·综述·

有氧运动改善脑卒中后抑郁与肠道菌群相关性的研究进展*

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脑卒中后抑郁(post-stroke depression,PSD),患者主要表现为情绪低落、对事物缺乏兴趣、焦虑及睡眠障碍,甚至出现厌世、自杀等一系列行为改变[1]。研究报告称脑卒中后PSD患病率约为30%,其中严重抑郁症患病率为17.7%[2—3],且患PSD患者死亡风险显著增高,严重影响脑卒中患者日常生活能力恢复,并给家庭及社会带来巨大经济负担[4]。PSD发病机制尚不清楚,目前研究较多的有内源性生物机制学说和反应源机制学说[1]。随着新一代测序技术及生物信息分析技术的快速发展,近年来肠道菌群在干预脑血管及神经疾患方面成为科研人员的关注热点。有研究认为,脑卒中后肠道菌群的紊乱与PSD的发生发展密切相关[5],而有氧运动可以增加益生菌的定植,改善肠道菌群的构成及功能。因此探讨有氧运动、PSD与肠道菌群之间的内在机制联系,能够为以肠道菌群为治疗靶点,为PSD患者制定合理有效的运动处方提供理论证据。

1 肠道菌群与中枢神经系统疾病

人体肠道内存在数量庞大且功能复杂的微生物群落,其所编码的基因数量约为人类基因组的150倍,被视为人体"第二大脑"[6]。随着有关肠道微生物对人类健康与疾病影响研究的深入,探讨肠道菌群与中枢神经系统功能之间的关系已成为研究热点。肠道菌群可通过脑-肠轴经神经、内分泌和免疫等多种途径与大脑进行双向信息交流。肠道菌群与脑卒中及其继发性中枢神经系统损伤、焦虑、抑郁、自闭症、阿尔茨海默病等一系列神经精神疾病的发生发展密切相关[7],其中,脑卒中及抑郁与肠道菌群的关系是目前的研究热点。研究发现,脑卒中及抑郁患者存在明显的肠道菌群失调,而菌群失调及继发的肠道功能变化可导致患者预后不良。研究发现,可通过调节菌群构成及恢复肠道功能缓解卒中及抑郁病情程度[8—9]。

1.1 脑卒中与肠道菌群

肠道菌群与高血压、糖尿病和高血脂等脑卒中高危诱因密切相关。肠道菌群代谢的短链脂肪酸(short chain fatty acids, SCFAs)可调节血压,肠分泌物脑肠肽可维持血糖血脂稳态[10—11]。研究发现,脑卒中高发人群肠道内肠杆菌科和韦荣氏菌科增多,产生SCFAs的毛螺菌科和疣微菌科含量降低[12]。运动缺乏、应激事件诱发的肠菌群紊乱及肠道炎症可致血脂异常,并参与高血压及糖尿病的发生发展[13—14]。此外,肠道菌群可通过炎症、脂质代谢,三甲胺氧化物(trimethylamine-N-oxide, TMAO)产生等途径促进动脉粥样硬化形成与发展[15]。研究发现,嗜酸小球菌可诱导耐受性树突状细胞减轻动脉粥样硬化(atherosclerosis, AS)[16]。

肠道菌群与脑卒中的发病机制密切相关。肠道菌群通过代谢TMAO促使血栓形成外[17],还可经白细胞介素17(interleukin 17, IL-17)的驱动发生血管炎并参与颅底动脉瘤的形成[18—19]。肠道菌群释放的内毒素可通过激活Toll样受体(toll-like receptors, TLR)4导致脑血管畸形及增加AS破裂风险,促使脑卒中发生[20—21]。卒中后炎症反应可破坏肠屏障及肠道菌群稳态,经肠屏障入血的内毒素及炎症因子可损害血脑屏障,加重脑组织氧化应激[22—23]。激活的HPA轴及交感神经可加剧肠功能障碍,抑制肠道神经递质的合成及神经传导,导致脑卒中预后不良,增加卒中后精神疾病发生的风险。研究发现,乳酸杆菌可改善血管内皮功能,降低卒中发生风险,还可抑制氧化应激及神经细胞凋亡,减轻脑卒中损伤程度[24—25]。

1.2 抑郁与肠道菌群

压力应激作为抑郁主要致病因素与肠道菌群密切相关,来自外源性及内源性应激可激活HPA轴,交感神经及肠神经系统,导致肠道运动及通透性改变,引发肠道炎症等肠功能障碍[26]。研究发现,患有炎症性肠疾病的儿童及成年人出现焦虑及抑郁的风险增加[27]。

肠道菌群与HPA轴、神经递质、炎症因子等抑郁发病机制密切相关。长期处于应激环境中可激活HPA轴损害肠屏障,促使细菌及内毒素进入体循环,诱发机体免疫并持续激活HPA轴加剧肠通透性,减少肠道5-羟色胺(5-hydroxytryptamine, 5-HT)、多巴胺(dopamine, DA)、γ-氨基丁酸(γ-

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aminobutyric acid，GABA)等递质合成并抑制肠迷走神经活性,减少与中枢的信号传导[28]。此外,肠道炎症引发的外周炎症可扩散入脑诱发神经毒性并阻碍相关神经递质及脑源性神经营养因子(brain-derived neurotrophic factor，BDNF)的合成,诱发抑郁情绪[29—30]。而抑郁症患者持续存在的负面情绪可进一步触发对各种应激源的强烈反应及敏感性,形成恶性循环。研究发现,瑞士乳杆菌及双歧杆菌可恢复应激大鼠肠屏障,降低HPA轴及自主神经活性[31]。抗抑郁药5-羟色胺再摄取抑制剂可抵抗革兰氏阳性菌,三环类抗抑郁药可阻止肠道病原菌的定植生长而维持肠道稳态[32]。

1.3 脑卒中后抑郁与肠道菌群

目前研究较多的PSD发病机制主要涉及神经递质、炎症因子、HPA轴、BDNF等方面。脑卒中所致的肠功能障碍及肠道菌群失调可通过免疫、内分泌及神经系统等多种途径参与PSD的发病机制。

1.3.1 神经递质与肠道菌群:脑卒中后肠道菌群失调可影响神经递质合成及神经传导而诱发抑郁。脑卒中通过激活自主神经及HPA轴抑制肠蠕动、增加肠渗透性而破坏肠稳态[33]。肠蠕动抑制可使肠球菌属、梭菌属及拟杆菌属等潜在致病菌过度繁殖,而使产生5-HT的植物乳杆菌、分泌GABA的双歧杆菌、合成去甲肾上腺素(norepinephrine，NE)的酵母菌等益生菌的减少。此外,肠道乳杆菌属及酪酸梭菌的减少可降低SCFAs生成而减少5-HT分泌。肠菌群紊乱可使外周5-HT水平失调并影响海马谷氨酸-谷氨酰胺-GABA循环而诱发异常情绪[34—35]。研究发现,缺乏肠道菌的应激小鼠脑内多巴胺能转换率降低并伴情绪障碍[36]。肠神经递质减少可减弱对肠内炎症的抑制,加重机体炎症对神经递质通路的破坏。此外,肠道菌群合成的神经递质可通过迷走神经与大脑沟通,而中枢神经系统损伤可使肠粘膜下和肌间神经元部分丢失,减少与迷走神经的突触连接,抑制与中枢的信号传输而诱发抑郁[33],研究发现,摄入鼠李糖乳杆菌可调节小鼠中枢GABA受体表达及情绪行为,而切断迷走神经作用则消失[37]。

1.3.2 炎症细胞因子与肠道菌群:脑卒中后肠道免疫诱发的机体炎症可致脑部神经毒性而诱发抑郁。脑卒中可激活肠道髓样细胞触发受体-1促使肠通透性增高及菌群移位[38]。革兰氏阴性菌、大肠杆菌及肠球菌等衍生的内毒素可渗入循环系统引发内毒素血症,诱导释放的肿瘤坏死因子-α(tumor necrosis factor-α，TNF-α)、γ-干扰素(interferon-γ，IFN-γ)、白细胞介素1β(interleukin-1β，IL-1β)、白细胞介素-6(interleukin-6),白介素18(interleukin 18，IL-18)等细胞因子可经体液或神经途径进入大脑,促使小胶质细胞转化为促炎的M1型,导致神经炎症促使抑郁发生[39]。研究发现,罗伊氏乳杆菌和青春双歧杆菌可降低血液中脂多糖(lipopolysaccharide,LPS),IL-6含量并抑制海马内小胶质细胞的活化而缓解焦虑及抑郁情绪[40]。并且,渗入脑部的炎症因子可介导代谢犬尿氨酸为具有神经毒性的喹啉酸,其所诱导的谷氨酸兴奋性毒性是炎症引起抑郁的常见途径[41]。此外,肠道菌群失调介导的神经炎症可阻碍5-HT、DA及NE的合成而诱发抑郁[39]。研究发现,乳杆菌和长双歧杆菌可通过抑制肠道核因子κB(nuclear factor kappa-B,NF-κB)活化和TNF-α表达减轻抑郁[42]。

1.3.3 HPA轴与肠道菌群:脑卒中后肠道菌群的变化可持续激活HPA轴,抑制海马神经再生而诱发抑郁。脑卒中可激活HPA轴释放GC,导致肠通透性增加及菌群失调。肠道菌群衍生物脂多糖、肽聚糖和肠道释放的IL-1β、IL-6和TNF-α是HPA轴的有效激活剂,其与菌群紊乱形成恶性循环[43]。肠有益菌的减少可减弱SCFAs对编码HPA轴中相关蛋白质基因表达的调控,从而增强对HPA轴的响应[44]。大肠杆菌产生的酪蛋白水解酶B可刺激促肾上腺皮质激素(adreno-corticotropic-hormone，ACTH)前体阿黑皮素原的释放,从而增强HPA轴活性[45]。GC的持续增多,可致其受体抵抗或信号缺失,抑制海马神经元再生而触发抑郁情绪。将抑郁患者肠道菌群移植给无菌小鼠,发现GC受体下游Stat5a基因下调并伴异常行为[46]。GC可降解色氨酸及酪氨酸,减少5-HT及NE合成而诱发抑郁。研究发现,香肠乳杆菌可维护肠屏障,降低脂多糖水平从而减弱HPA对应激的反应,减轻抑郁情绪[47]。

1.3.4 BDNF与肠道菌群:脑卒中所致的肠道菌群紊乱可通过影响BNDF水平诱导抑郁产生。肠上皮细胞,肠神经胶质细胞和神经元中存在的BDNF及其酪氨酸激酶受体B(tyrosine kinase receptor B，TrkB)对调节肠道感觉和运动功能起着基本作用[48]。脑卒中所致的菌群紊乱可改变肠道BDNF和TrkB表达,改变肠道运性及敏感性,所导致的胃肠疾病与情绪障碍的产生密切相关。脑卒中后肠道功能障碍诱发的神经炎症可导致脑内BDNF含量降低,抑制神经可塑性,诱导情绪障碍的发生。研究发现,摄入植物乳杆菌可通过调节海马TLR4/BDNF信号通路,降低海马TLR4表达,增加BDNF含量[49]。约翰逊乳杆菌及干酪乳杆菌可改善肠道菌群组成及调节BDNF-TrkB信号通路改善抑郁行为[50—51]。

2 有氧运动可有效改善PSD

研究发现,有氧运动可有效提高脑卒中患者日常生活能力、缓解脑卒中患者抑郁情绪并提高其生活质量[52]。临床研究表明[53—64]:干预PSD的有氧运动主要包括有氧耐力训练和肢体功能训练,如步行训练、气功训练、肢体主被动训练等,结合患者病情和机能状况,运动负荷多为中等强度,频率每天15—60min,每周1—5次,疗程多在5—12周。运动对脑

卒中后抑郁情绪干预效果的meta分析研究结果显示：较高运动强度具有更好的改善效果[65]。运动形式及运动负荷的选择需根据患者机体情况做出合理及时地调整，临床中进行有氧运动干预可选用最大摄氧量及心率对患者的运动强度及安全进行监测。

3 有氧运动通过肠道菌群改善PSD的作用机制

已有研究发现，有氧运动可有效改善脑卒中、抑郁及PSD[66—68]，也可通过调节肠道菌群组成，维持肠道菌群稳态发挥对人体的有益作用。因此，探讨有氧运动、PSD、肠道菌群之间的联系对于寻找PSD治疗新靶点具有重要意义。

3.1 有氧运动可通过影响肠道菌群组成调节神经递质

有氧运动可增加脑内神经递质含量改善PSD，Arida RM等[69]总结以往研究发现对大鼠进行跑步运动可调节脑内5-HT、DA、GABA及谷氨酸等神经递质水平缓解抑郁情绪，而对肠道菌群进行干预可调节神经递质水平[70]，有氧运动可促进肠道可调节神经递质水平的菌群及SCFA含量增加。Mailing LJ等[71]通过对比经常运动与久坐女性肠道菌发现，经常运动的女性肠道普氏栖粪杆菌和丁酸菌丰度增加，二者可增加具有影响神经递质释放功能的SCFA含量。动物研究发现，通过对大鼠进行6天自由轮转运动后大鼠肠道来自硬壁菌门的乳杆菌属和真杆菌属增加，放线菌门的双歧杆菌属增加，3个属可促进GABA及5-HT合成，增加SCFAs含量而降低肠道pH值，抑制病原菌的生长及炎症反应。此外，乳酸杆菌，双歧杆菌水平与可调节食欲及饮食行为的血清瘦素含量成正相关[72]。因此有氧运动可能通过调节肠道菌群的组成影响神经递质及行为的变化。

3.2 有氧运动可通过增加肠道抗炎有益菌发挥抗炎作用

有氧运动可通过抑制炎症反应改善PSD，Li C等[68]发现对PSD大鼠进行4周的跑台训练可抑制磷酸酯酶与张力蛋白同源物升高介导的TLR4、NF-κB、NLRP3信号上调而发挥对海马神经元的保护，改善PSD。研究发现通过对大鼠进行自由轮转运动可减少肠道内TNF-α、促凋亡蛋白及IL-17含量并增加普氏栖粪杆菌含量。普氏栖粪杆菌产生的丁酸可调节NF-κB活化、氧化应激及肠道免疫并可向周围环境分泌抗炎物质，抑制机体炎症发展[73]。此外，有氧运动可抑制脑卒中后肠道菌群紊乱所诱发的炎症反应，Estaki M等[74]报道了运动受试者中产生LPS的革兰氏阴性菌减少，SCFA增加，在恢复肠道屏障同时可抑制LPS易位并阻碍其与细胞外TLR4结合，减轻炎症反应。有氧运动可能通过抑制肠道炎症及继发的神经炎症改善PSD。

3.3 有氧运动可增加肠道有益菌调节HPA轴

有氧运动可抑制GC水平上调，抑制HPA轴过度激活，缓解PSD[75]。肠道乳酸杆菌、双歧杆菌及鼠李糖乳杆菌等有益菌可纠正HPA轴的过度激活，Mahdieh MS等[76]通过临床研究证实有氧运动可增加人体肠道乳酸杆菌和双歧杆菌含量。Queipo-Ortuño MI等[72]研究也发现有氧运动可增加肠道双歧杆菌属及乳杆菌属含量。有氧运动并非都是有益的，强迫运动可被大鼠视为压力源，反而增强了HPA轴活性，降低了肠道内有益菌的含量，因此适度的有氧运动对于调节HPA轴活性具有较好的作用。

3.4 有氧运动可通过增加肠道有益菌上调BDNF

有氧运动可增加BDNF与脑源性神经营养因子前体之比，上调BDNF水平，增强神经可塑性，改善PSD[77]。陈凤等[78]通过动物实验证明肠道菌群的变化可影响BDNF的表达，研究发现，双歧杆菌和乳酸杆菌可上调BDNF水平，有助于神经元的增殖分化，从而发挥抗抑郁作用[79]。有氧运动可增加上述益生菌的含量，上调BDNF水平，双歧杆菌及乳酸杆菌的增加可减轻肠道菌群紊乱，保护肠道屏障，维护与迷走神经的传导，调节大脑BDNF浓度[80]。可知，有氧运动可通过增加有益菌调节BDNF浓度发挥抗抑郁作用。

4 小结

研究已证实肠道菌群与PSD紧密相关，但其深层机制尚未阐明。脑卒中可通过激活自主神经系统、释放GC增高肠通透性，升高粪肠球菌、变形杆菌及大肠杆菌等条件致病菌，降低合成神经递质的丁酸梭菌、乳酸菌及双歧杆菌等益生菌含量。肠道菌群失调诱发的肠道免疫通过肠脑轴引发神经毒性、破坏神经递质通路及神经营养因子含量、抑制HPA轴负反馈，分泌的GC不断诱发肠道菌群的失衡，导致肠道与大脑经脑肠轴相互影响的恶性循环，促使抑郁的发生发展。

有氧运动可增加肠道内双歧杆菌，乳酸菌等有益菌及SCFAs含量促进神经递质及BDNF含量增加。普氏栖粪杆菌及约翰逊乳杆菌的增多可抑制肠道炎症反应进而调节HPA轴活性，减少GC的释放，抑制机体炎症的发展而缓解卒中及PSD的严重程度。因此，适度的有氧运动可通过维护肠道菌群的平衡状态，发挥对PSD的有益作用。未来研究还需应用宏基因组学技术，通过有氧运动，揭示与PSD相关的菌群紊乱，并鉴别出有关的特定肠道细菌及功能，获得对PSD发生、发展的机制及诊断、治疗的新认识，以实现通过有氧运动调节PSD患者肠道菌群以改善患者健康的目的。

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