微生物学报
Acta Microbiologica Sinica
2024, 64(5): 1364–1377
http://journals.im.ac.cn/actamicrocn
DOI: 10.13343/j.cnki.wsxb.20230647

Review 综 述

肠道菌群-肠-脑-肌轴信号交流的研究进展

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孙丽薇, 耿倩, 郑国华. 肠道菌群-肠-脑-肌轴信号交流的研究进展[J]. 微生物学报, 2024, 64(5): 1364-1377.
SUN Liwei, GENG Qian, ZHENG Guohua. Research progress in signaling of gut microbiota-gut-brain-muscle axis[J]. Acta Microbiologica Sinica, 2024, 64(5): 1364-1377.

摘　要：肠道菌群及其代谢产物在老年神经退行性疾病、胃肠道疾病以及肌肉骨骼系统性疾病的发病与康复中的作用越来越受到关注。肠道菌群及其代谢产物可通过免疫、内分泌和神经系统等多种途径调节大脑神经或肌肉骨骼系统功能；反之，肠道、大脑或肌肉骨骼系统也可通过炎症、代谢或线粒体通路作用于肠道系统，调节肠道菌群微生态，形成肠道菌群与肠-脑、肠-肌、肠-脑-肌之间的双向信号交流机制，从而影响机体健康。因此，本综述总结了肠道菌群如何通过代谢产物、肠道通透性和免疫-神经通路建立起肠-脑-肌之间的相互联系，为促进大脑神经的可塑性和改善肌肉健康提供新思路。

关键词：肠道菌群；肠-脑-肌轴；肠道；大脑；骨骼肌

Research progress in signaling of gut microbiota-gut-brain-muscle axis

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Abstract: The roles of gut microbiota and its metabolites in the pathogenesis and rehabilitation

资助项目：国家自然科学基金(82074510)
This work was supported by the National Natural Science Foundation of China (82074510).
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Received: 2023-10-23; Accepted: 2024-02-29; Published online: 2024-03-08

of neurodegenerative diseases, gastrointestinal diseases, and musculoskeletal systemic diseases in the elderly are receiving increasing attention. Gut microbiota and its metabolites can regulate the functions of the cranial nervous system and the musculoskeletal system through various pathways, involving the immune, endocrine, and nervous systems. Conversely, the gut, brain, and musculoskeletal system can act on the intestinal system via inflammatory, metabolic, and mitochondrial pathways to regulate the gut microbiota. Accordingly, bidirectional signaling mechanisms are formed *via* the gut-brain, gut-muscle, and gut-brain-muscle axes, which affect the organism health. This review summarizes that gut microbiota establishes gut-brain-muscle interconnections mainly through metabolites, intestinal permeability, and immune-neural pathways, providing new ideas for improving the brain neuroplasticity and muscle health.
Keywords: gut microbiota; gut-brain-muscle axis; gut; brain; skeletal muscle

随着对肠道菌群研究的不断深入，人们逐渐认识到肠道菌群具有独立代谢的功能，其代谢物质可参与机体的神经—内分泌—免疫功能的调节过程，在维持机体动态平衡中发挥重要作用。肠道菌群与宿主相互作用、相互影响，共生形成较为稳定的肠道微生态，被称为人类的“第二大脑”，在维持机体健康、促进疾病发生与发展过程中发挥着至关重要的作用，逐渐被认为是宿主生理学和病理生理学的关键调节因子[1]。研究表明，肠道菌群和中枢神经系统之间可通过肠-脑轴进行双向调节，也可通过肠-肌轴的交流机制调节肌肉骨骼系统的生理、病理过程，影响神经系统和肌肉骨骼系统疾病的发展进程[2]。为了深入了解和探究肠道菌群与肠、脑、肌之间的信号交流机制，本文就其研究进展进行综述。

1 人体肠道菌群与健康的关系

肠道菌群和肠黏膜以及肠道免疫系统共同构成复杂的肠道微生态系统[3]，而作为肠道微生态的核心，肠道菌群主要包括厚壁菌门、拟杆菌门、变形菌门、放线菌门及疣微菌门 5 个门类，其中厚壁菌门与拟杆菌门是人体主要的菌群，占健康个体肠道细菌的 90%以上[4]。正常情况下，人体和肠道菌群间维持着一种相对稳定的“动态平衡”，共同维护人体健康；而当这种动态平衡失调时，可能诱发多种疾病[5]，如代谢性疾病[6]、神经系统与心理疾病[7]、肌肉骨骼疾病[8]的发展进程。

1.1 肠道菌群对人体健康的维护

肠道菌群对人体健康的作用是多维度、动态、复杂且广泛的，其对机体的健康维护作用主要是通过参与机体新陈代谢和免疫系统的调节，并维持机体的动态平衡。如一些有益的肠道菌群能将食物中不可消化的多糖分解成各种代谢产物，如短链脂肪酸(short chain fatty acids, SCFAs)，不仅可为肠道上皮细胞提供能量，维持肠道上皮黏膜屏障的完整性，还是一种有效的抗炎化合物，可通过抑制核因子-κB (nuclear factor-κB, NF-κB)的活性而减少白介素-6 (interleukin-6, IL-6)、肿瘤坏死因子-α (tumor necrosis factor alpha, TNF-α)等细胞因子的产生[9]，在控制慢性炎症等方面发挥重要作用。Leeuwendaal 等[10]发现一些肠道菌群可促进人类维生素 K、维生素 B12、叶酸和必需氨基酸的合成，参与骨代谢、脂质代谢及血糖代谢的生理过程。在免疫方面，有些肠道菌群可通过与肠道上皮细胞的竞争性结合，直接或间接地触发对外源性病原体的保护性免疫反应；也可通过诱导免疫

球蛋白 A (immunoglobulin A, IgA)、T 细胞来激活获得性免疫系统，参与全身免疫调节[11]。如有研究发现，肠道炎症可导致内分泌紊乱、影响肠道免疫功能，随着肠道菌群失衡，肠道中免疫球蛋白 M (immunoglobulin M, IgM)、IgA 的表达量显著降低[12]。

1.2 肠道菌群失调参与多种疾病的发展进程

正常情况下，肠道菌群与肠上皮细胞和免疫细胞共同维持着肠道微生态的平衡，但当受到年龄、饮食、药物、遗传、环境等的不良影响时，肠道微生态的平衡被破坏而引起肠道菌群失调，可促进人体多种疾病的发生与发展。肠道菌群失调，包括细菌组成失衡或对共生菌群的异常免疫反应等，是炎症性肠病(inflammatory bowel disease, IBD)、代谢性疾病、阿尔茨海默病(Alzheimer's disease, AD)及肌肉骨骼疾病发生发展的潜在机制。失调的肠道菌群可引起机体免疫、炎症反应，诱发炎症性肠病的发生。例如，当厚壁菌门丰度下降，变形菌门和放线菌门丰度上升，脆弱拟杆菌的功能及活性降低，可能会促进 IBD 的发生发展[13]。有文献报道，普拉梭菌在体内外均具有很强的抗炎作用，可维持肠道健康，而该菌减少可致肠黏膜保护功能降低，加速肠道疾病的发展进程[14]。另外，肠道炎症也会损伤正常的肠屏障功能，导致肠道菌群失调并发生细菌移位，从而加大炎症反应和代谢相关疾病的风险。有研究发现，长期进行高脂饮食的肠道菌群会增加肠道黏膜通透性、加剧全身炎症和脑部炎症[15]。如嗜黏蛋白阿克曼菌是一种黏蛋白分解细菌，能够有效改善高脂饮食诱导的结肠黏膜屏障功能障碍[16]。失调的肠道菌群也可影响机体淀粉样蛋白和神经递质的产生，并通过人体中枢系统影响认知以及情绪。如阿尔茨海默病是典型的中枢神经系统退行性疾病，其神经病理学特征是淀粉样蛋白 β 沉积，引发神经炎症，导致突触缺失和神经元死亡[17]。有研究发现，在肠道菌群失调的情况下，肠道菌群中的某些成分，如枯草芽孢杆菌和大肠杆菌，可分泌大量的脂多糖(lipopolysaccharide, LPS)和淀粉样蛋白，它们可能直接穿过因衰老或疾病而受损的肠道屏障或血脑屏障，促进 AD 的发展[18]。失调的肠道菌群也可影响营养的代谢与摄取、肠道炎症、胆汁酸代谢、维生素合成和肌酸降解过程从而影响肌少症的发生发展[19]。有研究发现，肌少症患者肠道菌群结构显著改变，肠杆菌科丰度增加，乳酸杆菌丰度明显减少[20]。

2 肠道菌群-肠-脑轴信号交流机制

肠道菌群-肠-脑轴(microbiota-gut-brain axis, MGBA)作为机体的肠道和大脑神经系统之间的双向交流途径，可通过免疫、内分泌和神经系统等多种途径对机体的大脑行为及认知功能产生影响，在维持肠脑关系中起着重要作用。

2.1 免疫调节途径

许多研究表明肠道菌群可通过影响先天免疫和适应性免疫参与肠脑轴的调节。先天免疫包括外周系统中的单核细胞和巨噬细胞、大脑中的小胶质细胞和星形胶质细胞等神经胶质细胞以及肠道中的树突状细胞和先天淋巴样细胞[21]。肠道的先天免疫反应包括激活 NF-κB 为特征的炎症反应[22]，也可以通过识别大多数微生物表达的病原相关分子模式(pathogen/microbe-associated molecular patterns, PAMPs/MAMPs)来激活[23]。上述反应一方面会产生趋化因子、促炎细胞因子诱导炎症反应[24]；另一方面也可激活免疫细胞释放抗菌素来维持和保护肠上皮黏膜屏障[25]。适应性免疫中肠道菌群及其代谢产物可通过促进 T 细胞释放炎症因子和抗炎细胞因子，影响

大脑的功能和精神状态[21]。Powell 等[26]发现肠道菌群代谢产物 SCFA、LPS 可以促进调节 T 细胞产生白介素-10 (interleukin-10, IL-10)。另有研究也发现无菌小鼠(GF 小鼠)免疫系统功能较无特定性病原体小鼠(SPF 小鼠)明显降低，但将正常菌群定殖 GF 小鼠后免疫功能会恢复正常状态[27]。因此，在维持大脑-肠道稳态中，免疫系统发挥关键的调节作用。

2.2 内分泌信号途径

下丘脑-垂体-肾上腺(hypothalamic-pituitary-adrenal, HPA)轴是机体主要的神经内分泌系统，可通过调节激素的分泌，影响消化、免疫系统，以及情绪和行为，是 MGB 轴双向调节的重要途径。当机体处于应激状态时，HPA 轴被激活，下丘脑的脑室旁核可分泌促皮质素释放因子(corticotropin releasing factor, CRF)释放到垂体前叶后增加促肾上腺皮质激素(adrenocorticotropic hormone, ACTH)的合成和释放，后者又作用于肾上腺，促进糖皮质激素(glucocorticoids, GCs)的合成[28]。GCs 是 HPA 轴的主要效应分子，可与多种组织细胞内受体结合，调节压力应激的生理适应。有研究报道肠道菌群及其代谢产物可激活肠道内分泌细胞释放促皮质素释放因子、肾上腺皮质酮以及酪酪肽(peptide YY, PYY)、生长素释放肽、胰高血糖素样肽-1 (glucagon-like peptide-1, GLP-1)等脑肠道肽，进而激活内分泌和神经信号影响中枢神经系统的能量调节[29]。例如，有研究表明肠道代谢产物 SCFAs 可以通过调节肠道激素的内分泌途径来改变肠道-大脑轴的功能。SCFAs 通过激活 G 蛋白偶联受体(G-protein-coupled receptors, GPCR)促进肠内分泌 L 细胞释放 PYY 和 GLP1[30-31]。GLP-1 已被证明能增强海马突触可塑性，改善学习、记忆和运动功能，这表明它对中枢神经退行性疾病具有潜在的神经保护作用。

2.3 神经信号通路

神经信号通路主要依靠中枢神经系统(central nervous system, CNS)、自主神经系统(autonomic nervous system, ANS)以及肠神经系统(enteric nervous system, ENS)三者之间进行交流。ENS 是 ANS 中最大的分支，在调节肠道菌群结构、肠道菌群相关的代谢物、神经递质和免疫信号，以及保护肠道屏障方面发挥着多方面的作用[32-33]。CNS 和 ENS 之间的双向交流通路构成 MGBA 的部分网络。迷走神经是大脑和肠道交流最直接的通路，肠道菌群或其代谢产物能够直接作用于肠神经系统内初级传入神经元的功能突触而向迷走神经传入发出信号[34]，一方面促进迷走神经调节代谢平衡和进食行为；另一方面促进迷走神经参与大脑、肠道和身体其他器官的炎症机制[33]。如鼠李糖乳杆菌分泌的神经递质 γ-氨基丁酸(γ-aminobutyricacid, GABA)、5-羟色胺、组胺等可以通过迷走神经传递到中枢神经系统，发挥抗抑郁或抗焦虑作用[35]。在小鼠实验研究中，迷走神经切断术已被证明可以阻断乳酸杆菌和双歧杆菌属的中枢信号传导。具体而言，影响乳酸杆菌和双歧杆菌代谢产生的乙酰胆碱，进而改变体内神经递质水平，导致其情绪调节作用失效[35-36]。也有研究发现肠道代谢产物 LPS 和 SCFA 与肠内分泌细胞受体结合时可释放 GLP-1 和 PYY 等介质，作用于迷走神经内的受体，调节肠道运动和分泌功能、炎症反应和黏膜防御等各种自主神经反应[37]。

3 肠道菌群-肠-肌轴信号交流机制

肠道菌群-肠-肌轴(microbiota-gut-muscle axis, MGMA)是指肠道菌群通过炎症、代谢及线粒体通路调控肠道屏障，促进蛋白质等营养物质的消化与吸收，参与骨骼肌能量代谢等途径。

3.1 炎症通路

肠道菌群的调节可以影响肠道的屏障功能，从而在维持促炎和抗炎反应的平衡方面发挥重要作用[38]。健康的肠道微生态环境可以在肠黏膜内诱导多种宿主反应，从而加强肠道屏障功能，在肠道内外发挥免疫调节作用[39]。抗炎因子和炎症因子的免疫平衡不仅可以抵御外来细菌的入侵，而且可以增加身体免疫耐受能力[40]。在一定条件下，肠道菌群的改变会损害肠道屏障的完整性，使 LPS 等有害产物进入血液，引发全身炎症，导致代谢紊乱，肌肉功能和质量下降[41]。有研究发现 LPS 水平升高会激活 Toll 样受体 4 (Toll-like receptors 4, TLR4)信号传导，促进自噬小体的形成以及肌肉萎缩相关基因 1 (atrogin-1)和肌肉环指蛋白-1 (muscle ring finger protein-1, MuRF-1)的表达而诱导 C2C12 肌管细胞萎缩[42]。TLR4 信号通路还可通过炎症级联反应释放大量炎性因子，诱导全身炎症反应，激活多条骨骼肌蛋白分解代谢通路，导致蛋白质合成与分解失衡[43]。Zhang 等[44]研究也发现，将老年菌群定殖给年轻大鼠，可增加年轻小鼠肠道通透性，使血浆中 LPS 浓度增加。Bindels 等[45]在白血病小鼠实验中明确了补充乳杆菌菌株的小鼠中肌肉萎缩标记物的表达下降，小鼠的肌肉质量和力量增加。因此，炎症反应在骨骼肌质量和功能中起着关键作用，TLR4 信号通路与肠道菌群-肠-肌轴密切相关。进一步研究炎症反应和肠道菌群之间的关系可能有助于治疗以骨骼肌质量和功能降低为特征的疾病。

3.2 代谢通路

肠道菌群是重要的“内分泌器官”，能够分泌多种生物活性物质，通过代谢通路影响人体骨骼肌代谢。过氧化物酶体增殖物激活受体(peroxisome proliferator-activated receptors, PPAR)是由配体激活的转录因子，参与调控骨骼肌葡萄糖和脂质代谢，是肌纤维表型的主要调节因子。研究发现，一些肠道菌群(如厚壁菌、梭杆菌、放线杆菌、粪肠球菌等)及其代谢产物是对过氧化物酶体增殖活化受体 δ (peroxisome proliferator-activated receptors δ, PPARδ)强有效的激活因子[46]。PPARδ 的表达可以激活腺苷单磷酸激活的蛋白激酶(AMPK)信号通路，增加过氧化物酶体增殖物激活受体 γ-共激活因子 1-α (peroxisome proliferators-activated receptors gamma co-activator 1α, PGC-1α)的水平，从而促进脂肪酸摄取和氧化、葡萄糖摄取和糖原合成，抑制脂肪生成和糖酵解[47]。有研究发现在 PPARδ 敲除小鼠肌肉和脂肪细胞中观察到能量代谢异常和肌纤维减少，以及葡萄糖耐受不良伴胰岛素抵抗[48]。PPAR 激动剂则可改善强直蛋白缺乏，补偿肌纤维损失，从而改善强直性肌营养不良[49]。另有研究证实肠道菌群产生的次级胆汁酸(bile acids, BAs)可作为信号分子调节肌肉中 G 蛋白偶联胆汁酸受体 1 (G protein-coupled bile acid receptor 1, GPBAR1)，促进甲状腺激素的活化，从而改善人体骨骼肌细胞的能量消耗[50]。同时 BAs 也可以通过激活核受体法尼糖 X 受体(farnese X receptor, FXR)调节机体能量、葡萄糖和脂质代谢[51]，改善骨骼肌细胞的能量代谢。

3.3 线粒体通路

骨骼肌线粒体功能障碍是肌肉质量和功能下降的原因之一。线粒体通过产生三磷酸腺苷(adenosine triphos-phate, ATP)满足肌肉纤维内的代谢需求，同时也是活性氧(reactive oxygen species, ROS)的主要来源。在衰老等情况下线粒体稳态的破坏造成 ROS 产生过多，合成骨骼肌蛋白质所需的 ATP 减少，从而加速衰老所引起的肌肉质量与力量的丧失。Lahiri 等[8]将 GF 小鼠的骨骼肌与 SPF 小鼠的骨骼肌进行了比较，发现 GF 小鼠表现为肌肉萎缩，胰岛素样生长因

子-1 (insulin-like growth factor-1, IGF-1)、骨骼肌生长和线粒体功能相关琥珀酸脱氢酶表达减少；而将 SPF 小鼠的肠道菌群移植到 GF 小鼠肠道后，参与 ATP 生成的各种酶在线粒体中被高度乙酰化，可显著改善 GF 小鼠肌肉萎缩程度和增加线粒体中能量的生成。提示肠道菌群代谢产物参与骨骼肌与线粒体的功能调节。最近有研究报道肠道菌群与线粒体在不同疾病的病理生理学中的密切联系[52]。肠道菌群通过释放代谢物、蛋白质或毒素来调节 ROS 的产生和线粒体的活性，从而加强与线粒体的联系。因此，肠道微生物群代谢物可能是导致线粒体功能失调的关键介质，是肌少症等疾病的重要促进因素[53]。建立菌群与线粒体之间的交流模式对于理解环境、微生物组和宿主之间错综复杂且不断变化的相互作用至关重要，最终将有助于更好地理解它们对健康和疾病的影响[54]。

4 肠道菌群-肠-脑-肌轴信号交流机制

肠道菌群通过肠-脑轴和肠-肌轴实现肠道菌群与大脑、肠道菌群与骨骼肌之间的双向交流，调节机体大脑和骨骼肌的功能。最近多项研究显示肠道菌群也可通过肠-脑-肌轴(gut-brain-muscle axis, GBMuA)与机体进行信号交流，参与 GBMuA 的潜在交流途径包括菌群代谢产物、肠道通透性、免疫-神经通路等。

4.1 肠道菌群代谢产物

4.1.1 短链脂肪酸

SCFAs 是由杆菌属、双歧杆菌属、丙酸杆菌属等发酵膳食纤维产生的代谢产物[55]。在胃肠道系统中的 SCFAs 能通过与肠上皮上的 G 蛋白偶联游离脂肪酸受体结合实现信号传导，也可以通过被动或主动转运进入到循环系统之中。细胞研究证实，SCFAs 可以穿过血脑屏障进入大脑影响小胶质细胞的形态和功能，调节神经营养因子水平，促进血清素生物合成，改善神经元稳态和神经炎症[56-58]。目前的研究者普遍认为，SCFAs 具有抗炎作用[59-60]，也可通过维持肠道屏障的完整性、调节紧密连接蛋白的表达来增强肠道屏障功能以及促进胃肠道的黏液生成，保护上皮细胞免受胃酸的损伤，抑制胃肠道炎症[61]。SCFAs 还可通过循环与骨骼肌上的游离脂肪酸受体 2 和 3 (free fatty acid receptor 2/3, FFAR 2/3)结合，并通过促进葡萄糖摄取和代谢的机制释放 IGF-1，激活胞内磷脂酰肌醇激酶(PI3K)-苏氨酸蛋白激酶 C (Akt)-雷帕霉素靶蛋白(mTOR)信号通路，刺激骨骼肌组织中的蛋白质合成并阻断蛋白质水解[62]。

研究表明骨骼肌的运动收缩可以调节肠道菌群组成，增加体内 SCFAs 水平，上调 PGC-1α 的表达，显著提高纤连蛋白 III 型结构域蛋白 5 (fibronectin type III domain containing 5, FNDC5)和鸢尾素的表达水平，激活肠-肌轴，改善线粒体功能和扩充肌肉线粒体体积，发挥其生物效应进而改善线粒体功能障碍，从而延缓肌少症的发生发展。而鸢尾素可经血液循环透过血脑屏障(blood brain barrier, BBB)进入脑组织，促进脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)表达，产生神经保护效应。另外，SCFAs 也可通过激活肠-脑轴，增加下丘脑与海马体中 BDNF 的释放，进一步影响学习、记忆及抗焦虑行为[63]。

4.1.2 犬尿氨酸

肠道菌群可以直接分泌色氨酸-犬尿氨酸代谢途径所需的酶，如铜绿假单胞菌可产生吲哚胺-2,3-双加氧酶(indoleamine 2,3-dioxygenase, IDO)和色氨酸-2,3-双加氧酶(tryptophan 2,3-dioxygenase, TDO)[64]，对色氨酸进行分解代谢，调节犬尿氨酸(kynurenine, KYN)的生成。GF

小鼠因免疫系统中识别胃肠道微生物成分的 Toll 样受体表达减少、激活 IDO 的作用下降，直接导致 KYN 代谢下降[65]。KYN 在中枢神经系统中通过不同细胞代谢产生不同的代谢产物，星形胶质细胞代谢产生具有神经保护性的犬尿喹啉酸(kynurenic acid, KYNA)，小胶质细胞代谢产生具有神经毒性的喹啉酸(quinolinic acid, Quin)，二者相互拮抗[66]。大量研究表明，色氨酸代谢及其下游代谢分支紊乱与阿尔茨海默病密切相关。在患有 AD、帕金森病、亨廷顿病等神经退行性疾病的老年患者中观察到 KYN 的失调，具体表现为 Quin 水平升高及 KYNA 下降[67-69]。Kaiser 等[70]发现，通过给予小鼠 KYN 药物治疗会降低肌肉质量和大小，同时增加肌肉脂质过氧化、蛋白质分解代谢和 ROS 水平。ROS 水平长期升高和脂质过氧化产物增加均由高水平的 KYN 诱导，与肌肉减少有关[71-72]。自愿轮跑可促进骨骼肌 PGC-1α 和犬尿氨酸转移酶(kynurenine aminotransferase, KAT)的释放，增加野生型小鼠血浆中 KYN 代谢物 KYNA 的水平[73]。这表明运动可以通过 PGC-1α/KAT 途径平衡 KYN 代谢，减轻 KYN 的神经毒性作用，从而改善认知功能。

4.1.3 脂肪酸酰胺

脂肪酸酰胺(fatty acid amides, FAAs)是由革兰氏阴性菌产生的肠道代谢物[74]。研究显示 FAAs 可通过模仿人类信号分子参与机体的神经传递和免疫调节作用[75]。动物实验[76]也发现 FAAs 可调节小鼠的身体活动，提高小鼠的运动表现，其机制为脂肪酸酰胺通过与内源性大麻受体 CB1 结合刺激肠内感觉神经，经脊椎与大脑相连，使大脑的腹侧纹状体增加，提高机体内多巴胺的含量，从而加强运动欲望来提高运动表现。

4.2 免疫-神经途径

肠道菌群-免疫-神经机制是连接肠道菌群-肠-脑-肌轴的另一个重要途径，肠道菌群在黏膜屏障免疫平衡中发挥重要作用。肠道菌群生态失衡所产生的 LPS 等有害肠道代谢产物进入血液后，可激活 TLR-4[77]，导致 NF-κB 蛋白水平和 c-Jun N 端激酶(c-Jun N-terminal kinase, JNK)磷酸化显著升高，诱导促炎细胞因子 IL-6 和 TNF-α 上调，从而导致代谢紊乱，肌肉功能和质量下降，诱导全身炎症[78]。Rubio 等[79]发现老年大鼠产 LPS 的肠道菌群明显增多，加剧肠黏膜屏障受损，使通透性增加形成“肠漏”。此外，LPS 也可通过激活 TLR4 促进自噬小体的形成，使得促炎细胞因子分泌增加，肌肉萎缩盒 F 基因(muscle atrophy F-box protein, MAFbx/atrogin-1)和肌肉环指蛋白-1 (muscle ring finger protein-1, MuRF-1)释放诱导 C2C12 肌管细胞萎缩[80]。

作为内分泌器官，骨骼肌可分泌 IL-6、IL-10，一方面改善肠道炎症反应，重塑肠道微生物系统，增加肠道菌群多样性，加强肠道屏障功能，降低细菌易位率和调节肠道通透性[81]；另一方面刺激肠道 L 细胞分泌 PYY、胰多肽和 GLP-1 等脑-肠肽在血液中释放，触发迷走神经传入神经作用于中枢神经系统[82]。骨骼肌还可通过独立于肠道菌群的免疫途径降低外周炎症反应水平，如通过促进肌肉 PGC-1α 的表达，抑制外周 NF-κB 活性[83]；激活 HPA 轴，减少 TNF-α 释放，改善外周炎症反应[84]。

4.3 肠-脑-肌轴与疾病病理机制的潜在关联

最近的研究结果表明，肠道菌群通过肠-脑-肌轴在改变或调节大脑和骨骼肌的功能方面发挥着重要作用，主要通过调节肠道通透性、SCFAs 生成、炎症作用等途径影响多种疾病的发生发展进程[85]。研究表明由于增龄等因素所引起的“肠道生态失调”可导致肠漏增加，使细菌易位进入血液[86]，一方面使产生 SCFAs 的有益菌(如厚壁菌和放线菌)的数量减少而无法抑制 LPS

诱导的炎症；另一方面有害菌如拟杆菌等生成过多的 LPS，通过刺激 TLR2、TLR4 受体，引发炎症反应[87]；而有些菌群如变形杆菌可产生丰富的细菌淀粉样蛋白，如卷曲纤维等可与 Toll 样受体-2 结合激活巨噬细胞，促进 TNF-α、IL-6 和白介素-1β (interleukin-1 β, IL-1β)等炎症细胞因子升高[88]，生成更多的 ROS 并促进氧化应激反应，导致神经炎症和肌肉萎缩[89]；这些细胞因子还可激活 NF-κB 信号通路，刺激促炎微小 RNA (microRNA, miRNA)的转录，激活神经炎症介质，并抑制小胶质细胞中的吞噬作用，导致神经退行性疾病的进展[90]，同时还会影响骨骼肌代谢和线粒体生物合成，进而影响骨骼肌和身体功能[91]。另外，肠道菌群改变也可引起肠道屏障损伤、促进肠道菌群及其代谢产物进入血液循环，进而通过促进炎性细胞因子的表达导致全身处于慢性低度炎症状态，而慢性低度炎症可通过炎症自噬等途径影响肌肉中的蛋白质分解合成，进而影响肌肉的质量和强度，甚至造成肌肉功能的损失[92-93]。肠道慢性炎症还可以激发免疫反应，降低血脊髓屏障和血脑屏障膜完整性，引起中枢神经系统炎症反应，进而导致神经变性，并通过引起脑部炎症和破坏 BBB 功能来促进认知衰弱的发展(图 1)[94]。

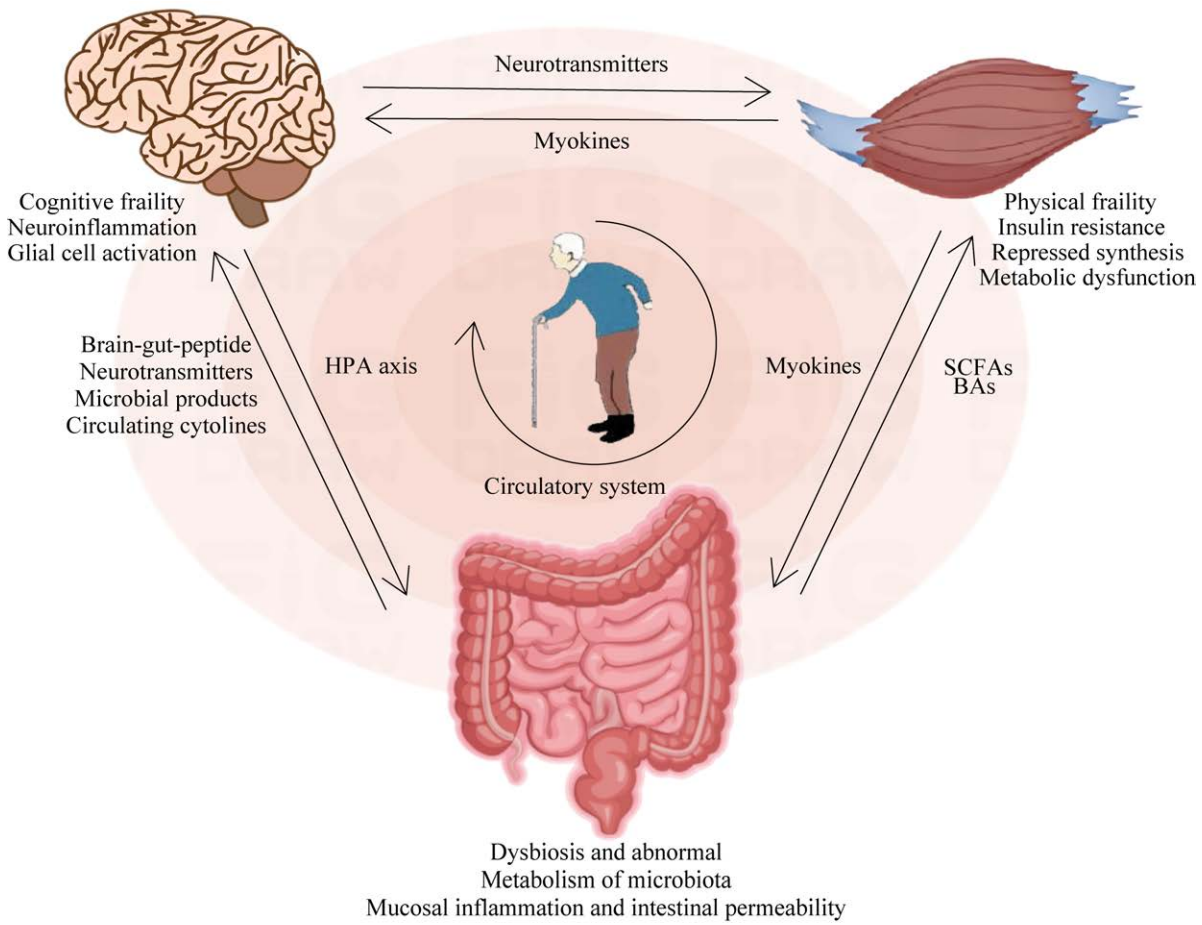

图 1　肠-脑-肌轴与认知衰弱间的潜在机制　SCFAs：短链脂肪酸；Bas：胆汁酸；HPA 轴：下丘脑-垂体-肾上腺轴

Figure 1　Gut-brain-muscle potential mechanism between the shaft and cognitive decline. SCFAs: Short-chain fatty acids; BAs: Bile acids; HPA axis: Hypothalamic-pituitary-adrenal axis.

5 小结

综上所述，肠道菌群及其代谢产物通过肠-脑、肠-肌或肌-肠-脑轴与机体进行双向动态的信号交流，并调节机体的免疫、代谢、神经系统和骨骼肌肉系统功能，对维持机体胃肠道、中枢神经、免疫和微生物系统的内环境平衡具有重要作用。肠道菌群与机体之间的双向交流影响多种疾病的发生发展，有助于深入探讨肠-脑-肌轴失调相关疾病的早期诊断等相关问题，同时也为防治这些疾病开辟了新的途径，拓宽了对认知功能、骨骼肌功能、最佳肠道菌群状态之间联系的理解。然而，虽然不断扩大的临床前研究为肠-脑-肌轴所涉及的机制途径提供了关键的见解，仍然需要强有力的临床研究来转化这些临床发现。

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