观察到一致的证据,证明电针可以通过抑制星形胶质细胞和小胶质细胞的病理激活发挥镇痛作用<sup>[8, 10, 25-26]</sup>。

小胶质细胞中的转录因子干扰素调节因子8(interferon regulatory factor 8, IRF8)和表面趋化因子受体CX3CR1对小胶质细胞激活发挥重要作用,而电针可以抑制选择性神经损伤模型(spared nerve injury, SNI)中这些分子的过表达<sup>[27]</sup>。另有研究表明,电针可以抑制SNI和化疗痛模型中脊髓Toll样受体4(toll-like receptor 4, TLR4)/髓样分化因子88(myeloid differentiation factor-88, MyD88)/核转录因子 $\kappa$ B(nuclear factor  $\kappa$ B, NF- $\kappa$ B)通路的激活,该通路位于小胶质细胞<sup>[21, 28]</sup>。电针还能下调脊髓中高迁移率族蛋白B1(high mobility group box 1, HMGB1),该分子能通过与小胶质细胞表面跨膜受体TLR4结合激活小胶质细胞,并参与介导神经病理痛的发展<sup>[29-30]</sup>。电针抑制星形胶质细胞激活的作用被证实可由腺苷酸A1受体介导,鞘内给予特异性拮抗剂阻断A1受体可以反转电针对星形胶质细胞的抑制,并抵消电针的镇痛效果<sup>[31]</sup>。

电针对神经损伤后小胶质细胞、星形胶质细胞病理性激活的抑制作用将进一步对胶质细胞中的痛

相关分子及通路产生负向调节,如丝裂原活化蛋白激酶 p38 (p38 mitogen-activated protein kinase, p38 MAPK) 通路等<sup>[24]</sup>;而一些介导胶质细胞-神经元的痛相关通路也受到抑制,如脑源性神经营养因子 (brain-derived neurotrophic factor, BDNF)/原肌球蛋白相关激酶受体 B (tropomyosin-related kinase receptor B, TrkB) 通路等<sup>[26]</sup>。

**调节脊髓炎症因子** 有证据表明,电针 14 天可以显著降低化疗痛大鼠脊髓中 IL-1 $\beta$  和 TNF- $\alpha$  的蛋白含量<sup>[21]</sup>。在 SNI 和 CCI 模型中,脊髓 IL-1 $\beta$  在 mRNA 及蛋白水平的上调均被电针有效抑制<sup>[22, 31-32]</sup>,SNL、CCI 模型中 IL-6 蛋白在给予电针后显著下调<sup>[23, 31]</sup>。对于电针抑制炎症因子的机制,有研究发现电针能通过抑制脊髓 P2X7 型离子通道阳性的小胶质细胞激活从而减少 IL-18 和 IL-1 $\beta$  的合成与释放<sup>[33]</sup>,而星形胶质细胞 A1 受体参与介导电针对 TNF- $\alpha$  的调节<sup>[31]</sup>。

电针对 SNI 损伤后脊髓抑炎因子 IL-10 的表达与释放有促进作用,且阻断 IL-10 可以翻转电针的镇痛效果,而进一步观察证实电针仅上调表达在小胶质细胞的 IL-10,而对星形胶质细胞中的 IL-10 无显著影响<sup>[34]</sup>。本实验室在小鼠足跖切口痛模型上观察到电针后 IL-10 mRNA 及蛋白水平上调,鞘内阻断 IL-10 能翻转电针对脊髓 LTP 的抑制和对机械痛敏的缓解,提示 IL-10 是电针发挥镇痛作用的重要靶点之一<sup>[35]</sup>。

**激活内源性阿片系统** 对于电针激活内源性阿片肽系统的研究之前有大量报道,如低频 (2 Hz) 和 高频 (100 Hz) 电针可分别通过体内的  $\mu$ 、 $\delta$  阿片受体和  $\kappa$  受体介导镇痛<sup>[36]</sup>,而低频电针的镇痛效果较高频更为显著<sup>[37-39]</sup>,说明  $\mu$ 、 $\delta$  系统可能在镇痛中发挥更大的作用。最新研究表明,电针通过上调脊髓 IL-10/ $\beta$ -内啡肽通路缓解 SNL 神经病理痛<sup>[34]</sup>。在疱疹后遗神经病理痛模型中发现低频电针可通过激活  $\mu$  阿片受体,降低脊髓轴突导向因子-1 (Netrin-1) 及其受体结肠癌缺失蛋白 (deleted in colorectal cancer, DCC) 的表达,进而形成抑制传入神经出芽的脊髓环境,减轻触诱发痛<sup>[40]</sup>。

**抑制脊髓水平痛相关信号通路** 在神经病理痛的发展过程中,已知一些脊髓水平的信号通路如 c-Jun 氨基末端激酶 (c-Jun N-terminal kinase, JNK)/c-Jun、细胞外调节蛋白激酶 1/2 (extracellular

regulated protein kinases 1/2, ERK1/2)、环磷酸腺苷 (cyclic adenosine monophosphate, cAMP)/蛋白激酶 A (protein kinase A, PKA)/环磷腺苷效应元件结合蛋白 (cAMP-response element binding protein, CREB)、L-精氨酸 (L-arginine, L-Arg)/一氧化氮 (nitric oxide, NO)/环磷酸鸟苷 (cyclic guanosine monophosphate, cGMP) 通路显著激活,这些通路被证实参与病理状态下痛觉敏化的形成<sup>[41-44]</sup>。而大量研究<sup>[43-46]</sup>表明,电针可以通过对脊髓痛相关分子通路的调节起到镇痛作用。在吗啡引发神经病理痛的模型中,电针激活脊髓大麻素 I 型受体 (cannabinoid-type 1 receptor, CB1),进而抑制下游 ERK1/2 通路<sup>[47]</sup>。电针能降低 CCI 大鼠脊髓 ERK1/2 和 P2X3R 的蛋白水平,而特异性阻断 ERK1/2 也可导致 P2X3R 的下调,提示电针可能通过调节 ERK1/2 通路降低 P2X3 受体表达,从而影响痛信号的传递<sup>[48]</sup>。

**对痛相关脑区及脑环路的调节** 对电针镇痛的早期研究集中于探索外周和脊髓机制,而近些年有更多研究关注电针对病理痛状态下感觉、情绪与认知相关脑区及脑环路的影响。Ma 等<sup>[49]</sup>通过建立臂丛神经损伤模型 (brachial plexus avulsion injury, BPAI),利用 fMRI 成像建立全脑连接模型,根据以往 fMRI 数据选定躯体感觉皮层 S1、下丘脑、杏仁核及其间的双向投射为关注区域 (region of interest, ROI),经比较分析发现,长期电针使下丘脑和杏仁核向 S1 的有效投射减弱,从而一定程度阻断了皮层-边缘系统间双向投射介导的痛信号放大和维持。

另一在 BPAI 模型中的研究<sup>[50]</sup>运用 PET/CT 成像,以 18F-氟代脱氧葡萄糖 (18F-fluorodeoxyglucose, 18F-FDG) 显示脑区代谢活性,在电针 4 周后检测显示,对侧感觉及运动皮层,双侧中脑导水管周围灰质 (periaqueductal gray, PAG)、对侧扣带回及岛叶 (与痛相关),对侧眶额叶皮层和同侧的腹侧海马 (与情绪、认知相关) 均表现出活性改变。

对 CCI 后 PAG 和海马脑区兴奋/抑制性递质系统的研究发现,给予电针后 PAG 和海马的  $\gamma$ -氨基丁酸 ( $\gamma$ -aminobutyric acid, GABA) 受体表达增加,同时海马中兴奋性递质谷氨酸下调,而 PAG 中抑制性递质 GABA 下调<sup>[51]</sup>。另有研究显示,电针通过作用



于腹外侧 PAG (ventrolateral periaqueductal gray, vPAG) 中谷氨酸能及 GABA 能神经元上的 CB1 受体,促进 vPAG 脑区的激活以加强对痛觉的下行抑制<sup>[52]</sup>。这些结果提示电针对痛感觉与情绪、认知高级中枢的调节是介导电针镇痛的一个重要机制,值得更深入的研究。

**结语** 电针可通过对神经病理痛形成和发展中涉及的各个环节实现整体调控,包括外周传入神经、脊髓、脑和免疫系统等等,多种机制形成复杂的网络并相互影响。在各个层面,电针主要通过调动人体内源的修复、抑制性机制(包括抗氧化机制、抑制细胞因子、GABA 能抑制性系统、PAG 等下行抑制相关脑区),并同时抑制病理状态下产生的过度激活(兴奋性离子通道、促炎因子、胶质细胞激活、兴奋性信号通路及痛相关脑区的激活),通过对机体系统“正”“负”平衡的调节起到治疗神经病理痛的效果。

随着对电针镇痛的分子、细胞及环路机制的探索不断加深,将为针刺治疗神经病理痛的临床推广提供更加完善的理论基础。而对电针镇痛靶点的理解,为电针与其他治疗手段的协同应用提供了支持。

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