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微生物-肠道-脑轴在神经系统疾病中的研究进展*

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[摘要]　近 10 年来,针对微生物-肠道-脑轴(MGBA)在调控神经系统发育和功能方面的生理、病理学研究迅速展开;肠道菌群的失调可能通过肠道神经系统、微生物代谢物(如短链脂肪酸)、神经炎症和免疫介导的"屏障缺陷"推动多种神经系统疾病的发生和发展。该文就 MGBA 在阿尔茨海默病、帕金森病和创伤性脑损伤中的潜在致病机制进行综述,为临床干预和治疗神经系统疾病提供新的思路。未来研究将更加侧重于由动物模型向临床试验的转化,以及阐明 MGBA 特异性影响神经系统疾病的深层机制。

[关键词]　肠道微生物;微生物-肠道-脑轴;阿尔茨海默病;帕金森病;创伤性脑损伤
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Research advances of microbiota-gut-brain axis in neurological diseases*

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[**Abstract**]　In the past ten years, the physiological and pathological research on the microbe-gut-brain axis (MGBA) in regulating the development and function of the nervous system has been rapidly launched. Gut microbiota dysbiosis might promote the occurrence and development of neurological diseases through the enteric nervous system, microbial metabolites such as short-chain fatty acids, neuroinflammation and immune-mediated "defective barrier". This paper reviews the potential pathogenesis of MGBA in Alzheimer's disease (AD), Parkinson's disease (PD) and traumatic brain injury (TBI) to provide the new ideas for clinical intervention and treatment of neurological diseases. Future studies will focus on the transition from animal models to clinical trials and clarify the deep mechanism of MGBA specific influence on neurological diseases.

[**Key words**]　gut microbiome; microbiota-gut-brain axis; Alzheimer's disease; Parkinson's disease; traumatic brain injury

微生物-肠道-脑轴(microbiota-gut-brain axis, MGBA)作为一个新兴的名词在过去 10 年内反复出现,并于近年来迅速成为研究热点[1-2]。所谓 MGBA,即肠道内存在大量微生物与宿主共存,称为共生微生物群,该类微生物群可直接或间接参与调节交感神经兴奋性、副交感神经乙酰胆碱的释放、产生类神经递质(如多巴胺、去甲肾上腺素、肾上腺素、组胺、血清素等生物胺[3])、调控免疫细胞(T 淋巴细胞及调节性 T 淋巴细胞[4])、激活炎症因子,甚至是通过其代谢产物影响宿主颅脑正常生理活动,包括脑功能、情绪、认知功能,甚至是宿主的行为[5]。还有研究表明,孕妇体内细菌代谢产物(细菌肽聚糖)可通过胎盘影响胎儿神经发育及认知功能[6]。不仅如此,肠道共生菌群的多样性对婴儿的神经发生同样也具有重要的调节作用[7]。本文总结了肠道共生菌群和神经系统疾病之间潜在联系的机制及关联的多样性,而这些联系可能有助于更明确地揭开 MGBA 的神秘面纱。

1　MGBA 与神经系统的联系

近年来,有学者发现,MGBA 具有"双向性",完美地整合了宿主肠道和大脑活动,即大脑通过调控胃肠道及免疫功能,完善并影响肠道生理及共生微生物的构成[8],迄今已有多种证据表明,啮齿动物大脑可调节内脏敏感性,以及肠道运动、分泌、通透性等;而肠道微生物通过神经活性化合物作用于大脑[9]。最近一项研究表明,肠道共生菌源性代谢植酸和肌醇三磷酸调节组蛋白去乙酰化酶 3(histone deacetylase 3, HDAC3)能保护小鼠肠道上皮细胞修复,从而验证了 HDAC3 是校准宿主对微生物信号反应的收敛表观遗传传感器[10],这无疑从表观遗传学层面揭示了宿主和益生菌的共同进化导致宿主-微生物共生关系的发展。

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有学者在探讨微生物与社会脑的关系时，发现“宿主-微生物”关系可能通过 MGBA 内源的一系列极其复杂的机制影响着社会脑和行为的进化[11]。这些结论从遗传与进化角度间接为 MGBA 的探索开拓了更为广阔的空间。

肠道共生菌群除参与宿主神经系统的生理活动外，还通过 MGBA 对多种神经系统疾病的发生、发展起着至关重要的作用。早期研究发现，功能性胃肠疾病与焦虑、抑郁，甚至是认知障碍等功能性神经疾病相互影响[9,12]。病理状态下肠道微生物的组成与生理状态时的菌群组成有明显差异，且在不同疾病及同种疾病的不同时期均存在其共性和特异性[13]。脑卒中患者粪便中细菌多样性升高，而阿尔茨海默病（Alzheimer′s disease，AD）患者粪便中细菌多样性降低；但二者拟杆菌门细菌均减少，反之，反刍乳酸菌增多[4]。当针对性差异处理肠道菌群后患者预后便产生明显变化。联用万古霉素和氨苄西林抑制肠道菌群对脑卒中小鼠神经元具有保护作用[13]；将无特异性病原体小鼠粪便移植入无菌小鼠肠道从而逆转了无菌小鼠血脑屏障缺陷[14]。

2 AD

AD 是一种呈渐进性加重的神经退行性病变，表现为早期学习和记忆障碍，随之可出现语言和视觉空间功能、执行功能及社会行为等方面的障碍[15]。其经典的病理特征为细胞外 β 淀粉样蛋白（amyloid beta peptide，Aβ）沉积并形成神经炎斑块，细胞内高度异常磷酸化 Tau 蛋白蓄积形成神经原纤维缠结[16]。

目前的研究普遍认为，AD 发病机制包括神经炎症、免疫介质激活和氧化应激[17-18]。近年来，也有学者提出“传染性假说”，即颅内细菌感染诱导机体抗菌防御机制的激活——Aβ 纤维化[19]。小鼠脑实质内接种沙门菌所引起的细菌性脑脊髓炎可诱导 Aβ 产生；老年 AD 患者粪便微生物组中引起促炎条件的类群丰度较高，并与 Aβ 的产生具有相关性。这些证据均提示肠道微生物群与 AD 病理进程的发生、发展关系紧密。CCAAT/增强子结合蛋白（CCTTA enhancer binding proteins，C/EBPs）家族可促进肠道微生物失调的 5XFAD 转基因小鼠小胶质细胞和星形胶质细胞内炎症介质的生成和释放，进而通过 C/EBPβ 天冬酰胺内肽酶（C/EBPβ/AEP）信号轴促进 Aβ 和高度异常磷酸化 Tau 蛋白沉积；慢性抗生素或富含 R13 益生元的干预可抑制该炎症通路的激活，缓解 AD 病理进展[20]。

事实证明，影响 AD 发病的炎症介质绝不仅存于颅内，全身急、慢性炎症均会对认知功能产生影响并加速病变过程，原因可能是血脑屏障（blood-brain barrier，BBB）的功能缺失，如肠道菌群产生内毒素破坏 BBB 完整性，进而使炎症因子浸润及微生物衍生代谢物（如苯丙氨酸或异亮氨酸）产生促炎作用[21]。革兰阴性菌产生的脂多糖（lipopolysaccharide，LPS）可通过激活炎症通路中的核因子 κB（nuclear factor kappa B，NF-κB）降低补体因子 H 的表达[22]或促进微小 RNA-146a 表达，从而启动慢性免疫反应，最终促进 AD 进展。但共生菌群似乎存在一个自身的“稳态”系统，即某些肠道益生菌可修复已被内毒素破坏的 BBB 通透性，而其缺失同样可以造成 BBB 功能受损[12,23]。

3 帕金森病（Parkinson′s disease，PD）

作为神经退行性变的家族成员 PD 被定义为一种进行性运动障碍，包括运动迟缓、强直、震颤及严重的非运动障碍表现。PD 潜伏期长，表现为嗅觉缺失、便秘、睡眠障碍等[24]。其典型的病理改变包括大脑黑质和纹状体多巴胺能神经元丢失，以及神经元和轴突内 Lewy 小体（由多种蛋白质如 α-synuclein-positive 组成的蛋白质集合体）形成[25]。

最新研究发现，在 PD 的典型病理改变中，Lewy 小体内的 α-synuclein 表达于肠内神经元和肠内分泌细胞，有学者猜想，PD 病理可能起源于肠道[26]。而将 α-synuclein FPP 注入啮齿动物肠道示踪发现，其可通过迷走神经扩散入脑组织，切断迷走神经可阻断其传播通路，从而降低患 PD 的风险[27]。这些发现无疑将肠道微生物与 PD 通过 MGBA 更为紧密地联系在一起。同样，越来越多证据提示，肠道微生物的失调，包括肠道微生物的定性和定量变化均可能是 PD 的危险因素之一，并与其疾病进展密切相关[28]。

益生菌作为一类肠道定植菌也可以参与抵御有害微生物（竞争排斥）、产生短链脂肪酸（SCFA，肠道微生物发酵膳食纤维产生的代谢副产物），如小鼠通过口服肠道内的酪酸梭菌可逆转肠道微生物失调，进而改善运动缺陷、多巴胺能神经元丢失、突触功能障碍及抑制小胶质细胞的激活，并降低结肠及脑组织内胰高血糖素样肽-1 受体水平[28]。一项针对 PD 患者与正常老年人肠道微生物的差异性回顾性研究结果显示，PD 患者肠道内可产生丁酸盐的肠道微生物丰度较对照组明显下降，但该研究中强调肠道菌群的“丰度”而并非是“多样性”[29]；而丁酸盐可能通过介导肠道屏障完整性和神经免疫机制改变肠道通透性及 MGBA 通讯，进而导致 PD 患者肠道内普雷沃菌科和益生菌种水平下降[26]。同样，作为肠道菌群代谢产物的内毒素——LPS 可介导 BBB 功能障碍，从而激活核苷酸结合寡聚化结构域样受体 3（NLRP3）炎症小体，进而导致线粒体功能障碍、白细胞介素-1β 表达及胰岛素抵抗，最终导致神经功能的损伤和 PD 的发病[27,30]。事实证明，PD 患者粪便中参与 LPS 生物合成的基因明显增多，而参与代谢的基因明显减少[27]。

4 创伤性脑损伤（traumatic brain injury，TBI）

TBI 的致死、致残率极高，在过去 10 年中不断攀

升的发病率使其成为危及人类健康的全球性问题[31]。TBI 可分为原发性损伤和继发性损伤，其中继发性损伤可通过炎性反应、钙离子超载、BBB 通透性改变等一系列病理生理过程，最终导致神经元凋亡[32]。

近年来，随着对 MGBA 研究的不断深入，已逐渐接受并发现肠道微生物不仅可影响神经退行性变相关慢性疾病的发生、发展，而且参与了继发性脑损伤的病理进程。目前，较为被接受的是肠道菌群与继发性脑损伤相互影响的通路为迷走神经传导的神经信号、肠道激素相关的神经-内分泌轴、神经免疫及炎症因子相关通路[33-35]。实验证实，小鼠在 TBI 早期便可通过激活交感神经增加肠道通透性，最终使肠道微生物发生改变和移位，如嘉斯利乳杆菌、普雷沃菌科减少，而舒尔茨真杆菌、消化球菌科增加[36]。此外，肠道菌群还可通过 TBI 后免疫通路激活介导而发生转移，所谓“肠道屏障”除阻挡肠道微生物入侵肠道黏膜外，还包括固有层潘氏细胞免疫细胞分泌的抗菌肽[37]。TBI 可导致高迁移率球蛋白 B1 释放，进而与肠上皮的受体 CD24 结合，抑制 Paneth 细胞释放抗菌肽，促进炎性反应，并可结合 NF-κB 信号通路最终破坏肠道微生物稳态[38]。

5 小结与展望

MGBA 这一概念的出现将肠道菌群失调与神经系统疾病有机地结合在一起，并在近年来的基础研究和临床研究中取得重大发现，尤其是在神经退行性变领域，如 AD、PD、自身免疫性脱髓鞘、自闭症谱系障碍、多发性硬化和癫痫，甚至 TBI 及抑郁、焦虑等神经心理疾病[39-40]。而其关键性机制大多与肠道屏障和 BBB 的完整性有着密切关联，甚至可以将其称为“屏障缺陷性疾病”；而消化道生态失调和“屏障缺陷”为肠道微生物源性神经毒素的跨界运输提供了重要的通道，即从全身炎症到中枢神经系统炎症及免疫激活，最终发展成为神经系统病变。

然而，现有对于肠道菌群影响神经系统疾病的发生、发展的研究，多以现象性描述及回顾性研究为主，缺少关键机制的研究和大样本前瞻性研究。未来的研究应进一步关注肠道菌群失调通过 MGBA 影响神经系统疾病的机制及单一菌种对神经系统疾病的特异性影响。

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(上接第 146 页)

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