基于肠道菌调控的癫痫治疗药物及干预新策略研究进展

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摘要: 癫痫及其共病影响全球数以千万人的健康, 病因复杂且尚未完全明确。目前, 临床上以药物治疗为主, 但抗癫痫发作药物普遍存在耐药性强、不良反应严重等问题, 亟需开发新型治疗药物与干预策略。肠道菌群在中枢神经系统疾病的发生发展中扮演重要角色, 通过神经、内分泌、免疫和代谢途径与大脑相互作用, 进而影响疾病的进程。研究表明, 通过生酮饮食、粪菌移植、益生菌等以肠道菌群为靶点的干预方式在癫痫的治疗中展现出巨大潜力。肠道菌群在癫痫发病和治疗中发挥的作用仍有诸多未解之谜, 深入探索肠道菌群对癫痫的调控作用, 对于开发新疗法意义重大。

关键词: 癫痫; 肠道菌群; 发病机制; 抗癫痫发作药物; 干预新策略

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Research progress on drug and new intervention strategies for epilepsy based on gut microbiota regulation

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Abstract: Epilepsy and its comorbidities affect the health of tens of millions of people, characterized by complex and poorly understood etiology. While anti-seizure medications (ASMs) remains the primary treatment approach, antiepileptic drugs face issues like drug resistance and severe side effects, highlighting an urgent need for novel drugs and therapeutic strategies. The gut microbiota plays a crucial role in the pathogenesis of central nervous system diseases. They can interact with the brain through the nervous, endocrine, immune and metabolic systems, thereby influencing the course of the disease. Some researches have indicated that gut microbiota-targeted interventions, such as the ketogenic diet (KD), fecal microbiota transplantation (FMT), and probiotics, demonstrate the significant potential in the treatment of epilepsy. However, there are still many unsolved mysteries regarding the role of gut bacteria in the onset and treatment of epilepsy. Investigating the regulatory role of the gut microbiota in epilepsy and its comorbidities holds great significance.

Key words: epilepsy; gut microbiota; pathogenesis; antiepileptic drug; new intervention strategy

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癫痫是一种由多种病因引起、以脑部神经元异常同步放电为特征的中枢神经系统慢性疾病, 具有发作突然、短暂、可自行缓解及反复发作等特点。据世界卫生组织 (WHO) 报告, 癫痫是全球最常见的慢性神经系统疾病之一, 影响全球超过 5 000 万人的健康, 每年新增病例约 500 万。在我国, 癫痫的总体患病率约为 4‰～7‰, 患者总数近千万。该疾病不仅导致较高的致残率和过早死亡率, 还带来了巨大的社会经济负担, 其伤残调整年在所有神经系统疾病中位于前列。目前癫痫治疗以药物和手术为主, 但仍面临患者对药物反应不佳、不良反应明显及病情反复等问题[1]。尽管抗癫痫药物研发已取得显著进展, 新型药物不断应用于临床, 流行病学数据显示, 一旦发展为难治性癫痫, 患者死亡率显著上升。并且, 约 20%～40% 的患者对现有的一线或二线抗癫痫药物存在耐药性, 疗效欠佳, 且常出现反复发作、撤药综合征及认知损害等不良反应[2]。现有抗癫痫药物多通过降低神经兴奋性或增强抑制性来控制发作, 属于对症治疗, 且作用机制较为单一。阐明癫痫的发病机制、研制针对病因的治疗策略, 仍是当前科研面临的重要挑战。

肠道菌群是人体最庞大而复杂的微生物群落。最新研究表明, 人体内肠道菌群数量达 10^{14} 以上, 主要包括厚壁菌门 (如乳杆菌)、拟杆菌门、放线菌门、变形菌门 (如大肠杆菌) 和疣微菌门[3]。肠道菌群编码的基因超过 300 万个, 远多于人类基因组, 极大地丰富了宿主的遗传信息功能。肠道菌群作为“隐形器官”, 与人体的相互作用研究逐渐受到科学界的重视。研究发现, 肠道菌群处于动态变化中, 并受遗传背景、生活习惯及疾病状态等多种因素影响; 与肥胖、糖尿病等代谢性疾病[4-7], 心血管系统疾病[8], 肿瘤[9]及中枢神经系统疾病[10-12]的发生发展密切相关。其中, 癫痫作为一种常见慢性神经系统疾病, 其与肠道菌群的关联近年来受到广泛关注。

肠道和大脑之间存在复杂的、多维的相互作用, “肠–脑”轴概念的提出促使肠道菌群在许多中枢神经系统疾病发病机制中的作用成为研究热点[13-15]。多项研究已表明, 肠道菌群参与帕金森病和阿尔茨海默病等神经系统疾病的发展[16-18]。肠道菌群可通过多种途径与大脑交互, 包括产生代谢产物[4]、改变神经递质水平[19]、激活迷走神经, 以及调节内分泌和免疫反应等。研究显示, 通过生酮饮食、粪菌移植、益生菌等恢复肠道菌群稳态的干预方式, 已成功应用于癫痫治疗。癫痫患者除癫痫发作外, 还常伴有代谢性和神经性共病, 严重影响患者的生活质量并增加死亡风险[20]。本文将从癫痫的分类、基于肠菌调控的癫痫发病机制、治疗药物及干预新策略等方面进行论述, 以期为癫痫的防治提供科学依据。

1　癫痫的分类

根据临床症状, 国际抗癫痫联盟 (International League Against Epilepsy, ILAE) 建议将癫痫发作 (seizure) 分为两种主要类型[21]: 局灶性发作和全身性发作。该分类基于 3 个关键因素: 发作起源的脑区位置、发作时意识状态及发作特征。局灶性发作起源于大脑局部区域异常放电, 可分为单纯部分性发作 (意识保留) 和复杂部分性发作 (伴意识障碍)。全身性发作俗称“大发作”, 涉及大脑双侧同时异常放电, 包括 6 种亚型: 全面性强直–阵挛发作、失神发作、肌阵挛发作、阵挛发作、强直发作和失张力发作[22]。

并非所有癫痫发作 (seizure) 的患者均被诊断为癫痫 (epilepsy)。根据发作类型, 癫痫可分为局灶性癫痫、全身性癫痫及局灶性继发全身性癫痫。按病因 ILAE 将癫痫分为免疫性、代谢性、感染性、遗传性、结构性和未知性癫痫[22]。根据发病机制, 又可将其分为原发性 (特发性) 癫痫和继发性 (症状性) 癫痫。原发性癫痫与脑损伤无关, 病因未明; 而继发性癫痫与脑损伤相关, 如头部创伤、脑部疾病 (肿瘤、中枢神经系统感染、脑血管病、神经退行性疾病)、感染、围产期损伤、发育异常 (如皮质发育不良) 及代谢紊乱等[23,24]。

2　基于肠道菌群调控的癫痫发病机制

癫痫的发病机制极为复杂, 主流观点认为其核心是神经元异常放电。癫痫发作可导致神经元损伤, 与细胞凋亡密切相关。反复发作还会引起胶质细胞增生、苔藓纤维出芽、突触重构等脑结构与功能改变, 进而加重癫痫, 形成恶性循环, 这也是癫痫频繁发作和难治的主要原因之一。发病机制涉及神经递质失衡、离子通道功能异常、胶质细胞功能障碍、神经免疫炎症及分子遗传机制等[25-28], 同时还与突触可塑性、线粒体功能及神经血管单元完整性相关。近年研究表明, 肠道菌群可能成为癫痫治疗的潜在靶点。

2.1　癫痫患者的肠道菌群特征

与健康人相比, 癫痫患者肠道菌群组成发生显著改变, 菌群代谢物变化及与宿主免疫系统的相互作用可能导致多样性降低和生态失调。癫痫患儿的肠道菌群结构常呈现不成熟特征, 表现为多样性较低和拟杆菌门丰度下降[29-33]。多项人群研究显示癫痫患者存在肠道菌群失调, α-多样性存在显著差异, 但不同研究中多样性变化趋势不一致。肠球菌、乳杆菌和双歧杆菌在癫痫患者中普遍呈增加趋势, 不同研究结果存在一定差异。如癫痫患儿中放线菌门增加, 而成年患者则表现为变形菌门升高、厚壁菌门降低。这些差异

可能受年龄、癫痫类型、样本量、地区、季节及饮食习惯等因素影响。此外, 癫痫患者常伴有胃肠道不适, 炎症性肠病患者也更易发生癫痫[34,35]。肠道菌群失调甚至可能诱发遗传性癫痫, 研究表明恢复肠道菌群对雷特综合征等遗传性癫痫具有一定的治疗作用[36-38]。因果关系研究发现, 宿主遗传驱动的Melainabacteria水平升高与全面强直−阵挛发作风险降低相关; β-变形菌 (Betaproteobacteria) 和伯克霍尔德氏菌 (Burkholderiales) 水平变化与青少年肌阵挛癫痫风险降低相关; 而韦荣球菌 (Veillonellaceae) 则与儿童失神癫痫风险升高相关[39]。不同类型的癫痫患者的肠道菌群改变如表1所示[30-32,35,40-49]。

尽管多项研究一致表明癫痫患者存在肠道菌群失调, 但在具体门或属的变化上 (如变形菌门、放线菌门、厚壁菌门等) 仍存在矛盾的结论。这些差异可能源于多种因素, 如研究对象的高度异质性: 各研究纳入的癫痫患者在年龄 (儿童和成人)、癫痫类型 (局灶性和全身性)、病因 (特发性和症状性)、疾病严重程度 (耐药性和药物敏感性) 及用药方案上的差异。这些因素会独立地影响肠道菌群的构成。此外, 还有地域与饮食等混杂因素, 如表1所示, 研究人群来自中国、土耳其、意大利、韩国等不同地区。饮食习惯、生活环境、遗传背景等因素对肠道菌群的结构和功能具有重要影响。目前的研究结果仅揭示了肠道菌群与癫痫存在相关性, 未来研究需要通过更大样本量、更严格的纳入标准 (如同质化的癫痫类型和用药状态)、多中心协作以及宏基因组学等更精准的技术手段, 来控制这些混杂因素, 从而阐明现有结果存在差异的原因, 并深入挖掘肠道菌群作为癫痫诊断和干预靶点的巨大潜力。

2.2 肠道菌群介导的癫痫发生机制

肠道菌群通过多种途径与中枢神经系统形成双向连接, 包括调节神经递质合成、神经免疫与炎症系统、下丘脑−垂体−肾上腺轴 (hypothalamic-pituitary-adrenal axis, HPA) 及迷走神经 (vagus nervous system, VNS) 等[50,51], 并通过影响神经发生、胶质细胞功能、髓鞘形成、神经传递、神经炎症及血脑屏障通透性等过程参与癫痫的发生与发展[52,53]。

2.2.1 神经递质 神经递质既可被菌群直接分泌, 也可通过其代谢产物间接刺激宿主细胞产生。肠道菌群可调节神经递质的合成与代谢。菌群可合成γ-氨基丁酸 (γ-aminobutyric acid, GABA)、去甲肾上腺素、谷氨酸、多巴胺和5-羟色胺等[54]。如肠球菌、埃希氏菌和链球菌可产生5-羟色胺; 双歧杆菌和乳杆菌生成GABA; 埃希氏菌和芽孢杆菌则产生去甲肾上腺素和多巴胺[55]。此外, 肠道菌群还能够产生苯二氮卓类结构的代谢物[56]。除GABA可通过血脑屏障转运体进入大脑外, 其他肠道神经递质虽可穿过肠黏膜, 但难以直接作用于大脑[57]。肠道菌群代谢物 (如色氨酸代谢物、短链脂肪酸等) 通过肠神经系统、迷走神经及外周受体间接影响脑功能, 是菌群调控中枢神经递质的主要方式[58,59]。

研究显示, 短链脂肪酸水平降低会破坏兴奋性与抑制性递质平衡, 导致GABA和5-羟色胺减少[60,61], 炎症细胞因子和谷氨酸水平升高, 从而诱发癫痫[62,63]。除直接影响神经递质外, 菌群还可调节GABA和*N*-甲基-*D*-天冬氨酸 (*N*-methyl-*D*-aspartic acid, NMDA) 受体在海马、杏仁核和蓝斑等脑区的表达, 影响谷氨酰胺−谷氨酸-GABA循环[64]。长期使用乳酸菌和双歧杆菌可增加小鼠海马体中$GABA_A$受体表达及海马中GABA和谷氨酸水平[58,65-67]。菌群代谢物胆汁酸也可通过毒蕈碱受体及GABA、NMDA受体影响认知功能[68]。菌源γ-谷氨酰化氨基酸的减少及海马GABA/谷氨酸水平的升高与癫痫发作相关[69]。此外, 肠道菌群发生结构和功能的改变, 影响机体诸多代谢通路的变化。癫痫患者体内乳酸、柠檬酸、胆碱、酪氨酸、牛磺酸、腺苷等代谢物可能成为潜在生物标志物, 相关代谢途径包括丙氨酸、天冬氨酸和谷氨酸代谢, 甘氨酸、丝氨酸和苏氨酸代谢等[70]。可见, 肠道菌群可以通过直接或间接作用影响神经递质或/和其受体参与癫痫发病的调控。

2.2.2 免疫炎症 肠道免疫系统主要通过肠道相关淋巴组织维持肠道菌群与宿主之间的平衡。细胞毒性T细胞$CD8^+$和辅助性T细胞 (helper T cells, Th) $CD4^+$是上皮层中最具代表性的免疫细胞。肠道菌群可以调节肠道内和全身免疫细胞的分化和功能。特定共生菌可以塑造肠道固有层中的辅助性T细胞和调节性T细胞 (regulatory T cells, T-reg), 如诱导Th17细胞分化并促进IL-17分泌[71]。在稳态状态下, 肠道菌群引起免疫系统的低激活状态, 刺激多种类型的T细胞和巨噬细胞分泌促炎因子 (IL-1β和TNF-α)[72]。慢性免疫激活可导致肠屏障和血脑屏障破坏 (occludin和ZO-1表达下降) [73], 全身炎症水平升高, 激活外周免疫反应, 再通过神经元传递细胞因子/趋化因子信号, 触发中枢炎症[64], 增加神经元兴奋性, 加剧癫痫发作[74,75]。神经炎症虽可增强海马齿状回网络兴奋性, 但其本身不足以致痫, 而是通过降低发作阈值增加了癫痫的易感性, 因此炎症被视为重要的致痫驱动因素[76]。

肠道菌群可以通过复杂的神经免疫信号调节小胶质细胞和星形胶质细胞的成熟、活化, 进而影响癫痫的疾病进程[77]。如可以通过产生代谢物调控神经组织的

Table 1　Alterations in gut microbiota in patients with epilepsy

Participant	Alteration in gut microbiota	Reference
Thirteen Chinese patients with epilepsy (average age of 4.6 ± 2.7 years), and 7 healthy infants (average age of 4.9 ± 2.5 years)	Decreased levels of Proteobacteria phylum and abundance of increased Actinobacteria phylum	[40]
Twenty-two Chinese patients with epilepsy (average age of 30.4 ± 8.8 years) and 10 normal controls (average age of 28.9 ± 7.6 years)	Increased levels of Actinobacteria phylum, Bacteroidetes, and Proteobacteria phylum; decreased abundance of Firmicutes phylum; reduced genera of *Dialister*, Alistipes, *Faecalibacterium*, *Phascolarctobacterium*, *Subdoligranulum*, *Megamonas*, *Enterobacter*, *Clostridium*, *Holdemanella*, *Roseburia*, *Kocuria*, *Bacteroides* and *Coprococcus*; increased genera of *Ruminococcus*, *Blautia*, Dorea, *Collinsella*, *Hafnia*, *Parabacteroides*, *Turicibacter*, *Streptococcus*, *Eubacterium*, *Prevotella*, *Fusicatenibacter*, *Romboutsia*, *Bifidobacterium*, *Enterococcus*, *Lactobacillus*, *Veillonella* and *Escherichia*	[41]
Twenty Turkish patients with epilepsy (average age of 8 ± 2.6 years) and 7 healthy children (average age of 7.3 ± 2.9 years)	Higer the genera *Flavobacterium*, *Holdemania*, and *Hyphomicrobium*; the genera of *Megamonas* and *Coriobacterium* were observed only in the epilepsy group	[42]
Ten Chinese children with focal epilepsy (average age of 6.35 years) and 14 healthy children (average age of 5.15 years)	Significant differences in alpha diversity, higer Actinobacteria phylum; increased levels of *Escherichia/Shigella*, *Streptococcus*, *Collinsella* and *Megamonas*; decreased abundance of *Faecalibacterium* and *Anaerostipes*	[43]
Forty-one Chinese patients with epilepsy (average age of 31.6 ± 12.2 years) and 30 healthy controls (average age of 34.6 ± 7.6 years)	Increased genera of *Fusobacterium*, *Megasphaera*, *Alloprevotella* and *Sutterella*	[44]
Twenty-four Chinese patients with epilepsy (average age of 30.21 ± 15.53 years) and 50 healthy controls (average age of 30.1 ± 5.72 years)	The *α*-diversity was lower; increased levels of Proteobacteria phylum and Actinobacteriota phylum, while the relative abundance of *Bacteroidota* decreased; 23 genera were enriched, including *Faecalibacterium*, *Escherichia-Shigella*, *Subdoligranulum* and *Enterobacteriaceae-unclassified*; 59 genera including *Bacteroides*, *Megamonas*, *Prevotella*, *Lachnospiraceae-unclassified* and *Blautia* decreased	[45]
Twelve Chinese patients with epilepsy (average age of 26.33 ± 12.05 years) and 12 healthy controls (average age of 28.5 ± 4.27 years)	The *α*-diversity was higher; increased levels of Actinobacteria phylum; increased genera of *Enterococcus*, *Anaerostipes*, *Bifidobacterium*, *Bacteroides* and *Blautia*	[46]
Eight Italian children with epilepsy (average age of 8.9 ± 4.3 years) and 7 healthy controls (average age of 8.0 ± 4.2 years)	Increased genera levels in *Akkermansia* and *Proteobacteria*; reduced abundance in *Faecalibacterium*	[47]
Fifty-five Chinese patients with drug-resistant epilepsy (average age of 26.33 ± 12.05 years) and 46 healthy controls (average age of 28.5 ± 4.27 years)	Enrichment of bacterial taxa in Actinobacteria and Verrucomicrobia and Nitrospirae; and the genera *Blautia*, *Bifidobacterium*, *Subdoligranulum*, *Dialister*, and *Anaerostipes*	[35]
Eight Korean patients with intractable epilepsy (average age of 3.17 years) and 32 healthy parents	The levels of Bacteroidetes and Proteobacteria were lower, and Actinobacteria was higher; increased abundance of *E. faecium*, *B. longum* and *Eggerthella lenta*	[31]
Thirty Turkish patients with idiopathic focal epilepsy (average age of 41.3 ± 12.2 years) and 10 healthy conrols (average age of 31.7 ± 6.8 years)	Proteobacteria phylum was higher; increased genera of *Campylobacter*, *Delftia*, *Haemophilus*, *Lautropia*, and *Neisseria*; 10.6% of the patients were detected genera of *Leptotrichia* and *Fusobacterium*	[48]
Twenty-five Chinese paediatric patients with cerebral palsy and epilepsy (average age of 108.13 ± 42.83 months) and 21 healthy controls (average age of 70.43 ± 20.93 months)	Incaresed genera of *Bifidobacterium*, *Streptococcus*, *Akkermansia*, *Enterococcus*, *Prevotella*, *Veillonella*, *Rothia*, and *Clostridium IV*; drcreased genera of *Bacteroides*, *Faecalibacterium*, *Blautia*, *Ruminococcus*, *Roseburia*, *Anaerostipes*, and *Parasutterella*	[32]
Forty-two Chinese patients with drug-resistant epilepsy (average age of 28.4 ± 12.4 years), 49 drug-sensitive patients (average age of 25.1 ± 14.6 years), and 65 healthy controls (average age of 29.4 ± 13.8 years)	Patients with four seizures per year or fewer showed an increase of *Bifidobacteria* and *Lactobacillus* than those with more than four seizures per year	[30]
Fourteen Chinese pediatric patients with refractory epilepsy (average age of 1.95 ± 3.10 years) and 30 healthy infants (aged up to 3 years)	Increased the level of Proteobacteria	[49]

炎症状态。色氨酸可激活星形胶质细胞中的芳香烃受体调节中枢神经系统炎症; 短链脂肪酸可调节小胶质细胞成熟、影响其形态和功能[78,79], 还可以促进T淋巴细胞分化为调节性T淋巴细胞, 诱导其释放IL-10从而抑制效应T淋巴细胞Th1和Th17的激活和炎症反应的发生。癫痫本身也可以通过肠道菌群激活免疫细胞和小胶质细胞, 产生促炎细胞因子, 形成恶性循环[80]。可见, 肠道菌群参与介导的神经炎症可能在癫痫发生

中具有重要作用。

2.2.3 神经内分泌系统 研究表明, 肠道菌群可以通过HPA与大脑相互作用[81]。应激是癫痫发作的常见诱因, 而HPA轴是应激反应的核心神经内分泌组成部分。下丘脑促进促肾上腺皮质激素释放因子分泌, 使垂体释放促肾上腺皮质激素、肾上腺释放糖皮质激素 (皮质醇、皮质酮、脱氧皮质酮和促皮质素) 和儿茶酚胺。上述效应分子影响肠道运动及分泌、通透性, 以及局部及全身免疫功能与炎症反应, 还会对菌群组成和功能产生影响。研究表明, 慢性压力是肠道菌群紊乱的潜在诱因, 而菌群失调会上调脂多糖 (lipopolysaccharide, LPS) 等促癫痫代谢物生成。通过调节肠道菌群影响HPA轴可逆转慢性应激, 从而缓解癫痫。尽管HPA与肠道微生物群的双向联系已被充分认识且在精神疾病中得到广泛研究[82], 但癫痫、HPA轴和肠道菌群之间的直接关联尚需进一步研究。

2.2.4 迷走神经 迷走神经由传入和传出神经元组成, 是大脑和肠道之间最直接、快速的通道, 在调节炎症、食欲、情绪和应激反应等方面发挥关键作用[81]。与大脑的通讯主要通过迷走神经的传入感觉通路和椎前神经节的传出运动通路, 经由交感神经系统实现[83]。刺激迷走神经能够有效减少癫痫发作频率和药物用量, 是治疗难治性癫痫的有效疗法[84,85]。肠道菌群可通过迷走神经直接影响中枢神经系统疾病的发生和发展, 也可以通过影响肠神经系统 (enteric nervous system, ENS) 并产生可穿越血脑屏障的代谢产物 (如5-羟色胺、去甲肾上腺素、谷氨酸、GABA等) 间接调节中枢兴奋性来影响癫痫的易感性[84,86]。ENS可直接支配胃肠道的周围神经系统亚结构, 在机体反射性生理调控中起关键作用[87]。ENS由超过1亿个相互连接的神经元组成, 是一个高度复杂的微环路系统, 可独立于中枢神经系统和脊髓自主支配, 但仍与中枢神经系统保持双向通讯。

3 癫痫的干预策略

癫痫病因复杂、机制未明, 尚无根治方法。目前的干预手段主要包括临床常规治疗和以肠道菌群为靶点的新兴策略。前者主要是通过药物干预和手术治疗控制癫痫发作, 而生酮饮食、粪菌移植、补充益生菌作为新兴干预新策略, 在难治性癫痫治疗中显示出良好前景。

3.1 临床常规治疗策略及其局限性

抗癫痫发作药物 (anti-seizure medications, ASMs) 是控制癫痫发作的主要治疗方法, 通过作用于GABA、谷氨酸、离子通道 (钠离子、钾离子和钙离子) 发挥作用[28]。抗癫痫发作药物大部分具有单一作用机制。常用药物包括钠通道阻滞剂 (如苯妥英、卡马西平、拉莫三嗪)、钙通道阻滞剂 (如乙琥胺、丙戊酸)、钾通道激活剂 (如瑞替加滨)、突触囊泡蛋白调节剂 (如左乙拉西坦) 及GABA能药物 (如巴比妥类、苯二氮卓类) 等[28,88]。

尽管新型药物不断涌现, 仍有30%～40%的患者对至少两种药物无反应。ASMs治疗窗窄, 且伴随多种不良反应, 如共济失调、肝损伤、皮疹、认知障碍、体重增加、胃肠功能紊乱、嗜睡、头晕头痛、易怒等, 导致10%～30%的癫痫患者因无法耐受这些药物不良反应而停药, 联合用药时尤为明显。患者多需长期甚至终身服药, 但仍无法根治, 仅能减少发作频率和严重程度, 更难以预防和改善共病。

值得注意的是, ASMs与肠道菌群之间存在相互作用。肠道菌群通过其丰富的肠道酶系参与多种药物的代谢, 影响其生物利用度、疗效和毒性。同时, ASMs本身也会显著改变宿主肠道菌群的组成[89,90]。如怀孕期间服用丙戊酸 (VPA, valproic acid) 降低了粪便肠道菌群的丰度, 并改变其组成[91], 这也可能是其引起胃肠道不良反应和体重增加的机制之一。同样, 托吡酯 (topiramate) 也被报道可改变菌群结构[92]。药物引起的菌群失调会影响疾病的进程和治疗效果, 突显了将肠道菌群作为癫痫治疗潜在靶点的重要性。

3.2 以肠道菌群为靶点的干预新策略及其潜在优势

肠道菌群易受环境、饮食、药物、病理生理等因素的影响, 根据需要重塑肠道菌群组成及功能可以达到治疗疾病的目的。目前, 基于这种肠道菌群调控的疗法逐渐走入人们的视野。与传统抗癫痫药物不同, 以肠道菌群为靶点的干预策略 (生酮饮食、粪菌移植、益生菌) 表现出其独特的优势。首先, 具有多靶点治疗特点: 肠道菌群调控可同时影响神经递质平衡、免疫炎症反应、内分泌稳态及迷走神经信号等多个“上游”致病通路, 可达到标本兼治的作用。其次, 具有良好的安全性: 生酮饮食、益生菌等策略不良反应低、依从性好。最后, 具有潜在的“治本”潜力: 通过恢复菌群稳态, 可能重塑机体内环境, 从而长期稳定地控制发作甚至改善共病, 为难治性癫痫患者带来新希望。

3.2.1 生酮饮食 生酮饮食是一种容易获得, 且经过100多年的临床实践, 成功地作为治疗难治性癫痫的干预策略[93]。它是一种高脂肪、适量蛋白质和低碳水化合物的饮食方式, 脂肪与蛋白质和碳水化合物的比例在2∶1到4∶1之间。其通过提升血液中的酮体水平、改变代谢和激素状态, 阻断谷氨酸突触传递、抑制糖酵解, 激活ATP敏感钾离子通道, 降低神经元兴奋性和癫痫发作频率。但生酮饮食对于癫痫患者的应答率不到

50%[94], 潜在作用机制尚未完全阐明。

近年来, 大量的研究表明肠道菌群可能是生酮饮食抗癫痫机制之一[33,55]。生酮饮食可通过改变肠道微生物群的组成和功能, 影响代谢物、信号分子和免疫反应。生酮饮食治疗会改变难治性癫痫患儿肠道菌群的*α*-多样性, 升高拟杆菌门水平, 降低厚壁菌门和放线菌门水平[95], 减少变形杆菌和克罗诺杆菌数量, 增加拟杆菌、普雷沃氏菌和双歧杆菌数量[49], 从而降低癫痫发作频率。还有研究结果表明, 生酮饮食干预后, 患儿双歧杆菌 (*Bidobacteria*) 以及 *E. rectale* 和 *Dialister* 的相对丰度显著减少, 大肠杆菌 (*E. coli*) 的相对丰度增加[96]。并且, 无应答患者中 *Clostridiales*、*Ruminococcaceae*、*Rikenellaceae*、*Lachnospiraceae* 和 *Alistipes* 等显著富集[95]。此外, 还可通过生酮饮食和抗生素调控肠道菌群, 进而影响海马线粒体功能, 改变癫痫易感性。同时, 也提示靶向线粒体功能相关的菌群是潜在的癫痫治疗策略[97]。可见, 大量临床试验结果支持生酮饮食不仅可以改善肠道菌群的组成和功能[98], 恢复肠菌稳态, 还有助于预防癫痫发作, 恢复大脑神经递质的水平, 降低癫痫发作频率。同时, 还能改善齿状回中小胶质细胞的形态和功能[99], 降低促炎因子水平[100]。但是, 生酮饮食可能会有各种不良反应, 最常见的包括胃肠道紊乱和血脂异常, 严重的不良反应包括胃炎、血小板减少性紫癜和呼吸衰竭[101]。

3.2.2　粪菌移植　菌群移植是将健康人肠道中的功能菌群移植到患者体内, 重建具有正常功能的肠道菌群, 以恢复肠道菌群多样性, 改善肠道菌群平衡, 从而实现疾病治疗。2013 年, 美国食品和药物管理局批准菌群移植用于治疗复发性和耐药艰难梭菌感染。2017 年首例癫痫合并克罗恩病患者接受菌群移植后癫痫发作完全缓解, 并停用抗癫痫药物 (AEDs)[102]。尽管有成功案例, 但菌群移植实施较为困难, 且要求较高, 移植粪菌的质量需严格控制, 安全性和疗效尚需更多研究验证。

3.2.3　益生菌　益生菌具有安全性高、不良反应低、依从性好的特点, 逐渐引起越来越多的关注。研究表明, 含有多种益生菌的混合物 (嗜酸乳杆菌、植物乳杆菌、乳酸菌、干酪杆菌、*helveticus* 乳杆菌、短乳杆菌、乳酸双歧杆菌、乳酸杆菌和唾液链球菌) 可以调整肠道菌群、恢复肠稳态, 降低 IL-6 等炎症指标, 提高 GABA 水平, 减少难治性癫痫发作[103]。益生菌还可降低轮状病毒相关癫痫发生率, 可能是通过博氏弧菌抑制轮状病毒结构蛋白 4 实现的[104]。益生菌可以改变癫痫病理进展及其共病[36,105], 虽然存在腹泻、便秘等肠道反应, 但大都可自愈。目前益生菌种类、剂量、治疗周期缺乏统一标准, 未来需优化给药方案, 推进个体化应用。

4　总结与展望

癫痫及其共病给癫痫患者带来了沉重负担, 新治疗策略需从对症转向对因治疗。肠道菌群可通过多种途径和大脑之间进行复杂的双向调节, 通过改变肠道通透性、局部/外周免疫反应及产生必需代谢物和神经递质对癫痫及其共病的发生发展发挥关键作用, 有望成为新的治疗靶点。与传统 AEDs 相比, 菌群干预策略具有多靶点、安全性高和长期稳态调节等优势。

由于肠道菌群、机体、癫痫及其共病涉及众多潜在通路和变量, 使得相关研究面临巨大挑战。目前研究的局限性在于现有临床证据多以小样本观察性研究 (如横断面研究、队列研究) 和机制探索为主, 高质量、大样本的随机对照试验相对较少。未来仍需开展更多设计严谨、大规模的前瞻性临床研究来进一步验证肠道菌群干预策略的有效性和安全性, 并阐明调控机制。并且, 大量机制研究主要来自啮齿类动物, 尽管动物研究为肠道菌群调控癫痫发生相关机制研究提供了依据, 但是需要谨慎解读动物水平数据, 未来应着重强调和临床研究的结合。此外, 癫痫患者是经药物干预的状态, 环境混杂因素多等诸多问题导致临床效果不一致的现象, 现有研究结果存在错综复杂且自相矛盾等问题。未来研究须对人群进行精准分层, 同时, 须采用与药物临床试验同等严谨的研究方法, 以确保结果可靠性。

未来研究不仅要着重于癫痫与肠道菌群互作机制的因果关系研究, 以确定其对癫痫病因和病理生理学的临床意义和价值, 还应注重肠道菌群–癫痫的生物标志物 (不限于特征菌、特征代谢物、肠菌靶蛋白) 的发现、新的基于肠道菌群 (如菌药联用、工程菌等、益生元/益生菌) 治疗策略的发明, 以及以实现人以“群”分、个体化精准治疗为目的的、根据患者“肠道菌群谱”制定的诊疗方案的出台。这些研究对于理解癫痫的发病机制、发现新的生物标志物、开发以肠道菌群为靶点的个体化防治干预新策略、改善癫痫患者的生活质量和预后, 具有重大意义。

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