

针刺保护肠道屏障干预帕金森病的机制研究进展

沈歆玥¹, 石佳添², 朱悦扬¹, 张昕玥³, 吴焕淦⁴, 崔花顺¹

(¹上海中医药大学附属曙光医院, 上海 201203; ²上海市浦东新区中医医院, 上海 201299;

³上海中医药大学附属龙华医院, 上海 200032; ⁴上海市针灸经络研究所, 上海 200030)

【摘要】 帕金森病(PD)是全球第二大神经退行性疾病,近年来,越来越多的研究发现PD的发病与肠脑轴紊乱密切相关,其中肠道屏障损伤被视为关键的起始环节。本文综述了针刺通过多靶点机制保护肠道屏障,从而干预PD的研究进展。证据表明,针刺能重塑肠道菌群平衡,增加短链脂肪酸、减少脂多糖;上调紧密连接蛋白(闭锁小带蛋白-1、闭合蛋白)与黏蛋白(黏蛋白2)表达,直接加固肠道物理屏障;同时有效清除结肠内异常聚集的 α -突触核蛋白,并抑制NOD样受体相关蛋白3、核转录因子 κ B通路以减轻肠道炎症反应。这些机制协同作用,共同维护肠道屏障完整性,阻断了从肠道向大脑的病理信号传递。

【关键词】 针刺;帕金森病;肠道屏障;肠脑轴;机制;综述

Research progress on the mechanism of acupuncture in protecting the intestinal barrier to intervene in Parkinson's disease

Shen Xinyue¹, Shi Jiatian², Zhu Yueyang¹, Zhang Xinyue³, Wu Huangan⁴, Cui Huashun¹ (¹Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China; ²Shanghai Pudong Hospital of Traditional Chinese Medicine, Shanghai 201299; ³Longhua Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai 200032; ⁴Shanghai Research Institute of Acupuncture and Meridian, Shanghai 200030)

【ABSTRACT】 Parkinson's disease (PD) is the second most common neurodegenerative disorder worldwide. Accumulating evidence from recent years indicates a strong association between PD pathogenesis and gut-brain axis dysfunction, with impairment of the intestinal barrier being recognized as a critical initiating factor. This review summarizes current research on the multi-target mechanisms through which acupuncture protects the intestinal barrier and thereby intervenes in PD progression. Evidence suggests that acupuncture can restore gut microbiota homeostasis by increasing short-chain fatty acids and reducing lipopolysaccharide levels; upregulate the expression of tight junction proteins (zonula occludens-1, occludin) and mucin (Muc 2), thereby directly reinforcing the intestinal physical barrier; effectively clear aberrant α -Syn aggregates in the colon and suppress the NOD-like receptor 3 and nuclear factor κ B pathway to alleviate intestinal inflammation. These mechanisms act synergistically to maintain intestinal barrier integrity and block the transmission of pathological signals from the gut to the brain.

【KEYWORDS】 Acupuncture; Parkinson's disease; Intestinal barrier; Gut-brain axis; Mechanism; Review

帕金森病(PD)是一种以中脑黑质中 α -突触核蛋白(α -Syn)异常聚集,引发多巴胺能神经元死亡为主要病理表现的中枢神经退行性疾病^[1]。近年来的研究逐渐揭示,肠脑轴机制在PD的发病过程中具有重要作用。2003年,Braak等^[2]基于对PD患者与无症状个体脑组织的尸检比较,首次提出PD可能起源于胃肠道的假说,认为病理过程可能沿迷走神经的内脏运动投射细胞,经由无髓节前纤维进入中

枢神经系统。随后在2006年,该团队在5例PD尸检病例的黏膜下迈斯纳丛神经元中检测到 α -Syn复合物——路易小体,进一步证实了外周病理的存在,为肠脑轴假说提供了组织学支持^[3]。2014年,Holmqvist等^[4]将PD患者脑裂解液中的 α -Syn及不同构型的重组 α -Syn注射至大鼠肠壁,观察到其可自肠道经迷走神经轴突逆行运输至脑干迷走神经背运动核,这一结果为“ α -Syn可自外周组织(如胃

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通信作者:崔花顺, E-mail:huashunchoi@126.com

肠道)经由迷走神经途径向大脑传播”提供了直接实验证据。2020年,Horsager等^[5]通过多模态成像进一步支持了如下观点:PD可根据 α -Syn最初聚集的部位分为“大脑优先”和“身体优先”两个亚型。在“身体优先”的亚型中, α -Syn病理起源于肠道或外周自主神经系统,然后扩散到大脑。上述系列研究均提示,肠道可能是PD发病的起源部位之一。

肠道屏障是功能复杂的多层结构,也是物质进出的一扇大门,在生理及病理条件下均发挥着至关重要的作用^[6]。在生理条件下,肠道屏障呈半透性,允许部分抗原通过黏膜,促进与免疫系统的相互作用^[7]。在病理条件下,炎性细胞因子的释放、肠道菌群与肠上皮细胞的相互作用及免疫细胞穿越肠屏障等因素均可导致肠道屏障完整性受损,增加肠道通透性^[8]。研究发现,长期的通透性功能障碍可能导致慢性炎性反应和神经元损伤^[7]。结合PD小鼠模型和人类PD样本肠道通透性的研究,有学者提出肠道通透性和 α -Syn的聚集可能存在相关性^[9]。因此,我们认为,肠道屏障或许可以作为一个新的治疗靶点,对PD的发病与进展进行干预。

针刺具有多靶点、多途径治疗疾病的特性,多个研究团队^[10-15]证明其在PD步态失调、骨骼肌疼痛等运动症状及便秘、失眠、焦虑、吞咽障碍等非运动症状的改善方面具有显著疗效。基于既往研究,我们推测针刺可能主要通过以下途径发挥保护肠道屏障的作用,从而实现防治PD的目的:(1)调节肠道菌群及其代谢产物[如短链脂肪酸(SCFAs)、脂多糖(LPS)];(2)维护肠道黏蛋白及紧密连接(TJs)结构;(3)清除结肠内异常聚集的 α -Syn;(4)减轻肠道炎性反应。本文通过对现有研究结果进行系统归纳与整理,以期为该领域的后续深入研究与临床转化提供理论参考与方向指引。

1 肠道屏障破坏与PD关系的研究现状

肠道屏障主要由黏液层、肠道上皮屏障和肠道血管屏障组成,具有促进营养吸收及防止病原体进入的功能^[6]。黏液层作为管腔内容物和底层肠道层之间的物理屏障,塑造肠道微生物群,调节肠道吸收和分泌功能及肠道通透性^[6]。肠道上皮屏障在允许营养物质、电解质和水通过的同时,能够有效防止病原体入侵^[16]。其中由围绕上皮细胞顶端的连续网状蛋白质网络形成的结构被称为TJs,具有连接并紧缩相邻细胞之间的空间的能力,参与控制肠道屏障的通透性^[16]。闭锁小带蛋白-1(ZO-1)、闭合蛋

白(occludin)、密封蛋白-1(claudin-1)等都是其重要组成部分。肠道血管屏障位于肠道屏障的最深层,负责调节肠道内容物(如细菌、细菌代谢物、毒素、细胞因子、免疫和炎性反应细胞等)的转运,使其进入全身循环,并最终进入远离肠道的器官^[17]。

既往研究^[18-22]已通过临床试验及动物实验证实肠道屏障破坏与PD的发病及进展具有相关性。那么PD患者体内的肠道破坏是如何引起的呢?

1.1 肠道微生物群及其代谢物失调

鉴于肠道微生物群对大脑健康的影响,肠道也被称为“第二大脑”^[23]。有学者基于肠脑轴假说认为到肠道微生物群可能与PD相关,并首次通过粪便微生物群检测发现PD患者粪便中细菌丰度改变^[24]。后续研究表明PD中肠道菌群的紊乱主要通过产生SCFAs的细菌减少、产生LPS和降解黏液的细菌增多这3条相互关联的途径破坏肠道屏障并加剧疾病进程。

普雷沃特氏菌(*Prevotellaceae*)^[25]、罗氏菌属(*Roseburia*)^[26]可促进SCFAs生成,但在PD患者体内显著减少。SCFAs作为肠道细菌纤维发酵的最终产物^[27],对维持结肠上皮完整性至关重要^[28]。它能够触发肌成纤维细胞和上皮细胞释放前列腺素E1,与杯状细胞上的受体结合促进黏液的产生和分泌^[6]。或通过蛋白激酶B信号通路提升ZO-1和occludin表达,调控肠上皮屏障^[29]。此外,SCFAs还可以通过抑制促炎细胞因子,如白介素(IL)-6和IL-8的产生来减弱肿瘤坏死因子 α (TNF- α)和LPS诱导的内皮激活,保护肠道血管屏障^[30]。

同时,PD患者体内产生LPS的细菌不断增多,如肠杆菌科(*Enterobacteriaceae*)^[24]、假单胞菌(*Pseudomonadota*)^[31]。持续暴露于强效内毒素LPS会损害肠道通透性,促进 α -Syn在胃肠道神经元中过表达^[7]。LPS增多还能导致Toll样受体(TLR)4过度激活。Williams等^[32]研究表明高剂量LPS经由外周TLR4下游核转录因子 κ B(NF- κ B)2信号通路,诱导细胞凋亡,使肠道上皮屏障迅速丧失。低剂量LPS则通过TLR4/髓样分化因子88信号转导途径上调CD14^[33]和肌球蛋白轻链激酶,最终破坏TJs,导致肠道渗透性增加^[34]。

黏液素的降解也被认为是导致肠道屏障破坏的因素之一。Derrien等^[35]研究显示,阿克曼菌(*Akkermansia*)、双歧杆菌属(*Bifidobacterium*)、拟杆菌属(*Bacteroides*)均可以降解黏液。其中,阿克曼菌、双歧杆菌属在PD患者肠道内增多这一结论

已被证实^[36]。

1.2 结肠内 α -Syn 的异常聚集

肠道内 α -Syn 的异常聚集在 PD 早期就已出现^[37]。一项研究发现,鱼藤酮诱导的 PD 大鼠结肠中 α -Syn 的免疫荧光强度增加,表明 α -Syn 聚集^[38]。这些异常的蛋白质寡聚体可以直接影响肠道上皮细胞生物膜的结构,破坏其完整性,产生细胞毒性^[39];也可以激活并改变肠道屏障上的 TLR2 和 TLR4 的表达,引起进一步炎症反应,破坏肠道上皮屏障功能^[40]。Pellegrini 等^[41]的研究还发现,在 PD 小鼠模型中,早期肠道 α -Syn 的积累有助于通过直接激活胱天蛋白酶-1(caspase-1)产生炎症因子,导致肠道屏障受损。同时,肠道屏障破坏又会进一步促进 α -Syn 的错误折叠和聚集,形成恶性循环。

1.3 肠道炎症反应

肠道炎症反应自身也是破坏肠道屏障、促进 PD 进展的原因之一。刘祥云等^[8]的研究发现,经葡聚糖硫酸钠(DSS)处理过后的 1-甲基-4-苯基-1,2,3,6-四氢吡啶(MPTP)小鼠与未经处理小鼠相比,其结肠组织表现出更明显的病理损伤,包括严重的隐窝结构破坏、排列紊乱,发现肠道炎症反应能够通过破坏肠道屏障并激活肠脑轴的炎症反应,降低 PD 小鼠纹状体多巴胺水平,并增加黑质炎症反应因子的表达,从而加重 PD 小鼠的神经损伤。肠道炎症反应还能经神经递质介导,破坏肠道屏障。通过刺激肠嗜铬细胞释放大量的 5-羟色胺(5-HT)^[42],激活免疫细胞释放 TNF- α ,进而调节肠道黏液的分泌和构成,以及通过 TJs 控制细胞旁途径^[43]。积累在淋巴组织的交感神经末端的 5-HT 还可以与去甲肾上腺素一起释放^[44],进一步增加肠道通透性。

除上述因素之外,衰老、自主神经受损、色氨酸代谢异常及胆汁酸代谢紊乱等亦参与 PD 肠道屏障破坏,其机制涉及炎症老化、黏液分泌失调、紧密连接蛋白表达异常及促炎因子水平升高等环节^[45-51]。

综上所述,肠道屏障破坏是 PD 发生发展中的重要环节。因此,针对肠道屏障的保护性干预,尤其是像针刺这样具有多靶点调节潜力的疗法,为 PD 治疗提供了新方向。

2 针刺多途径保护肠道屏障

肠道屏障功能的完整性,在结构上依赖由杯状细胞分泌的黏蛋白所形成的化学屏障和由上皮细胞间 TJs 构成的物理屏障。针刺保护 PD 肠道屏障的核心在于维护与修复黏蛋白及 TJs。针刺对肠道

菌群及其代谢物的调节、对肠道炎症反应的抑制是作用于该核心环节的上游调控途径;而对 α -Syn 异常聚集的调控,既是肠道屏障功能改善后的积极效应,同时也通过减轻病理蛋白的毒性间接巩固了肠道屏障。由此,我们构建了一个以“巩固核心屏障结构”为中心的多途径协同作用框架。

2.1 针刺调节肠道菌群及其代谢物

针刺能够通过调控上游肠道菌群及其代谢物,从根源上改善肠道微环境,增加有益菌代谢物,从而发挥保护肠道屏障的作用。Jang 等^[52]研究显示,针刺 MPTP 诱导的 PD 模型小鼠“阳陵泉”与“足三里”后,其肠道菌群的 Chao 1 指数、OTU 数量及 Shannon 指数均显著升高,表明针刺可调节菌群丰度;同时,针刺组小鼠体内产 SCFAs 的罗氏菌属丰度明显上升,而具有黏液降解功能的拟杆菌属则显著减少。王照钦等^[53]报道,经针刺干预的 MPTP 模型小鼠,肠道中阿克曼菌丰度显著下调,提示针灸可能通过抑制表面黏液降解从而维护屏障完整性。Guo 等^[54]的研究进一步表明,电针治疗可促进肠道内杯状细胞增殖,维持隐窝结构完整,并提升糖蛋白和黏液水平。此外,有研究指出针刺可以抑制埃希菌属志贺菌的增殖^[54],而该细菌的增多常伴随产 SCFAs 的细菌减少^[55],提示针刺可能通过调节菌群结构促进 SCFAs 的生成,进而增强屏障功能。Quan 等^[56]在 6-羟基多巴胺(6-OHDA)诱导的 PD 大鼠模型中观察到,电针能够逆转拟杆菌属的异常升高,抑制促炎相关菌群的过度生长,增加有益 SCFAs 产生菌的丰度,并降低结肠组织中 IL-1 β 和 LPS 水平;通过评估 occludin 和 ZO-1 的表达,证实电针可恢复肠道屏障中紧密连接蛋白水平,使肠上皮损伤得到缓解。另有研究显示,电针“中脘”“气海”“足三里”和“太冲”能够通过调节 6-OHDA 诱导的 PD 大鼠神经肽 Y、缩胆囊肽、生长抑素、胃泌素和酪酪肽等脑肠肽水平,从而缓解 PD 相关症状^[57]。

2.2 针刺维护肠道黏蛋白及 TJs

针刺能够通过直接维护肠道黏蛋白及 TJs 结构,从而保持肠道黏液层及上皮屏障的完整性。Ma 等^[58]的研究显示,PD 模型小鼠肠道中 ZO-1 与 occludin 的表达显著降低,而电针干预可有效逆转该变化,提示电针有助于增强肠道屏障完整性并降低其通透性。李亚楠等^[59]的研究进一步表明,鱼藤酮诱导的 PD 小鼠肠道内 occludin 阳性表达降低,黏蛋白数量减少,黏蛋白 2(Muc2)mRNA 水平亦明显降低。Muc2 是由肠道杯状细胞分泌的主要凝胶型

黏蛋白,是阻碍细菌到达上皮细胞的有效屏障^[60]。Muc2水平的降低会导致黏液屏障功能的丧失^[61],而电针治疗能够显著逆转上述病理改变。Yan等^[62]的研究还表明,6-OHDA诱导的PD大鼠体内乙酰胆碱(ACh)含量减少,导致其肠道内杯状细胞形态改变,Muc2分泌明显减少,肠道通透性增加。电针能够提升结肠内ACh水平,进而通过胆碱能受体刺激杯状细胞分泌Muc2,改善肠道黏液屏障^[63]。

2.3 针刺调控肠道中 α -Syn的异常聚集

针刺还能有效清除在结肠异常聚集的 α -Syn,通过去除对肠道屏障具有直接损害作用的毒性蛋白,减轻因肠道病理向大脑传播引发的PD。汪瑶等^[64]的研究显示电针“风府”“太冲”“足三里”可清除PD小鼠中脑黑质区和结肠组织中异常聚集的 α -Syn,同时上调紧密连接蛋白ZO-1 mRNA水平,改善肠道屏障损伤,调节硫氧还蛋白结合蛋白/NOD样受体相关蛋白3(NLRP3)信号通路,延缓PD的发生发展。电针早期干预鱼藤酮诱导的PD模型小鼠“神庭”“天枢”“曲池”“上巨虚”可延缓其行为障碍,这一作用可能与降低结肠及中脑黑质中 α -Syn的表达有关^[65]。还有两项研究发现电针能有效减少鱼藤酮诱导的PD大鼠结肠中 α -Syn的蓄积,减轻结肠损伤^[37,63]。Zhao等^[66]的研究表明,针刺“阳陵泉”“足三里”和“太冲”能够抑制 α -Syn的产生、加速 α -Syn的清除并减少 α -Syn的异常积累。

2.4 针刺抑制肠道炎症反应

PD被认为是一种慢性低度炎症反应性肠病^[67]。针刺可通过抑制炎症反应,减轻炎症反应因子对黏蛋白和TJs的破坏。Guo等^[53]通过电针刺激MPTP诱导PD模型小鼠的“风府”“太冲”“足三里”,观察到该干预能够抑制肠道NLRP3炎症小体的激活,并逆转PD小鼠肠道中claudin-1基因表达水平的异常,从而改善肠道屏障损伤。此外,电针还可通过调节NF- κ B/IL-6表达水平,抑制肠道炎症反应,进而修复PD小鼠的肠道屏障功能^[68]。结肠组织病理学检查显示,在PD组织中可见局部大量炎症反应细胞浸润;相比之下,电针干预减轻了炎症反应细胞浸润程度及组织病理损伤^[58]。另有研究报道,针灸对炎症反应通路激活也具有调节作用,经针刺治疗后的MPTP小鼠模型中,纹状体NF- κ B和TNF- α 表达均显著降低^[52]。电针还能够抑制6-OHDA诱导的PD大鼠各种组织中LPS、IL-1 β 和IL-18等促炎因子的释放,并下调NLRP3通路相关标志物的表达^[59]。此外,针灸还可调节包括5-HT、去甲肾上

腺素等神经递质的平衡^[69],通过抑制神经递质介导的肠道炎症反应,进一步维护肠道屏障完整性。

3 针刺保护PD肠道屏障的潜在机制

不仅PD中,针刺还在多种伴有肠道屏障破坏的疾病模型中也显示出保护作用。在功能性消化不良动物模型中,研究^[70]显示电针可能通过调控TLR4/NF- κ B p65通路改善小鼠肠道黏膜屏障功能。该通路是经典的上游炎症反应信号枢纽,在PD模型中同样存在持续的炎症反应及NF- κ B通路的激活。祁羚等^[71]的研究显示电针鱼藤酮诱导的PD大鼠能通过抑制中脑黑质TLR4/NF- κ B p65通路,减轻神经炎症反应,抑制病理性 α -Syn聚集,改善PD进展。电针通过调控该通路改善肠道屏障这一机制提示其可能以同样方式抑制PD相关的肠道炎症反应。

在溃疡性结肠炎小鼠模型中,针刺通过负向调控基质金属蛋白酶(MMPs),增加结肠长度与肠道杯状细胞数量,从而改善肠道屏障功能^[72]。多项研究已明确,MMPs(特别是MMP-3和MMP-9)在PD模型中同样存在过度表达,是导致血脑屏障破坏的关键病理因素^[73-74]。值得注意的是,针刺在PD模型中被证实能有效抑制中枢神经系统的MMPs活性^[73]。鉴于肠道屏障与血脑屏障在结构和功能上具有的同源性,以及MMP-3可介导 α -Syn的酶切并产生神经毒性片段^[75],我们推断:在PD状态下,针刺可能通过抑制肠道局部MMPs的过度活化,维护肠道黏膜屏障的结构与功能完整,从而阻隔肠道中异常聚集的 α -Syn向中枢神经系统传播,最终延缓PD的病理进展。

此外,基于现有研究,本文提出针刺可能通过调节B细胞淋巴瘤-2(Bcl-2)/Bcl-2相关X蛋白(Bax)通路保护PD肠道屏障的假说。研究表明,电针刺激“足三里”等穴位可通过上调Bcl-2并下调Bax,抑制脓毒症大鼠肠黏膜淋巴细胞凋亡,保护肠黏膜免疫屏障,并降低肠道通透性^[76]。Bcl-2作为抗凋亡的关键蛋白,在肠道上皮中高表达,对维持PD黏膜屏障至关重要^[77]。有研究显示,在PD模型中,针刺能通过调节纹状体Bcl-2/Bax比值,抑制多巴胺能神经元凋亡^[52]。基于这些发现,我们推测针刺可能通过调节肠道Bcl-2/Bax通路,抑制上皮细胞凋亡,从而增强肠道屏障功能。

上述针刺作用机制的推论试图从不同角度揭示针刺保护肠道屏障的共性机制,可能是针刺保护

PD肠道屏障的潜在通路,需要未来进一步验证。

4 讨论与展望

综上所述,本文系统论证了针刺通过多途径保护肠道屏障,从而干预PD进程的潜在机制。现有研究表明,肠道屏障功能障碍在PD的发病,尤其是遵循“身体优先”病理传播模式的亚型^[5]中,扮演着至关重要的起源性角色。本综述的核心论点在于,针刺疗法并非仅仅对症处理PD的某些症状,而是通过一种多系统、整合性的方式,直接作用于肠脑轴的“门户”——肠道屏障,发挥其治疗优势。具体而言,针刺能够重塑紊乱的肠道菌群生态,促进有益菌及其代谢产物SCFAs的生成,同时抑制LPS的产生;这一系列变化共同维护了肠道黏液层的完整性与肠道上皮紧密连接蛋白(如ZO-1、occludin)的正常表达。此外,针刺还被证实能够有效清除早期异常聚集在结肠的 α -Syn,并抑制由NLRP3、NF- κ B等信号通路介导的肠道局部炎症反应。这些机制构成了一个相互关联、协同作用的网络,最终起到对肠道屏障结构与功能的修复与强化作用,从而有望切断从肠道起源、经肠脑轴向中枢神经系统传递的病理信号,为PD防治提供新的思路。

为更科学地证实针刺的上述作用,今后应在以下方面做进一步的探索:首先,当前研究领域亟须建立一套标准化、量化的肠道屏障功能评估体系。未来的临床试验应将LPS结合蛋白^[78]、血清与粪便中的连蛋白(zonulin)水平^[79]、二胺氧化酶(DAO)^[44],以及结肠活检标本中紧密连接蛋白的定量分析等生物标志物作为评价针刺疗效的核心指标之一,从而为“针刺-肠屏障-PD”假说提供更直接的人类数据支撑。其次,应深入探究针刺信号从体表穴位到肠道的内在转导通路。例如,明确迷走神经、自主神经通路在其中的具体贡献;利用基因编辑技术与神经调控工具,解析针刺如何精确调节肠道固有免疫细胞功能与肠上皮细胞的再生与修复;利用粪菌移植等实验设计,明确重塑的肠道菌群是否为针刺效应不可或缺的中介。

展望未来,基于肠脑轴理论的针刺干预策略,有可能成为早期PD治疗的范式,以肠道屏障破坏和快速眼动睡眠行为障碍为首表现的“身体优先”型PD患者^[5],可能是从早期针刺干预中获益最显著的群体。针对这一亚群,设计前瞻性、多中心、大样本的随机对照试验,验证针刺延缓甚至阻断疾病进展的疗效,具有临床与科学价值。此外,探索

针刺与益生元、益生菌或特定靶向药物的联合疗法,以期产生协同增效作用,也是一个具有潜力的研究方向。

利益冲突 所有作者声明不存在利益冲突。作者吴焕淦为本刊编委,但未参与本文的审理。

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