

肠道微生物：连接锂暴露与癫痫风险的新视角

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收稿日期：2025年11月10日；录用日期：2025年12月3日；发布日期：2025年12月11日

摘要

癫痫是一种以反复发作作为特征的常见神经系统疾病，具有多种危险因素和强烈遗传易感性，影响着全球超过7000万人。锂作为一种重要的碱金属元素，在现代工业中广泛应用于各个领域，尤其是随着锂离子电池产业的爆炸式增长，其在电子产品、新能源汽车和储能设备中的需求激增，导致了锂在环境中的持续释放，通过废水、废弃物和粉尘等途径进入土壤和水体，造成了普遍的低水平环境锂暴露。环境及医疗锂暴露的神经毒性日益受到关注，尤其锂的促惊厥特性提示其可能加剧神经系统兴奋性失衡，然而其机制未明。本研究通过查阅国内外文献，综述锂诱导的肠道微生态失调特征，解析菌群紊乱调控癫痫易感性的潜在机制，为理解锂的神经毒性提供了新视角，亦为癫痫防治提供了潜在新靶点。

关键词

锂，肠道微生物，癫痫

Gut Microbiota: A Novel Perspective Linking Lithium Exposure to Epilepsy Risk

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Received: November 10, 2025; accepted: December 3, 2025; published: December 11, 2025

Abstract

Epilepsy is a common neurological disorder characterized by recurrent seizures, influenced by multiple risk factors and strong genetic predisposition, affecting over 70 million people worldwide. As an important alkali metal, lithium is widely used in various modern industrial fields, especially in electronics, new energy vehicles, and energy storage devices due to the rapid expansion of the lithium-ion battery industry. This growing demand has led to continuous environmental release of lithium through wastewater, waste, and dust, resulting in widespread low-level environmental lithium exposure.

文章引用：吴祺祺. 肠道微生物：连接锂暴露与癫痫风险的新视角[J]. 生物过程, 2025, 15(4): 265-272.
DOI: 10.12677/bp.2025.154034

Increasing attention has been drawn to the neurotoxicity of both environmental and medical lithium exposure. In particular, its proconvulsant properties suggest a potential exacerbation of neurological excitability imbalance, though the underlying mechanisms remain unclear. By reviewing domestic and international literature, this study summarizes the characteristics of lithium-induced gut microbiota dysbiosis and explores the potential mechanisms through which microbial disturbance modulates epilepsy susceptibility. The findings provide new insights into lithium's neurotoxicity and suggest potential targets for the prevention and treatment of epilepsy.

Keywords

Lithium, Gut Microbiota, Epilepsy

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1. 引言

锂在医学上作为情绪稳定剂的使用,在治疗急性躁狂和预防躁狂复发以及双相情感障碍和精神分裂症患者的自杀风险方面效果显著[1]。大量药理学与毒理学研究表明,锂暴露对中枢神经系统具有复杂影响:一方面,它被报道具有神经保护潜力[2];另一方面,更为明确的证据指出,尤其在较高剂量或特定情况下,表现出促惊厥特性,即可降低惊厥阈值,促进癫痫发作[3]-[5]。临床锂中毒案例中,当水平 > 2.5 mEq/L 时,患者可能会出现更严重的神经系统并发症,如癫痫发作、昏迷、心律失常和永久性神经功能损害[6];在动物模型中,锂处理已被证实能显著增强化学致病剂如匹罗卡品的敏感性,缩短潜伏期,增加发作的严重程度[7]。

基于这些临床与临床前证据,锂的促惊厥作用已经很明确。传统上,锂的神经兴奋性毒性多被归因于其直接诱导的氧化应激、线粒体功能障碍及神经递质系统紊乱等机制[7]。然而,这些机制仍难以完全阐明锂作用下神经网络兴奋性精细调控的失衡,表明可能存在尚未被充分认识的间接通路。大量研究表明肠道菌群通过免疫、神经、内分泌及代谢途径与大脑双向交流,深入调节神经功能,且与许多神经疾病有关,包括自闭症、焦虑症、癫痫、帕金森病和阿尔茨海默病[8]。值得注意的是,肠道菌群的紊乱已被证实与癫痫的病理过程密切相关[9]。本综述旨在通过综合分析现有文献,系统探讨锂暴露通过诱导肠道菌群失调,进而增加癫痫易感性的这一新机制的可能性,为理解锂的神经毒性提供新视角。

2. 锂暴露与肠道微生物

锂作为一种广泛应用于精神医学治疗和工业领域的元素,其对肠道健康的影响呈现出明显的剂量依赖性和双重性。

临床观察发现,服用锂剂的病人常伴随胃肠道症状,如恶心、呕吐、腹泻和食欲不振等副作用[10],提示其对肠道的直接作用。在治疗剂量下,锂可能表现出一定的肠道保护作用,如增强肠道微生物多样性,并促进有益菌群的生长。Huang 等人的研究发现,碳酸锂可缓解结肠炎症,通过增加嗜粘蛋白阿克曼氏菌等菌株的丰度,并激活 GPR43 依赖的 Treg 细胞响应,实现抗炎效果[11]。同样, Cussotto 等人[12]发现用锂治疗的大鼠的肠道微生物丰富度和多样性显著增加,进一步支持了这个观点。

然而,在较高剂量或毒性暴露下,锂可诱发肠道屏障损伤和菌群失调[13]。在 Lei 等[14]的研究中,对 C57 小鼠腹腔注射 200 mg/kg 的 LiCl,每天一剂,持续 5 天,结果发现小鼠肠道菌群 α 多样性下降,变

形菌门丰度降低,而拟杆菌目 S24-7_group、产碱菌科等菌群比例异常升高;同时结肠中促炎因子 TNF- α 和 IL-1 β 表达显著上调,表明锂可能通过激活巨噬细胞介导的炎症反应破坏肠道稳态,增加通透性,促进脂多糖等细菌产物入血[7]。

猪模型研究进一步证实了锂对肠道微生物的负面调控。Lopes 等人的研究显示,仔猪摄入不同来源的锂(碳酸锂或富锂蘑菇)后,肠道微生物多样性发生改变;在过量剂量(600 mg 碳酸锂)下,可观察到乳杆菌属丰度降低,而埃希氏菌-志贺氏菌属、弯曲杆菌属及梭菌属等潜在致病菌的相对丰度增加,并伴随腹泻、食欲不振等临床症状,其机制可能与锂竞争性替换 Na⁺、K⁺等必需离子,干扰细菌能量代谢有关[15]。该研究还报告,锂暴露导致粪便中短链有机酸(如乙酸、丙酸、丁酸和乳酸)产生减少,这可能源于产短链脂肪酸细菌的减少[11]。

尽管目前直接针对环境锂暴露与菌群失调关系的研究仍有限,但大量来自临床毒性案例及高剂量动物实验的证据强烈提示,锂是肠道菌群失调的一个潜在因素。未来需更多研究致力于阐明环境相关剂量下锂的长期效应,并深入探索其调控菌群的具体分子机制。

3. 肠道菌群失调与癫痫的关联

在癫痫相关的研究中,多项研究表明与健康人群相比,癫痫患者可能出现微生物群改变,多见于难治性癫痫患者[16]。部分研究表明,难治性癫痫患者肠道中厚壁菌门增多而拟杆菌门减少,这一现象在成人及婴幼儿患者中均有出现[17]-[19]。Gong 等[20]通过对癫痫患者与同组健康对照的粪便微生物群差异进行分析,发现癫痫患者粪便微生物群的 α 多样性指数显著低于健康对照组,癫痫患者粪便中放线菌门和疣微菌门增多、变形菌门减少;属水平上普雷沃氏菌_9、布劳特氏菌、双歧杆菌等菌属丰度上升。Lindfeldt 等人[21]的研究也表明,相对较低的微生物多样性与儿童药物难治性癫痫和其他中枢神经系统疾病相关。此外,Peng 等人的研究显示,双歧杆菌属(属放线菌门)和乳杆菌属(属厚壁菌门)在健康对照组中的分布高于癫痫患者[17]。

Xie 等[18]发现,拟杆菌属(属拟杆菌门)在健康对照组中的分布高于癫痫患者(42.68% vs 17.93%),而克罗诺杆菌属(属变形菌门)仅在癫痫患者中检出。与难治性癫痫婴儿相比,健康婴儿的肠道微生物多样性更高,并且在门水平上,癫痫婴儿粪便中厚壁菌门占优势,同时变形菌门富集,放线菌门减少;而健康婴儿则以拟杆菌门占优势,其次为厚壁菌门,并且存在放线菌富集。Safak 等人对特发性局灶性癫痫和健康对照组的粪便微生物组进行了对比分析,发现可引起自身免疫性疾病的变形菌门和梭杆菌门在特发性局灶性癫痫组中显著高于对照组,对免疫系统有积极作用的拟杆菌门和放线菌门显著降低[22],提示了自身免疫机制和炎症在癫痫病因学中的潜在作用。Peng 等进一步报道药物敏感性癫痫患者的菌群结构更接近健康对照,而异于耐药患者[17],提示特定菌群结构可能增加癫痫发病风险并影响药物疗效。上述研究表明癫痫患者肠道菌群失调,但有部分研究结果显示并不完全一致,可能是由于影响肠道微生物组的许多变量的差异,例如研究设计、年龄、饮食和生活环境等。

干预性研究为“菌群-癫痫”因果关系提供了更直接的证据[23]。生酮饮食治疗不仅可显著增加拟杆菌门、减少变形菌门,还可促使 43% 的患儿发作频率降低 50% 以上,表明其抗癫痫效应与菌群结构正常化相关[18][24]。动物实验进一步证实,益生菌干预可减轻 PTZ 点燃大鼠的癫痫严重程度[25][26];粪便微生物移植(FMT)可介导应激诱导的癫痫易感性变化,表明菌群具有调控发作阈值的功能。此外,颞叶癫痫大鼠模型中发现的菌群-代谢物互作网络(如脱硫弧菌属富集伴随谷氨酸水平升高)进一步表明,菌群可能通过调节神经炎症和兴奋-抑制平衡促进癫痫发生[27][28]。

肠道菌群失调不仅是癫痫的生物学特征,更可能通过微生物-肠-脑轴参与癫痫的易感性和疾病进程,菌群调控因此有望成为未来癫痫防治的潜在策略。

4. 肠道微生物群影响癫痫的潜在机制

由于癫痫病因复杂,肠道微生物群与癫痫相关的潜在机制尚未完全明确,但越来越多的证据表明,肠道微生物群可通过神经、内分泌及免疫系统和代谢信号通路与大脑相互作用[29],即“肠-脑轴”[30]。

大量证据表明,免疫炎症通路可能参与癫痫的发病机制[31]。具体而言,肠道微生物群可诱导包括小胶质细胞在内的胶质细胞释放促炎细胞因子,进而引发神经元过度兴奋,最终导致癫痫发作。星形胶质细胞和小胶质细胞之间的相互作用导致促炎细胞因子的产生和血脑屏障通透性的增加,从而允许外周免疫细胞和细胞因子浸润到中枢神经系统并导致慢性神经炎症,增强神经元兴奋性,同样最终诱发癫痫[32]。Liu 等人的研究表明,缺乏肠道菌群的小鼠表现出血脑屏障(BBB)通透性增加,且与紧密连接结构紊乱相关。值得注意的是,通过肠道菌群重建或补充短链脂肪酸(SCFAs)可逆转这一现象,凸显了肠道微生物组在维持 BBB 完整性和防止神经炎症中的关键作用[33]。动物模型研究显示,无菌小鼠移植癫痫患者粪便后,表现出增强的促炎响应和更高的惊厥敏感性,进一步证实了微生物群在免疫介导癫痫发病中的作用。

在代谢产物通路中,肠道微生物群能刺激机体产生多种神经递质、调节因子、细胞因子及代谢产物。例如 5-羟色胺(5-HT)、多巴胺、褪黑素、 γ -氨基丁酸(GABA)、组胺、乙酰胆碱、和短链脂肪酸(SCFAs)等[34]。这些物质可直接作用于肠神经系统和迷走神经系统,还可通过内分泌效应调节中枢神经系统。例如短链脂肪酸通过直接或间接途径在小胶质细胞成熟、肠神经系统与脑神经系统功能、血脑屏障(BBB)通透性及应激反应中发挥重要作用,与癫痫密切相关[35][36]。此外,短链脂肪酸还具有神经调节功能,例如降低癫痫发作强度和升高发作阈值。Li 等人的研究显示,在癫痫小鼠模型中,补充丁酸钠有效增加癫痫发作潜伏期,降低癫痫发作强度,并对海马神经元在发作后的损失具有神经保护作用,进一步突出了短链脂肪酸在癫痫发作中的作用[37]。

此外,迷走神经作为脑-肠轴的关键桥梁,也受微生物代谢物调控;该神经并不穿过肠上皮细胞直接与肠道微生物相互作用,而是通过肠内分泌细胞受体传递肠道信息,这些受体与迷走神经肠道分支中的突触结合。迷走神经受体通过感知调节性肠道肽、炎症分子、膳食成分和菌群代谢物,向中枢神经系统传递信号[38][39]。

在稳态条件下,肠道细菌刺激肠神经系统(ENS)的传入神经元,继而通过迷走神经诱导抗炎活性;而正常细菌丰度或功能的紊乱可能破坏该平衡,导致过度炎症[40]。肠道菌群所具备的抗炎性短链脂肪酸合成减少[20],是诱发继发性神经炎症并触发癫痫发作的重要致病机制。另外,肠道微生物组的改变亦可能通过干扰下丘脑-垂体-肾上腺(HPA)轴参与正常应激反应[22],或通过调节脑源性神经营养因子(BDNF)水平进而影响癫痫机制而发挥作用。

部分肠道微生物,如鼠李糖乳杆菌、脆弱拟杆菌及从中分离的多糖 A 可直接激活神经元,研究显示这些微生物均能直接激活肠道传入神经元[41]。Gochler 等人[42]将空肠弯曲菌口服接种于小鼠模型中发现,脑干迷走神经感觉节及初级感觉中继核中 c-fos 表达增加,而循环系统中促炎细胞因子水平未见升高。这表明肠道微生物通过迷走神经突触释放神经递质,与肠内分泌细胞受体相互作用,从而将信号传递至神经元并快速调节中枢神经系统中神经细胞兴奋性。迷走神经刺激已成为一种公认的癫痫治疗方法[43]。Ressler 与 Mayberg [44]发现,电刺激迷走神经传入纤维可改变大脑中 5-羟色胺(5-HT)、 γ -氨基丁酸(GABA)和谷氨酸的浓度,从而减少癫痫发作的持续时间、频率和严重程度。

屏障完整性机制涉及肠道和血脑屏障的相互作用。肠道屏障和血脑屏障(BBB)主要在微生物-肠-脑轴(MGB 轴)中起保护大脑稳态的作用[45]。这两种屏障的完整性均与肠道微生物群相关。肠道微生物群通过调节细胞生长、分化及促进紧密连接蛋白(如 occludin 和 claudin-5)的表达,以保护肠道屏障的完整

性[46]并维持肠道稳态[47] [48],从而阻止外周炎症因子和神经递质进入血液,最终维持 BBB 完整性并保障中枢神经系统稳态。肠道微生物组成的改变可能导致产脂多糖细菌过度增殖,进而通过提高脂多糖水平增加肠道免疫屏障的通透性[49] [50]。脂多糖通过上调脑内细胞因子 IL-1 β 、TNF 和 COX-2 介导其促癫痫作用[51]。外周产生的炎症因子可作用于血脑屏障,增加其通透性,使促炎介质得以进入中枢神经系统。

肠道菌群通过这些机制广泛参与了神经系统的功能发挥,这些机制并非独立的,而是相互交织,形成一个复杂的网络共同发挥作用,最终影响癫痫的易感性,因此靶向调节肠道菌群以恢复免疫代谢稳态,或为干预癫痫发生提供一种新颖的策略。

5. 总结与展望

本文系统总结了锂暴露、肠道菌群失调与癫痫易感性三者之间的潜在联系。大量证据表明,锂暴露,尤其是高剂量暴露,可破坏肠道微生物稳态,导致菌群多样性降低、有益菌减少、条件致病菌增多以及短链脂肪酸等有益代谢物产量下降。这种紊乱的肠道微环境通过微生物-肠-脑轴的多条通路,包括诱发神经炎症、改变神经递质平衡、破坏肠道及血脑屏障完整性、以及干扰迷走神经信号传导,共同加剧中枢神经系统兴奋-抑制失衡,从而降低癫痫发作阈值,增加疾病风险。这为理解锂的神经毒性机制提供了一个全新的、基于“肠脑对话”的视角,并将肠道微生物群推向了锂相关神经毒性及癫痫防治研究的前沿。

虽然目前已经有许多关于这方面的研究进展,但仍存在一些局限性。例如当前研究多集中于相关性分析,未来研究应致力于深化机制探索,利用无菌动物、粪菌移植(FMT)等模型并结合多组学技术,明确锂-菌群-癫痫间的因果关联与关键分子靶点;另外,环境低剂量长期暴露与临床高剂量短期暴露对菌群的影响模式可能截然不同,未来研究需要精确区分不同暴露场景,建立更完善的动物模型以模拟真实世界情况。

总之,从肠道微生物的角度审视锂的神经毒性,为预防和干预与环境毒物相关的神经系统疾病开辟了新途径。

致 谢

感谢本文涉及的所有研究内容的作者,感谢重庆医科大学及 PubMed 网站文献查阅及下载的支持。

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