·学术前沿:肠道菌群与屏障功能专题·

菌群-肠-脑轴在酒精性脑损伤中的研究进展

周弘艳，徐　平
(遵义医科大学附属医院神经内科,贵州 遵义 563000)

摘　要:长期酗酒作为全球范围内的公共卫生问题,已严重危害人体健康。酒精滥用通过多途径破坏人体多个器官和系统的功能。易受酒精影响的菌群-肠-脑轴在体内稳态、免疫成熟、内分泌代谢等方面起着至关重要的作用。长期过量饮酒不仅改变肠道菌群的组成和代谢物水平,还破坏肠道屏障的完整性,增加肠道通透性,使得有害代谢物进入血液循环,进而引发包括酒精性脑损伤在内的多种疾病。酒精性脑损伤是酒精使用障碍(AUD)未被识别或未得到有效治疗的严重后果之一,可导致广泛的神经损伤和神经认知功能障碍。尽管菌群-肠-脑轴在酒精性脑损伤中的潜在作用已被提出,但目前仍未明确其具体机制。因此,在本综述中,我们对长期酗酒、菌群-肠-脑轴和酒精性脑损伤之间的关联进行了分析,并探讨酒精通过该轴引发脑损伤的潜在机制。

关键词:酗酒;菌群-肠-脑轴;酒精性脑损伤;肠道菌群失调;干预措施
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Research Advances on the Microbiota-gut-brain Axis in Alcohol-related Brain Injury

ZHOU Hongyan, XU Ping
(Department of Neurology, Affiliated Hospital of Zunyi Medical University, Zunyi 563000, China)
Correspondence to: XU Ping; E-mail: xuping527@vip.sina.com

Abstract: Chronic excessive alcohol consumption is a major global public health concern that severely endangers human health. Excessive alcohol intake disrupts the functions of multiple organs and systems in the human body through diverse mechanisms. The alcohol-sensitive microbiota-gut-brain axis plays a critical role in maintaining systemic homeostasis, immune maturation, and endocrine metabolism. Chronic excessive alcohol consumption not only alters the composition of the gut microbiota and the levels of its metabolites, but also compromises intestinal barrier integrity, increases intestinal permeability, and allows harmful metabolites to enter the systemic circulation, thereby triggering a variety of diseases including alcohol-related brain injury. Alcohol-related brain injury is one of the most severe consequences of unrecognized or inadequately treated alcohol use disorder (AUD), which can lead to extensive neuronal damage and neurocognitive dysfunction. Although the potential role of the microbiota-gut-brain axis in alcohol-related brain injury has been proposed, the exact underlying mechanisms have not yet been fully elucidated. Therefore, in this review, we systematically analyze the associations among chronic excessive alcohol consumption, the microbiota-gut-brain axis, and alcohol-related brain injury, and explore the potential mechanisms underlying alcohol-induced brain damage via this axis.

Key words: chronic excessive alcohol consumption; microbiota-gut-brain axis; alcohol-related brain injury; gut dysbiosis; interventions

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作者简介:周弘艳,第一作者,研究方向:酒精中毒性神经系统疾病,E-mail:542431090@qq.com;徐平,通信作者,教授,主任医师,博士生导师,E-mail:xuping527@vip.sina.com

众所周知,饮酒在许多文化中根深蒂固,影响深远[1]。然而,饮酒超过推荐限度已成为全球范围内重要的公共卫生问题,并且难以控制[2]。2020年相关研究指出,2016年全球因酒精摄入导致的死亡人数超300万[3]。长期酗酒可以破坏许多器官和系统的结构和功能,从而对人类身体健康产生有害影响[4],是个人死亡和残疾的主要风险因素之一[5]。酒精性脑损伤作为酒精使用障碍(alcohol use disorder, AUD)未被识别或未得到有效治疗的严重后果之一[2,6-7],可导致广泛的神经损伤和神经认知功能障碍[8]。

酒精性脑损伤的发生并非单一机制作用的结果,而是酒精通过多条不同的生物学途径共同作用于大脑,进而导致神经功能的损害。研究表明,酒精通过多种途径(如氧化应激、神经炎症、P2×7受体激活等)破坏血脑屏障,导致血脑屏障通透性增加,从而使有害物质进入大脑,进而引发神经损伤和认知功能障碍[9-13]。其次,酒精代谢产生的大量活性氧通过损伤神经元和内皮细胞,激活氧化应激、炎症反应和凋亡通路,进而促进酒精相关神经退行性改变[14]。慢性酒精暴露还通过激活小胶质细胞和星形胶质细胞,促进促炎因子的释放,导致神经炎症的持续存在,这不仅直接损伤神经元,还破坏了神经修复的机制[15-16]。此外,酒精对神经递质系统的干扰,特别是对γ-氨基丁酸和谷氨酸系统的调节失衡,影响了神经传导和突触塑性,是酒精性脑损伤中认知障碍和情绪异常的重要机制之一[17]。上述多条生物学途径的相互作用,使得酒精性脑损伤的机制更为复杂。

近年来,菌群-肠-脑轴在酒精性脑损伤中的潜在作用机制也逐渐受到关注,相关研究越来越多[18-20]。研究表明,长期酗酒会损害肠道屏障,与肠道菌群组成的改变和肠道通透性的增加有关[21],并且可以诱发肠道菌群功能障碍、酒精性肝病发生以及部分脑功能障碍等情况[4-5]。但是,目前关于菌群-肠-脑轴在酒精性脑损伤中的具体作用机制尚不明确。因此,我们将对现有的相关文献进行综述,旨在探讨长期酗酒、菌群-肠-脑轴与酒精性脑损伤之间的关系,并分析菌群-肠-脑轴作为酒精性脑损伤的潜在次要机制的作用。

1 菌群-肠-脑轴与中枢神经系统

1.1 菌群-肠-脑轴

肠道作为一个重要的消化器官,在机体营养代谢和水分吸收中起着至关重要的作用,而存在于肠腔或肠道黏液外层的大型动态菌群落被称为肠道菌群,里面包含数万亿的细菌、古细菌、病毒和真核生物(如真菌和酵母)等多种菌群[22-23]。其中,细菌是人类肠道菌群的主要组成成分,并且以拟杆菌门和厚壁菌门为主,其次是变形菌门、放线菌门和疣微菌门等[24-25]。肠道菌群在整个生命周期中不断发展,并与宿主建立共生关系[26],提供必需的营养物质、代谢胆汁酸、抵御病原入侵,并帮助维持肠道屏障功能[27]。肠道菌群还与多种疾病相关,包括孤独症、焦虑、肥胖、精神分裂症、帕金森病和阿尔茨海默病等[28-31]。

此外,肠道由肠神经系统支配,该系统独立于中枢神经系统发挥作用[32]。然而,肠道及其菌群和宿主大脑之间通过多种途径相互作用,包括神经(中枢神经、自主神经和肠道神经)系统、免疫系统、内分泌系统、色氨酸代谢和血清素能系统等途径,并且涉及的菌群代谢物包括短链脂肪酸、胆汁酸、三甲胺N-氧化物、支链氨基酸和肽聚糖等多种物质,通常将这种肠道及其菌群与宿主大脑之间的交流称为菌群-肠-脑轴或肠-脑轴[28, 33-36]。并且,最近的研究还鉴定出一些新的代谢分子,即内源性大麻素、生物活性脂质、酚类衍生化合物和晚期糖基化终产物等及其特异性受体,如过氧化物酶体增殖物激活受体α和γ、芳香烃受体和G蛋白偶联受体(即GPR41、GPR43、GPR119、Takeda G蛋白偶联受体5)[33]。菌群-肠-脑轴也可以定义为肠道菌群的活动、胃肠道系统(包括肠道神经系统)和中枢神经系统之间的复杂相互作用,这种作用可能会影响各种脑部疾病的发展[32]。

1.2 菌群-肠-脑轴在中枢神经系统中的作用

肠道菌群可能通过神经调节、内分泌代谢和免疫反应等途径与中枢神经系统进行沟通,从而影响大脑的功能和行为[37]。大脑也通过自主神经系统调节肠道菌群的结构与功能,甚至可能通过直接作用于细菌基因表达的神经递质来调节肠道菌群[38]。菌群-肠-脑轴与中枢神经系统之间存在密切的相互关系,且在多种神经系统疾病中出现肠道菌群的改变[23]。研究表明,肠道菌群对大脑前额叶皮层髓鞘形成、血脑屏障通透性、神经炎症、精神行为和认知功能等方面具有调节作用[27, 37, 39-40]。此外,大脑功能和行为还受到菌群代谢物的影响[41]。如肠道细菌生成的神经递质及其前体(例如多巴胺、血清

素和γ-氨基丁酸等），可能影响它们在宿主大脑中的水平，进而影响大脑功能[32, 42-44]。此外，菌群-肠-脑轴可能在神经发育、衰老、缺血性脑卒中和神经退行性疾病的生物学和生理学基础上发挥关键作用[31, 34, 45-47]。因此，菌群-肠-脑轴对中枢神经系统具有至关重要的作用。

2　酒精对肠道菌群及其衍生代谢物和肠道屏障的影响

长期酗酒会导致肠道菌群的失调，改变肠道菌群的组成和多样性，尤其是减少拟杆菌门和厚壁菌门，增加变形菌门和放线菌门，同时也会改变粪便的pH值和使血浆内毒素增加[48]。酒精还会破坏肠道细菌与真菌的平衡[49]，影响宿主-菌群的相互作用[18, 50-51]，进而促进酒精依赖的发展。Rodríguez-González等[51]发现，酒精增加了梭状芽孢杆菌、龙氏芽孢杆菌、变形杆菌、双歧杆菌、类杆菌和肠球菌的水平。Dubinkina等[4]进一步指出，酒精依赖与产丁酸盐的梭状芽孢杆菌种类水平呈负相关，并与促炎性肠杆菌科的机会性病原体相关。Hsu等[52]发现，活动性AUD患者的丙酸杆菌、乳酸杆菌和乳球菌噬菌体丰度降低，但戒酒2周后，这些菌群的丰度增加。其他研究也发现，除了乳酸杆菌外，酒精也降低了肠道中振荡杆菌、梭状芽孢杆菌XIVa和XIVb的水平[51]。Yang等[53]则表明，酒精摄入导致结肠菌群区系的组成和结构发生改变，尤其是拉克诺螺科和普雷沃菌科中的共生菌群相对丰度显著下降。

除了肠道菌群失调外，对宿主生理学至关重要的许多代谢物也受到了长期酗酒的影响，包括胆汁酸显著改变，脂肪酸和类固醇增加，参与脂质代谢的肉碱和代谢物、所有氨基酸、支链氨基酸和短链脂肪酸均减少，而乙酸作为乙醇的代谢产物明显升高[54]。此外，长期饮酒会损害肠道屏障的完整性，增加肠道通透性，从而使菌群成分转移到血循环中，同时也导致了胆汁酸的肠肝循环障碍和由于摄入不足引起的硫胺素（即维生素B1）等微量元素缺乏[5, 21, 50, 55]。酒精还会影响肠道屏障中的免疫细胞，导致免疫防御功能减弱[56]。总体而言，长期酗酒通过改变肠道菌群及其代谢物、损害肠道屏障功能，进一步加剧酒精带来的健康损害。

3　菌群-肠-脑轴与酒精性脑损伤

3.1　酒精所致的脑损伤

研究表明，中枢神经系统作为酒精最敏感的靶器官，受到酒精的显著抑制，过量饮酒会诱发大脑的氧化应激以及海马体和前额叶皮层的神经炎症反应，导致谷氨酸兴奋性毒性增加，与营养不良相关的永久性神经元损伤或神经元坏死，损害神经再生，加速大脑老化，并改变神经免疫反应，导致情绪和行为异常、认知能力下降以及运动功能障碍等症状[57-62]。急性酒精刺激也可以促进活性氧产生，导致大脑处于氧化应激状态[63]。此外，长期饮酒会诱导额叶皮层和纹状体的脂质发生变化，其中，甘油磷脂、甘油脂类和脂肪酰基的显著增加，醇修饰的类脂物种中出现高度不饱和度的长碳链，这种改变可能会激活内质网应激并最终导致神经毒性[64]。酒精性脑损伤包括酒精相关性痴呆、Wernicke脑病、Korsakoff综合征、脑桥中央髓鞘溶解症、酒精性小脑变性、Marchiafava-Bignami病等多种疾病，主要由慢性酗酒或硫胺素缺乏引起，可以出现广泛的神经损伤和临床症状（如步态障碍、认知状态改变、意识模糊、记忆缺陷等认知功能障碍、虚构、眼球震颤和其他眼球运动障碍等），这是一类不可逆转且持久的酒精相关的神经系统疾病[2, 5, 7, 11, 65]。研究还发现，酒精性脑损伤患者的前额叶和视觉皮层中，磷脂和神经酰胺水平显著降低，多不饱和脂肪酸和鞘氨醇骨架减少以及胆固醇酯脂肪酸链选择性减少[66]。因此，长期酗酒会对大脑造成严重且持久的损害，并出现相应的临床症状。

3.2　酒精通过菌群-肠-脑轴参与酒精性脑损伤的可能机制

3.2.1　*免疫与炎症信号*　长期过量饮酒会显著改变肠道菌群组成和功能，这些变化可通过免疫调节和炎症通路影响中枢神经系统状态[20, 67-68]。Lowe等[55]发现，急慢性酒精给药处理诱导了小鼠神经炎症，而减少肠道细菌负荷可减轻酒精引起的中枢神经系统炎症，提示肠道菌群衍生的信号参与酒精相关的神经炎症。Leclercq等[69]发现，长期饮酒抑制了核因子κB（nuclear factor kappa-B，NF-κB）途径，但激活了丝裂原活化蛋白激酶/激活蛋白1途径及炎症小体复合物，导致促炎因子（如IL-8、IL-1β、IL-18）增加并激活促炎通路，引发低度全身性炎症。他们认为，酒精介导的肠道菌群代谢物（脂多

糖和肽聚糖)激活了外周血单核细胞,诱导炎症因子进入血液[69-70]。另外,酒精改变了粪便菌群和代谢物组成,破坏肠道和血脑屏障,增加内毒素通过血脑屏障渗透,激活前额叶皮质和海马中的小胶质细胞及炎症通路,导致神经炎症和空间记忆障碍[71]。此外,膳食菌群代谢物丁酸盐补充剂可抑制小胶质细胞介导的神经炎症,调节菌群-肠-脑轴,改善慢性酒精性中枢神经损伤并改善认知功能[60]。此外,酒精还通过肠-肝-脑轴相互作用,增加全身性炎症反应,进而影响脑功能。研究表明,长期过量饮酒会改变肠道菌群,导致毒素释放,损害胃肠道功能并引发炎症反应,进而损害肝脏和大脑功能,恶化神经功能[72]。酒精引起的肠道菌群失调和肝病通过肠肝循环相互作用,进一步诱发脑功能障碍和精神疾病[5]。尽管现有研究提供了初步的证据,但酒精通过菌群-肠-脑轴引起的慢性炎症是否是酒精性脑损伤的直接原因,仍需通过更多机制研究来进一步确认。

3.2.2 *神经递质通路* 长期过量饮酒可引起肠道菌群组成紊乱,干扰宿主的色氨酸代谢和血清素(5-hydroxytryptamine, 5-HT)合成,从而降低大脑中血清素的水平。酒精诱导的菌群失调会加速色氨酸经犬尿氨酸途径分解,减少用于合成5-HT的色氨酸前体供应[67]。例如,有研究比较了有无肠道菌群的小鼠,结果发现具有正常肠道菌群的小鼠(常规饲养)其海马和血清中的血清素及其代谢物水平均显著低于无菌小鼠,这表明肠道菌群的存在与脑内5-HT含量密切相关[73]。由于5-HT在调节情绪、认知和睡眠等方面发挥关键作用,肠道菌群失调所导致的脑内血清素缺乏很可能引发情绪低落、焦虑等情绪障碍,记忆/认知功能减退,以及睡眠节律紊乱等行为改变[67]。肠道菌群对中枢γ-氨基丁酸(gamma-aminobutyric acid, GABA)能系统的调节在酒精相关的脑功能损伤中可能起重要作用。酒精摄入可改变肠道菌群产生的代谢物,包括神经递质GABA、5-HT和多巴胺等。正常情况下,一些肠道共生菌(如乳酸杆菌和双歧杆菌)能够将谷氨酸转换为GABA。然而酒精导致的菌群紊乱会削弱这种转化,显著降低机体(包括中枢)中的GABA水平,并导致神经元兴奋性升高,即大脑兴奋-抑制平衡被打破[74]。此外,慢性饮酒诱发的肠黏膜通透性增加和全身炎症反应也会抑制GABA的合成及其受体活性,加剧中枢神经系统的过度兴奋[75]。因此,肠道菌群失调通过影响GABA能神经传递而改变大脑的兴奋/抑制平衡,这种机制可能导致焦虑易激动、失眠等情绪和睡眠问题,以及学习记忆障碍等认知功能受损,可能加剧酒精滥用的神经精神后果。目前的研究为这一机制提供了线索,但证据强度仍有限。要确认它在酒精性脑损伤中的真实贡献,仍需进一步的机制实验与更规范的临床研究。

3.2.3 *硫胺素缺乏* 长期酗酒可抑制肠道硫胺素(维生素B1)的载体介导主动吸收,并下调肠上皮硫胺素转运体表达,从而促发或加重硫胺素缺乏[76]。硫胺素缺乏会削弱丙酮酸脱氢酶、α-酮戊二酸脱氢酶等硫胺素依赖酶活性,造成ATP生成不足与神经元功能崩溃,是Wernicke脑病等酒精相关脑病的重要病理基础[77-78]。现有证据支持硫胺素缺乏与能量代谢障碍之间的关联,但其在酒精相关脑损伤中的作用强度可能受个体营养基础、肝功能与代谢状态影响,仍需在临床分层研究中进一步分析。

3.2.4 *代谢产物通路* 酒精通过改变肠道菌群,影响代谢产物的生成,尤其是短链脂肪酸(short-chain fatty acids, SCFAs)。SCFAs参与体内各种过程,如肠道功能、免疫功能和抗炎[27]。研究显示,慢性乙醇摄入会导致肠道菌群失调并减少SCFAs产生,同时出现肠屏障破坏、外周炎症信号增强及脑内神经炎症相关改变,以及焦虑抑郁样行为等表型,提示肠源性代谢失衡可能与酒精相关神经损害相伴发生[79]。SCFAs作为菌群-肠-脑轴的关键代谢介质,可通过FFAR2/GPR43等受体调节免疫反应并产生抗炎效应[36]。在慢性酒精模型中,丁酸盐补充可抑制小胶质细胞介导的神经炎症并改善学习记忆/认知结局,提示恢复SCFAs可能具有一定神经保护潜力[60]。

4 调控菌群-肠-脑轴的干预措施及疗效评价

4.1 益生菌、益生元和合生元

调节肠道菌群的微生态制剂是目前研究较多的干预策略。益生菌(如双歧杆菌、乳杆菌等)通过定植肠道可改善菌群失调,减少肠道通透性,降低内毒素水平,从而减轻全身炎症反应[20]。研究发现,给予特定乳酸菌或双歧杆菌菌株可显著缓解酒

精引起的胃肠道炎症，恢复肠道菌群平衡，其机制可能与降低髓过氧化物酶活性、减弱黏膜炎症及重建肠道屏障功能有关[80]。如乳杆菌LGG（*lactobacillus rhamnosus* GG）在小鼠实验中可以预防酒精所致的肠道菌群失调和内毒素升高，并减少炎症介质的释放[48, 81]。此外，LGG在酒精相关肝损伤模型中还能改善肠屏障功能、调节T细胞免疫，从而降低血清内毒素和炎症水平[82-83]。这些作用提示益生菌有望间接保护酒精性脑损伤中的神经免疫环境。

益生元（如菊粉、低聚糖等）通过促进有益菌增殖起作用[84]。动物研究显示补充益生元可提高短链脂肪酸等有益代谢物含量，改善应激反应[36, 85-86]。然而，在重度饮酒人群中的临床试验结果不一，一项针对严重酒精使用障碍患者给予菊粉的随机对照研究未见明显减少饮酒渴求的效果[87]。合生元则是益生菌与益生元联合使用，理论上能协同改善肠道生态。有研究发现，补充适当的益生菌（如乳酸杆菌、孢乳酸杆菌和双歧杆菌）和有益的干预措施（如发酵米酒和红酒多酚）可一定程度恢复酒精诱导的菌群改变并抑制肠道炎症[88]。

总体而言，基于微生态的干预在早期临床研究中展现出一定潜力，但不同益生菌菌株和剂量的疗效差异较大，疗效评价尚处于初步阶段。而且，现有临床试验样本量偏小、随访时间较短，益生菌/益生元的干预对认知功能和脑结构恢复的长期影响仍不明确[67]。因此，益生菌类干预虽显示出降低炎症反应、减轻情绪症状和酒精渴求等有益趋势，但其有效性和安全性有待更多大规模对照研究加以验证。

4.2　粪菌移植

粪便菌群移植（fecal microbiota transplantation，FMT）通过将特定的健康人粪便中的功能肠道菌群移植到患者肠道内，重塑失衡的肠道菌群，实现肠道及肠道外疾病的治疗[89-90]。在动物研究中，过量饮酒小鼠戒酒后可出现明显的焦虑样行为，其粪菌移植给无菌或健康小鼠后，受体也出现类似焦虑抑郁样表现[91]。相反，将健康小鼠的粪菌移植到慢性酒精暴露的小鼠体内，则可部分恢复酒精暴露小鼠的肠道菌群多样性，显著减轻其焦虑抑郁样行为[92]。上述证据表明酒精相关的肠道菌群失调在神经行为异常中起到促进作用，而重建正常菌群有助于改善酒精所致的脑功能紊乱。此外，将酗酒患者的肠道菌群移植到无菌小鼠的肠道中，可能通过调节胆汁酸代谢导致酒精引起的肝损伤和炎症[93]。临床方面，FMT在酒精相关疾病中的研究刚起步。一项针对酒精性肝硬化合并酒精使用障碍患者的1期试验报告称，多次FMT治疗后患者的饮酒渴求度显著降低[94]。另有初步研究提示FMT可改善酒精性肝炎患者的肠道菌群失调及酒精渴求[95]。

尽管这些结果令人鼓舞，但需谨慎解释其疗效评价。大部分研究受限于样本量小且缺乏双盲对照设计，目前尚无法明确FMT对酒精性脑损伤的长期疗效。FMT可能存在供体选择、免疫排斥及感染风险等问题，此外其作用机制复杂，涉及菌群整体的重建而非单一因子。未来需要更多随机对照试验来评估FMT在酒精所致神经损伤中的安全性和持久疗效，同时探索优化移植菌群的组成及干预时机，以提高其临床可行性。

4.3　人工智能与大数据驱动的精准干预

肠道菌群组存在显著的个体差异，且随饮食、药物与生活方式呈动态波动，因此同一益生菌、益生元或饮食干预在不同人群中的反应往往不一致，疗效存在较大异质性。近年来，机器学习与多组学整合的预测模型为“基于人群经验的统一方案”向“基于个体特征的精准干预”转变提供了方法学基础。Zeevi等[96]在大规模人群队列中联合肠道菌群、饮食与临床特征建立预测模型，用于个体化预测餐后血糖反应并指导饮食调整，提示菌群组信息联合大数据建模可转化为可操作的个体化干预策略。相关综述进一步指出，深度学习结合代谢组及临床指标有望提高对个体代谢表型、炎症状态等反应的预测能力，并为精准营养与精准菌群组干预提供可扩展的分析路径[97]。与此同时，针对纵向随访数据的菌群组动态建模也在推进，理论上可用于实现“监测—预测—调整”的迭代式管理[98]。利用人工智能（artificial intelligence，AI）和大数据分析个体独特的菌群组图谱，为“超个性化医疗”提供了现实路径，未来或能为每位患者提供优化的菌群组合。不过需要强调的是，现阶段多数算法仍停留在风险分层或结局预测层面，能否在临床场景中稳定复现、并真正指导可改变结局的干预，证据仍不足，真正面向因果干预的证据仍需更多前瞻性试验支持。

4.4 新型生物制剂与新疗法

近年来,针对菌群-肠-脑轴的干预正在从传统食品级益生菌逐步转向更具药物开发特征的新型生物制剂,其核心特征是菌株或产物可定义、质量可控、作用机制更明确,并能进入规范临床路径。活体生物治疗产品(live biotherapeutic products, LBPs)以特定胆株为活性成分,强调明确菌株定义、质量控制与临床试验路径。FDA已发布LBP早期临床试验的CMC指南,提示该领域正在走向规范化开发[99]。与此同时,合成生物学使活菌具备"按机制递送"的潜力。例如有研究通过工程化益生菌提高5-HTP生成,可使小鼠肠道与脑组织中5-HTP/5-HT水平升高并改善抑郁样行为,提示其在调控神经递质前体通路方面具备可行性[100]。除活菌本身外,后生元(如SCFAs、特定胆汁酸/吲哚衍生物等)更接近传统药物形态,成分明确、剂量可控。例如丁酸盐在慢性酒精模型中可抑制小胶质细胞介导的神经炎症并改善认知结局,为代谢物补充作为转化策略提供了实验依据[60]。总体而言,新型生物制剂的优势在于更明确的靶点与可控的产品质量,但其临床证据仍处于累积期,其长期安全性、定植稳定性、个体菌群基线差异导致的疗效波动仍需通过分层设计的大样本随机对照研究进一步明确。

4.5 特定药物干预

围绕菌群-肠-脑轴的胆汁酸信号通路,胆汁酸调节剂,如法尼酯X受体(Farnesoid X Receptor, FXR)激动剂等,被提出作为潜在干预手段。现有研究提示,激活FXR通路可在酒精暴露模型中改善菌群紊乱、减少有害次级胆汁酸蓄积,从而在一定程度上保护肝脏和脑组织不受酒精毒性损伤[101-102]。此外,在肝硬化与非酒精性脂肪性肝病模型中,FXR激动剂可通过β-连环蛋白相关机制增强肠血管屏障,从而减少细菌易位[103-105]。需要指出的是,上述证据多来自动物实验及相关疾病研究外推,针对酒精性脑损伤的直接临床验证仍不足,后续应进一步明确作用环节并开展更高质量的人体研究。

4.6 饮食与生活方式干预

良好的饮食和生活方式是维持菌群-肠-脑轴稳态的基础。高脂高糖饮食会加重肠道菌群失调,降低有益菌丰度并促进内毒素生成,可能加剧酒精对肠道和大脑的损害[106-107]。相反,富含膳食纤维、益生元和多酚类抗氧化物质的均衡饮食有助于恢复肠道微生态的多样性[84]。因此,在酒精性脑损伤的干预中,营养支持应强调足量维生素与膳食纤维、适度优质蛋白及多不饱和脂肪酸摄入,减少精制碳水和饱和脂肪。生活方式方面,适度有氧运动、规律作息、戒酒和心理干预是重要的调整措施。需指出的是,此类措施多体现为长期整体获益,短期神经损伤逆转效应不易量化。目前,虽然缺乏专门针对酒精性脑损伤患者的临床试验,但鉴于其安全性和广泛受益,应在综合治疗中加以重视。

5 总结与展望

长期酗酒已成为全球性的公共卫生难题。近年研究逐步关注酒精通过菌群-肠-脑轴参与酒精性脑损伤的可能路径,但总体证据仍不充分。现有研究多停留在菌群/代谢物改变与神经损害的相关性层面,尚难证明特定菌群变化为直接致病因素。肠道菌群失调究竟是酒精暴露的伴随结果,还是在脑损伤进展中具有促进作用,仍缺少一致结论。尽管粪菌移植等动物实验提供了初步因果线索,但在人群研究中受伦理与技术限制,因果验证仍具挑战。与此同时,针对菌群-肠-脑轴的干预研究样本量偏小、设计异质,缺乏多中心、大样本随机对照试验,使疗效与安全性评价仍存不确定性。未来应推动多组学整合研究(宏基因组/转录组、代谢组、免疫组学等)以更系统描绘关键通路,并借助无菌或条件敲除等模型对特定菌株/代谢物开展机制验证。临床层面需开展分层设计的高质量试验,结合个体菌群基线与病程阶段,探索更合适的干预窗口与个体化策略。

总体而言,围绕菌群-肠-脑轴的干预为酒精性脑损伤提供了新的切入点,弥补了传统神经治疗只关注脑部的局限性。需要强调的是,由于当前研究的局限性,机制链条与疗效的可重复性尚不充分。未来需要更多的高质量、随机对照的临床试验,以验证菌群-肠-脑轴干预的疗效。若上述问题得到解决,基于肠道微生态的调控有望成为综合治疗中的重要组成部分,尤其在减轻神经炎症、改善脑功能结局方面值得进一步期待。

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