

肠道微生物-肠-脑轴与卒中后认知障碍的相关性研究进展

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[摘要] 卒中后认知障碍(PSCI)是卒中后常见的功能障碍,严重影响患者的生活质量和正常功能。研究显示肠道微生物群失调与中枢神经系统疾病关系密切,肠道菌群通过调节肠-脑轴可维持神经、代谢和免疫系统的稳定性,对人类生理健康产生多方面的影响。众多研究发现,肠道微生物-肠-脑轴在卒中及相关PSCI的发生和发展中发挥重要作用,调节肠道微生物-肠-脑轴有望成为PSCI治疗的潜在靶标。本文对肠道微生物-肠-脑轴与PSCI的相关性研究进展进行综述,以期对相关机制探索和临床防治提供参考。

[关键词] 卒中后认知障碍; 肠道微生物-肠-脑轴; 血脑屏障; 中枢炎症

Research progress on the relation between gut microbiome-gut-brain axis and post-stroke cognitive impairment

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[Abstract] Post-stroke cognitive impairment (PSCI) is a prevalent functional impairments following stroke that seriously affects patients' quality of life and daily activities. Studies indicate a close relationship between intestinal microflora dysbiosis and central nervous system diseases. Intestinal microflora profoundly impacts on human physiological health, contributing to the stability of nervous, metabolic and immune systems through regulation of the gut-brain axis. An increasing number of studies confirmed the important role of the gut microbiome-gut-brain axis in the occurrence and development of stroke and its associated PSCI, and regulation of microbiome-gut-brain could be potential target to treatment of PSCI. This review summarizes research progress on gut microbiome-gut-brain axis and PSCI to provide a reference for exploration of related mechanisms and clinical prevention and treatment strategies.

[Key words] post-stroke cognitive impairment; gut microbiome-gut-brain axis; blood brain barrier; neuroinflammation

卒中是全球高发病率和高致残率的疾病^[1-2]。卒中后认知障碍(post-stroke cognitive impairment, PSCI)是卒中发病后1年内常见的功能障碍之一。卒中患者的PSCI发生率为7.4%~41.3%,严重影响患者的生活质量和正常功能^[3-4]。PSCI的诊断通常需要3个月甚至更长时间,其具体发生机制尚不明确,临床治

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疗手段有限^[5]。近年研究显示,神经系统疾病的发生与肠道微生物群失调密切相关,肠道菌群可通过调节肠-脑轴而维持神经、代谢和免疫系统的稳定性,对人类生理健康产生多方面的影响;肠道微生物-肠-脑轴在卒中及相关PSCI的发生和发展中发挥重要作用^[5-6]。本文对近年肠道微生物-肠-脑轴与PSCI的相关性研究进展进行综述,旨在为探索PSCI机制及其防治研究提供参考。

1 肠道微生物-肠-脑轴

肠道菌群是指肠道中复杂多样的微生物群,作为一个复杂的生态系统,由数量众多的细菌、病毒、螺旋体、真菌等组成。这些微生物与宿主存在共生关系,生理状态下并无致病性,其中以细菌数量最多^[7-8],它们的整个基因组被称为“人类微生物组”。在出生前,胎儿的肠道是无菌的;分娩后几个小时,在环境、饮食、母体转移甚至早期抗生素的使用等外部因素影响下,每个婴儿都形成了与成人相似的肠道微生物群,在1岁时其组成和数量达到稳定状态^[9-10]。人体的肠道微生物群主要由拟杆菌门、放线菌门、厚壁菌门、变形菌门等组成^[11]。肠道微生物群与人体新陈代谢、肠道内稳态、宿主免疫反应及神经行为效应相关^[12]。稳定且多样化的肠道微生物群可产生促进生理和代谢过程的代谢物,有利于人体健康^[13],其主要通过3个主要功能来维持正常的稳态^[14-15]:(1)通过营养竞争帮助并保护宿主免受病原菌感染;(2)刺激先天免疫,限制毒素的产生和病原微生物渗透入肠道组织,从而调节肠道敏感度和耐受性;(3)通过将不易消化的膳食纤维和三糖和四糖代谢为可产生B族维生素的单糖来促进营养吸收。肠道微生态失调可导致认知功能障碍、抑郁症、焦虑症等多种神经系统疾病^[16-19]。

肠-脑轴是指胃肠道与中枢神经系统之间的双向信号转导机制^[20-21]。多项研究发现,肠道微生物可通过肠-脑轴影响人脑的发育及功能。1880年,William James和Carl Lange首次提出“肠-脑轴”,并阐释了这些相互作用的复杂性。具体来说,肠-脑轴网络系统包括大脑、脊髓、下丘脑-垂体-肾上腺(hypothalamic-pituitary-adrenal, HPA)轴、肠道神经系统、自主神经系统和中枢神经系统^[22-23]。该系统组成了一个复杂的通信网络系统,不但可适当维持胃肠道稳态,而且可影响大脑的发育、情绪和认知功能^[24]。肠道微生物可通过迷走神经、免疫系统、HPA轴、代谢通路及产生的微生物代谢物影响肠-脑轴的功能^[25]。在认知障碍疾病中,肠道与大脑之间的相互交流起重要作用,肠道微生物可产生神经活性因子,促进肠道与大脑之间的交流。由乳酸杆菌、

双歧杆菌、肠球菌产生的神经递质(如乙酰胆碱、5-羟色胺)可直接或间接影响脑细胞的生理功能;同时,中枢神经系统产生行为、情绪、睡眠等所需的神经递质5-羟色胺90%是在肠道中产生的^[26-27]。肠道微生物群在血脑屏障(blood brain barrier, BBB)的形成、小胶质细胞的成熟及活化、神经生长过程中可发挥重要作用。胃肠道内各种细菌可激活相关神经通路和中枢神经系统^[28]。肠道微生物的主要代谢产物短链脂肪酸(short-chain fatty acids, SCFAs),在肠道微生物-肠-脑轴的双向传导中起关键作用^[29]。越来越多证据支持SCFAs可影响大脑的重要生理功能,其可通过肠道屏障和BBB,到达中枢神经系统并在细胞内积累;这些代谢物可影响中枢神经炎症反应及小胶质细胞的活化,从而改变神经元的通信和行为。另有研究显示,肠道微生物群与大脑之间的任何通信途径的中断都可能引发炎症反应。肠道微生物产生的分子和代谢物,可触发机体内的细胞因子反应,诱发肠道炎症及全身系统炎症反应,甚至引起中枢神经系统炎症,促进神经系统疾病的发生和发展^[30-31]。

2 肠道微生物-肠-脑轴与PSCI的相关性研究进展

2.1 SCFAs在PSCI中的作用 SCFAs包括乙酸、丙酸、丁酸和戊酸^[29,32-33],可通过维持肠道屏障的完整性,预防肠道炎症,维持肠道的健康。丁酸盐通过激活腺嘌呤核糖核苷酸(adenosine monophosphate, AMP)活化蛋白激酶或下调Claudin2的表达,调节紧密连接蛋白以增强肠道屏障功能^[34-35]。SCFAs是肠道与大脑沟通的主要信号分子,其经免疫和循环系统,再穿过BBB入脑,调节神经元及小胶质细胞的生长、发育、成熟以及神经递质的释放^[36-37]。大脑摄取的SCFAs以丁酸盐、丙酸盐和乙酸盐较多。研究显示,人脑组织中丁酸盐,丙酸盐的平均浓度分别为17.0 pmol/mg、18.8 pmol/mg^[29,38]。研究显示,大脑中动脉栓塞(middle cerebral artery occlusion, MCAO)模型大鼠粪便SCFAs中的丁酸、乙酸、丙酸浓度均低于对照组,提示SCFAs浓度与脑缺血再灌注疾病的发展密切相关^[39]。丁酸盐是中枢神经系统的重要调节剂,口服丁酸钠可明显促进Akt磷酸化,抑制小胶质细胞活化,减少脑梗死面积及神经元凋亡,明显改善卒中患者的认知功能^[40]。组蛋白去乙酰化与大脑发育和一系列神经精神疾病有关,组蛋白去乙酰化抑制剂可增强认知功能,而SCFAs可介导组蛋白去乙酰化的抑制,对大脑发挥作用。一项研究显示,对存在学习记忆障碍小鼠腹腔内注射丁酸钠[1.2 g/(kg·d),持续4周],可对组蛋白去乙酰化起到慢性抑制作用,进而明显改善认知障碍小鼠的学习记忆

功能^[41]。同时, SCFAs可影响神经发生、增殖和凋亡相关基因的表达,促进人神经祖细胞的生长和胚胎干细胞分化为神经元,并通过影响神经递质和神经营养因子的浓度调控大脑功能^[42-43]。因此, SCFAs可在PSCI疾病中发挥重要作用。

2.2 肠道炎症和肠道屏障在PSCI中的作用 肠道屏障由黏液层、肠上皮和固有层组成。肠道微生态失调致使细菌和有害代谢物迁移至血液循环中,可导致肠道及局部的炎症反应和肠道屏障通透性增加,称为肠漏综合征^[44-46]。结肠的黏液层可隔离大量细菌,而小肠的黏液层则不能阻止细菌穿透^[47]。肠道微生物群的组成可影响肠道黏液层的特性,大量降解黏液层的细菌可改善肠道屏障功能,减轻肠道及全身的炎症反应^[48-49]。部分益生菌如植物乳杆菌、大肠杆菌和婴儿双歧杆菌可增强肠道屏障功能,提高紧密连接蛋白的表达水平^[50]。而部分细菌产生的外毒素可破坏肠道上皮细胞的完整性,如弧菌、志贺氏菌、大肠杆菌、幽门螺杆菌、沙门菌和梭状芽胞杆菌等可介导肠道紧密连接的变化^[45];脆弱拟杆菌的外毒素可通过裂解钙黏附蛋白(epithelia cadherin, E-cadherin)来破坏肠道紧密连接。研究显示,缺血性卒中患者常出现胃肠道功能紊乱症状,考虑可能与肠道微生态失衡导致肠道屏障功能破坏有关^[51]。动物实验研究显示, MCAO模型小鼠的肠道屏障功能和肠道动力下降,且其肠道菌群组成变化与胃肠道症状可能存在联系^[52]。肠-脑轴通过肠道菌群与大脑双向交流,在卒中发展和转归中起着重要作用,其中神经递质的产生与PSCI发展密切相关^[53]。肠道黏膜由特殊的肠外神经支配,属于自主神经系统(交感神经和迷走神经)。卒中后去甲肾上腺素大量释放以及乙酰胆碱减少导致肠道黏液蛋白的产生发生变化。肠道通透性增加被认为与促肾上腺皮质激素释放、糖皮质激素的激活以及细菌定位的重排有关,与肠道屏障功能障碍相关的自主神经系统失调可能会导致卒中及相关的功能障碍等^[54-55]。在缺血性卒中疾病中,小肠中调节性T细胞水平增高,其可分泌抗炎细胞因子IL-10起到保护作用^[56]。由此可知, PSCI疾病发展过程中存在肠道屏障通透性增加及较高的肠道炎症水平。

2.3 神经炎症和BBB在PSCI中的作用 小胶质细胞是脑中重要的免疫细胞,可与大脑内的神经元串扰或接收来自外周循环的细胞因子信号,然后释放趋化因子,以激活淋巴细胞通过内皮细胞的迁移^[30,57]。病理条件下,小胶质细胞可分泌多种趋化因子或使单核细胞分泌炎症因子导致神经炎症反应。脑缺血后细胞进入释放危险相关分子模式(danger-associated molecular patterns, DAMPs),小胶质细胞的促炎表型

被激活,继而释放促炎因子,加重炎症反应和脑损伤^[58]。BBB是一种复杂的功能和解剖结构,由微血管内皮细胞、周细胞、小胶质细胞、星形胶质细胞与神经元结合形成^[59-60]。物质通过BBB在血液循环与脑实质之间通过两种方式转运,包括跨细胞囊泡转运和细胞旁途径。黏附连接的丢失会导致BBB通透性增加,紧密连接主要负责物质的细胞旁扩散^[61]。BBB的完整性对于维持脑内稳态和防止异物侵入脑组织具有重要意义,可保护大脑免受神经元的破坏及其他病原体和有害免疫反应的侵害^[62]。脂多糖(lipopolysaccharide, LPS)为全身炎症的重要标志物,其水平较高时可与免疫细胞上的跨膜识别受体家族的成员Toll样受体(Toll-like receptors, TLR)4结合,促进一系列促炎细胞因子的产生,引起全身炎症反应,使脑微血管内皮细胞电阻下降,进而导致BBB的破坏^[63-64]。在缺血性卒中损伤期间,大脑中的小胶质细胞分泌促炎细胞因子, BBB的紧密连接和黏附连接被破坏,致使大分子毒性代谢物、病原体、病毒等通过破坏的BBB进入大脑,从而加剧疾病进展^[65]。对轻度认知障碍患者脑脊液进行研究显示,周细胞有明显损伤,提示BBB的完整性与认知障碍具有一定的相关性^[66]。近年研究发现,肠道微生物失衡时,大肠杆菌、脆弱拟杆菌等革兰阴性菌会生成大量LPS,进而导致肠道屏障和BBB通透性增加,诱发全身系统炎症及神经炎症,导致神经退行性病变。SCFAs可促进肠道屏障的完整性以维持肠道健康,其部分还可进入全身循环,使位于脑血管上皮细胞的转运蛋白穿过BBB^[66-67]。Braniste等^[68]报道,与无特定病原体(specific pathogen free, SPF)小鼠相比,无菌小鼠紧密连接蛋白occludin和claudin 5的表达水平下降, BBB通透性增加;将SPF小鼠的粪便微生物群或生产SCFAs的菌群移植到无菌小鼠体内,可明显恢复无菌小鼠BBB的功能。因此,在PSCI疾病过程中存在BBB完整性被破坏及较强的神经炎症反应。

3 PSCI肠道微生物及其代谢物的特点

近年研究显示,在中枢神经系统疾病进展过程中,肠道微生物及其代谢物可发挥关键作用^[69-70]。Liu等^[3]分析了PSCI与肠道菌群的相关性,结果显示PSCI后肠道菌群及其代谢物可导致与健康人群不同的一系列改变,提出PSCI进展过程中肠道菌群及其代谢物发挥着关键作用;与健康人群相比, PSCI患者肠道菌群的多样性显著降低,微生物组成及相应的代谢物受到干扰,其中梭菌增多和SCFAs缺乏,而改善PSCI可能需要补充大剂量SCFAs或产生SCFAs的益生菌。一项临床研究显示, PSCI患者粪便中肠杆菌科丰度明显增加,产丁酸盐的细菌丰度

和丁酸盐水平显著降低；将PSCI患者的肠道菌群转移至MCAO模型小鼠体内，小鼠表现出更高丰度的肠杆菌科和更低的丁酸盐水平，而给予抗生素和丁酸盐治疗后，PSCI小鼠中肠杆菌科丰度明显降低^[71]。另一研究使用16S rDNA检测PSCI患者肠道菌群发现，拟杆菌门、放线菌门和厚壁菌门中的特定菌丰度明显降低，而变形杆菌、克雷伯菌、肠球菌等致病菌丰度明显升高^[52]。由此可知，在PSCI患者中肠道微生物特点主要表现为有益菌相对丰度较低，条件致病菌相对丰度较高，且肠道微生物代谢物SCFAs中丁酸、乙酸等含量明显降低。肠道微生物影响PSCI的相关机制见图1。

4 肠道微生物群调节作为PSCI的治疗靶点

通过了解肠道微生物及其代谢物在PSCI发病机制中的作用，以及肠道通透性增加与肠道、全身系统炎症反应，BBB通透性增加与中枢炎症反应和PSCI之间的密切联系，为PSCI的干预治疗提供了潜在的靶点^[72-73]。

大量研究显示，SCFAs在PSCI过程中调控BBB、小胶质细胞、神经炎症、神经元凋亡和神经营养因子而发挥作用^[74-75]。口服丁酸盐治疗可降低无菌小鼠BBB的通透性，并使其肠道微生物的菌群变化恢复至与无特定病原体小鼠相近的水平^[76]。丙酸通过降低大肠杆菌的丰度，进而保护LPS诱导的紧密连接蛋白occludin、claudin 5，起到保护BBB完整性的作用^[68]。相关研究显示，部分进入中枢神经系统的SCFAs具有神经活性，通过血脑灌流吸收的乙酸可明显影响下丘脑中神经递质氨基酸、谷氨酰胺和谷氨酸的水平，丙酸和丁酸可诱导酪氨酸羟化酶基因转录水平增高，还可参与多巴胺、肾上腺素和去甲肾上腺素的生物合成^[77-78]。丁酸盐还可通过提升神经生长因子、神经营养因子、胶质细胞衍生神经营养因子等的水平，影响神经元及突触的生长、分化，对大脑学习记忆认知功能的改善发挥重要作用^[75]。

众多研究显示，益生菌的有益作用是通过增强肠道上皮的完整性，防止肠道屏障破坏，减少肠道及全身炎症反应，改善BBB通透性，以及抑制神经炎症和神经变性实现的^[55,79]。体外研究显示粪肠球菌和鼠李糖乳杆菌可减少促炎因子TNF- α 的产生，实验动物服用这些益生菌菌株可明显降低氧化应激指标并诱导大脑中的抗氧化酶^[80]。较多的动物实验研究报道了乳酸杆菌和双歧杆菌的治疗潜力^[81-82]。另有研究显示，益生菌可减轻LPS诱导的神经炎症反应和记忆认知缺陷障碍，并可抑制乙酰胆碱酯酶和抗氧化酶的活性^[82]。在脑缺血再灌注动物模型中，使用益生菌酪酸梭菌治疗，可减轻脑缺血再灌注损

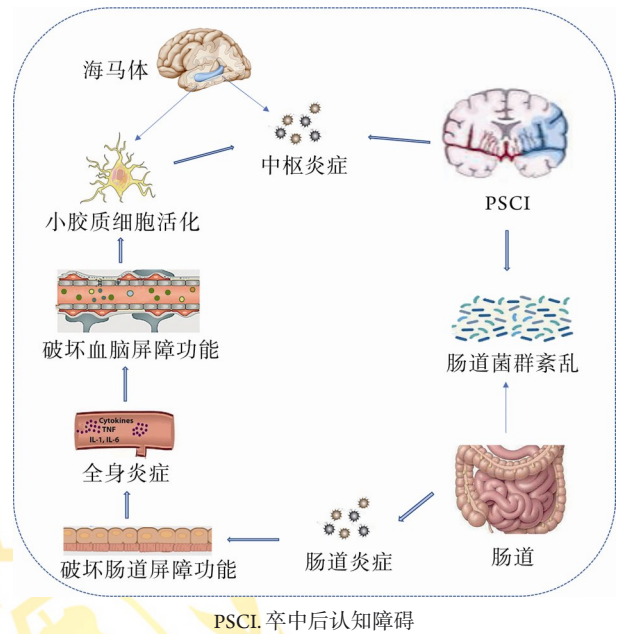


图1 肠道微生物影响PSCI的相关机制

Fig. 1 The effects and role of gut microbiome on post-stroke cognitive impairment

伤，并通过抗细胞凋亡作用起到神经保护作用^[83]。另一项卒中模型小鼠研究显示，使用益生菌，如嗜酸乳杆菌、干酪乳杆菌、短双歧杆菌和保加利亚乳杆菌等预处理后，脑缺血减少了约52%，神经系统症状也有明显缓解^[84]。

粪便微生物群移植是将粪便微生物从健康志愿者移植到患者体内，以调节患者肠道微生物群改变及肠道微生物群组成，其可通过鼻饲管、上内镜、结肠镜检查、乙状结肠镜检查、保留灌肠或胶囊给药。粪便微生物群移植目前可作为部分神经精神疾病和神经退行性疾病的有效治疗措施^[85]。Zhan等^[86]报道，先用广谱抗生素进行持续14 d治疗后，将健康小鼠的粪便菌群移植到老年伴认知障碍小鼠体内后，认知障碍小鼠的空间学习和记忆力明显改善。Lee等^[87]将青年小鼠粪便微生物植入老年卒中小鼠后，老年卒中小鼠的肠道微生物群发生了改变，认知功能增强，进一步研究显示这一变化与年轻小鼠粪便中含有较多的SCFAs产生菌株有关。Chen等^[39]研究显示，移植富含SCFAs的粪便微生物群可促进缺血性卒中大鼠体内丁酸浓度明显上升，从而有效治疗卒中认知功能障碍。另有研究显示，粪便微生物群移植可改变神经功能障碍小鼠的肠道菌群，改善BBB通透性，抑制小胶质细胞和星形胶质细胞的活化，提示粪菌移植可作为神经功能障碍的潜在治疗方法^[55,88]。

5 总结与展望

综上所述，越来越多的研究支持肠道微生物及

其代谢物通过肠-脑轴在PSCI进展中发挥重要作用。PSCI患者中存在肠道微生态失衡、有益菌丰度降低且条件致病菌丰度升高，肠道微生物代谢物SCFAs中的丁酸、乙酸含量降低。同时，致病菌菌株会损害肠道屏障的完整性，引起肠道及全身炎症反应，促使循环LPS含量升高，破坏BBB的完整性，诱导小胶质细胞活化，促使神经炎症反应和神经元的破坏，最终导致认知功能障碍。而肠道有益菌及丁酸、乙酸等可通过维持肠道屏障的完整性，调节神经递质、神经营养因子，抑制小胶质细胞的活化，维持BBB的完整性，以及减轻全身炎症及神经炎症反应等改善PSCI患者的认知功能。因此，通过服用乳酸杆菌、双歧杆菌等益生菌及丁酸盐、丙酸盐等SCFAs，或通过粪便微生物移植治疗，有可能改善PSCI患者的认知功能。这提示调节肠道微生物-肠-脑轴可作为PSCI治疗的潜在靶标。

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