•专家论坛•

# 药物基于“肠-脑”通路的研究进展

张正威[1], 赵朕雄[1,2], 王 琰[1*], 蒋建东[1*]

(1. 中国医学科学院、北京协和医学院药物研究所, 北京 100050; 2. 山东第一医科大学附属肿瘤医院, 山东 济南 250024)

**摘要**: 肠道菌群是由诸多共生及致病微生物组成的复杂而动态的群落, 并与宿主紧密合作。近年来, 越来越多的证据支持“肠-脑”轴理论, 肠道菌群与神经精神疾病之间的联系逐步被发现。由于神经精神疾病治疗药物大多经口服后进入肠道, 使得其与肠道菌群可能产生更广泛的相互作用。多项研究表明该类药物可改变肠道菌群的组成和功能, 同时肠道菌群也会参与药物的代谢, 进而对脑功能产生有益或有害的影响。因此, 肠道菌群在药物代谢中的作用越来越受到关注。本文综述了国内外有关两者相互作用的研究结果, 探讨了神经精神疾病对肠道菌群的影响以及肠道菌群对潜在精神活性药物的作用机制, 为临床各类神经精神疾病可能的治疗方案提供了新的思路。

**关键词**: 肠道菌群; 神经精神疾病; 药物代谢; “肠-脑”轴; 相互作用

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# Research progress on the interaction of neuropsychiatric drugs with the gut microbiota

ZHANG Zheng-wei[1], ZHAO Zhen-xiong[1,2], WANG Yan[1*], JIANG Jian-dong[1*]

(*1. Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, China; 2. The Affiliated Tumor Hospital of Shandong First Medical University, Jinan 250024, China*)

**Abstract**: The gut microbiota is an intricate and dynamic community composed of many symbiotic and pathogenic microorganisms, and works closely with the host. In recent years increasing evidence has supported the gut-brain axis theory, lending support for a link between gut microbiota and neuropsychiatric diseases. Since most of the drugs used to treat neuropsychiatric diseases enter the intestinal tract after oral administration, interaction with the gut microbiota is likely. A number of studies have shown that such drugs can change the composition and function of the gut microbiota. At the same time, the gut microbiota also participates in the metabolism of drugs, which in turn have beneficial or harmful effects on brain function. Therefore, the role of gut microbiota in drug metabolism also has attracted attention. This article reviews the research results of the interaction between the two, discusses the influence of neuropsychiatric diseases on the gut microbiota and the effect of the gut microbiota on psychoactive drugs, and provides new ideas for the treatment of various clinical neuropsychiatric diseases.

**Key words**: gut microbiota; neuropsychiatric disease; drug metabolism; gut-brain axis; interaction

人体胃肠道中存在大约$10^{14}$个细菌, 它们大多属于厚壁菌门、拟杆菌门、放线菌门和变形菌门, 统称为肠道菌群[1]。肠道菌群与人体相互共存, 并对机体的生理调节产生显著影响, 尤其是在参与脑部的正常发育和功能调节等方面发挥了独特的作用[2]。肠道菌群与脑之间的相互交流方式已有诸多报道[3-6]: 一方面, 来自生理和心理的压力因素可能会影响肠道菌群的组

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*通讯作者 Tel: 86-10-63165238, E-mail: wangyan@imm.ac.cn;
Tel: 86-10-83160005, E-mail: jiang.jdong@163.com

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成和代谢活性; 另一方面, 肠道菌群也能通过神经与体液机制影响大脑功能[7]。

这样, 以大脑为代表的中枢神经系统、肠神经系统和消化系统组成的信号通路, 可能由肠道微生物来调节, 以完成宿主的大脑、行为乃至应激反应等[8,9]而形成“肠−脑”轴概念[10]。目前, “肠−脑”轴代谢通路已从最初的假说逐步被科学实验证实, 并对神经精神疾病产生重要的影响。

肠道菌群与中枢之间联系主要是通过自主神经系统传导, 这或许是“肠−脑”轴的内在机制之一。自主神经系统 (autonomic nervous system, ANS) 作为一种神经的中继网络系统, 分布于中枢神经系统和末梢神经系统内, 包括交感神经系统和副交感神经系统, 可自主控制呼吸、心跳和消化等身体功能。ANS 与下丘脑−垂体−肾上腺轴结合, 在大脑和肠道之间形成广泛而复杂的整合通讯网络, 自发建立和调节了宿主的生理稳态[11]。ANS 与神经元和神经内分泌信号传导相结合, 可诱导中枢神经系统调控的肠道变化[12]。此外, 肠道蠕动和肠道通透, 肠上皮黏液和管腔渗透性的维持, 胆汁分泌以及黏膜的免疫反应等胃肠道的关键功能均由 ANS 所控制。

作为“肠−脑”轴的重要调控方式之一, ANS 的活动可能导致肠神经系统 (enteric nervous system, ENS) 与肠道菌群直接或间接的相互作用。交感神经系统和副交感神经系统会影响 ENS 的神经回路, 包括抗性淀粉、膳食纤维等营养物质的递送速度改变, 从而影响益生元和益生菌向小肠以及结肠分布[13]。

肠道菌群还能通过代谢物相互交流, 并与肠道 ANS 之间的突触相互作用, 这与宿主细胞识别方式相似[14]。肠道菌群来源的神经调节代谢物包括色氨酸前体和代谢物、血清素 (又称 5-羟色胺, 5-HT)、GABA 和儿茶酚胺。多个研究组已经证实[15-19], 肠道菌群代谢物对乙基苯磺酸盐 (4-ethylphenylsulfate) 可诱导小鼠产生焦虑样行为。此外, 肠道菌群衍生的代谢物已被证明可调节果蝇的自发活动[20,21]。这些发现表明, 在肠道菌群代谢物的刺激下, 肠道自主神经携带的感觉信息可以直接向大脑产生相关信号。这些物质基础正是肠道菌群与中枢之间相互联系的重要关键。

神经精神疾病是一系列因中枢神经系统受损引起的精神障碍性疾病, 其中, 神经发育性疾病 (孤独症谱系障碍等)、自闭症、抑郁症、焦虑症、阿尔茨海默病 (Alzheimer's disease, AD)、帕金森病 (Parkinson's disease, PD)[22,23]与“肠−脑”轴调控存在着重要的联系, 并且多数神经精神疾病的发作常常与肠道菌群组成改变或结构不稳定密切相关[24]。大脑、肠道和菌群之间相互作用研究有助于解释这些复杂的相互作用背后的潜在机制。干预肠道菌群或许会成为治疗神经精神疾病的潜在策略之一, 因此, “肠−脑”轴代谢通路介导的药物体内过程研究的前沿技术受到了广泛关注。

## 1 疾病下的肠道菌群特点

目前, 无论是动物模型和人类本身的研究均表明肠道菌群与各类神经精神疾病的症状表现存在联系。自闭症谱系障碍 (autism spectrum disorder, ASD) 是一种严重的神经发育疾病, 其特征是刻板行为、语言发育障碍和社会交往方面的缺陷。自闭症患者常常存在胃肠道症状, 如腹痛、腹泻、便秘等, 并通常伴随肠道菌群改变。Desbonnet 等[25]采用三箱社交测试观察了无菌小鼠的行为活动, 发现无菌小鼠与陌生小鼠的相处时间和已熟悉的小鼠相处时间相同, 而正常小鼠往往花费更多的时间接触陌生小鼠。与此同时, 无菌小鼠在空箱的停留时间更长, 这些异常行为表明完全缺乏肠道菌群的动物在社交行为上存在缺陷, 但恢复无菌小鼠的菌群后, 该类行为障碍可被纠正。自闭症儿童也存在相似的行为障碍, 并且其肠道菌群结构发生了变化, 包括拟杆菌和厚壁菌等水平变化和梭菌属丰度的增加[26], 而脱硫弧菌属也有升高的趋势[27], 而罗伊乳杆菌等益生菌可调节催产素水平并逆转自闭症的相关行为, 暗示了肠道菌群影响行为活动的可能[28]。

抑郁症是一种常见的危及生命并且高度复发的疾病,也是世界范围内致残的主要来源。有证据表明, 肠道菌群能显著影响抑郁症的发生与发展[29]。Davis 等[30]发现瘤胃球菌种的丰度增加与小鼠的快感缺乏等抑郁样行为增加相关。临床上, 抑郁症在影响肠道菌群组成方面起到了关键作用。抑郁症患者的肠道菌群相较于健康对照组也有显著改变, 包括其 $\alpha$ 多样性的增加、双歧杆菌和乳杆菌数量的明显减少等[31]。此外最近的一项研究表明, 重度抑郁症患者的肠道菌群与正常受试者也有着较大的变化, 譬如 *Eggerthella*、*Holdemania*、*Gelria*、*Turicibacter*、*Paraprevotella* 以及 *Anaerofilm* 等菌属显著增加; 而 *Prevotella* 和 *Dialister* 菌属显著降低[32]。当重症抑郁症患者的肠道菌群移植到无菌动物时, 抑郁症的行为和生理特征也会被转移, 这一研究支持了菌群异常和抑郁症之间的联系[33]。

肠道中致病菌引起的菌群紊乱还与焦虑症息息相关。Gaykema 等[34]发现肠道中空肠弯曲菌的感染可激活 c-Fos 蛋白 (一种神经元激活的标志物) 来加剧焦虑症的相关行为, 但机体的促炎细胞因子水平并未升高。相似的是, 鼠柠檬酸杆菌感染也会介导迷走感觉神经元加剧焦虑, 并且相关炎症因子水平不变[35], 揭示了肠道菌群可能通过“肠−脑”轴中免疫和代谢途径诱发和

加剧焦虑症。

此外, 肠道菌群也是AD、PD等神经退行性疾病的重要危险因素。Pistollato等[36]报道了大肠埃希菌属、沙门菌属、分枝杆菌属和枯草芽孢杆菌等可诱导神经系统产生淀粉样蛋白纤维, 而且大肠埃希菌属的内毒素还可促进$\beta$-淀粉样蛋白的形成, 进而诱导AD的发生发展。Scheperjans等[37]通过16S rRNA测序比较分析了72名PD患者和72名对照受试者, 发现PD患者的普雷沃菌水平显著降低, 并且肠杆菌科的水平与姿势步态异常的严重程度之间呈正相关性。另一方面, *Blautia*、*Coprococcus*、*Roseburia*等产丁酸菌属在PD患者粪便中丰度更高, 而丁酸等短链脂肪酸 (short-chain fatty acids, SCFAs) 正是肠道菌群代谢产物, 表明了肠道菌群参与了相关的发病机制。

## 2 神经精神类药物影响肠道菌结构

由于神经精神疾病具有复杂性, 因此治疗分子靶标的选择较为困难。目前, 最常用的5种中枢神经系统药物 (奥氮平、喹硫平、利培酮、舍曲林和文拉法辛) 具有共同的作用机制, 暗示了神经精神疾病的治疗药物可以通过共同的分子靶标或以其他方式改变靶标介导的信号传导途径, 包括多巴胺受体、5-HT受体、毒蕈碱受体、肾上腺素能受体等[38], 而肠道菌群可能影响宿主的神经递质水平。Asano等[39]发现无菌小鼠的盲肠腔和组织中的去甲肾上腺素水平显著降低, 而盲肠中去甲肾上腺素水平可以通过46种梭状芽孢杆菌等混合菌群在肠道中的重新定殖来恢复, 揭示了微生物会影响宿主管腔中的去甲肾上腺素水平。William等[40]也观察到无菌小鼠血液和结肠中的5-HT显著减少, 而产芽孢厌氧菌种的肠道再定殖能恢复这一病理状态。Mudd等[41]分析了雄性仔猪的血清生物标志物, 发现其粪便中的瘤胃球菌属 (*Ruminococcus*) 可独立预测血清中的5-HT水平。肠道菌群还可能影响宿主体内中的$\gamma$-氨基丁酸水平, Mitsuharu等[42]报道了无菌小鼠腔内和血清中的$\gamma$-氨基丁酸的水平大大降低, 此外, 几种共生菌也能产生$\gamma$-氨基丁酸, 包括双歧杆菌属和乳杆菌属[43]。这些研究均表明肠道菌群与神经递质存在着密切的关联性。

另一方面, 多数神经精神疾病治疗药物在体外显示了不同的抗菌活性。早期曾报道选择性5-HT再摄取抑制剂 (selective serotonin reuptake inhibitors, SSRIs) 如帕罗西汀、舍曲林和氟西汀等均具有广泛的抗菌活性, 包括对葡萄球菌、肠球菌、梭菌、假单胞菌和柠檬酸杆菌等各类菌属[44]。此外, SSRIs还能通过干扰细菌粘液层的生物合成来增加抗生素对各类细菌的敏感性。例如舍曲林可提高四环素与氟喹诺酮联用抑制解脲棒杆菌, 进而治疗尿路感染[45]。除了SSRIs以外, 单胺氧化酶抑制剂和三环类抗抑郁药也具有抗菌作用。Mandal等[46]分析了不同剂量的阿米替林对253种细菌菌株的体外抗菌活性, 其中对葡萄球菌、芽孢杆菌、霍乱弧菌的抑制率最高。这可能是细胞壁合成和质粒活性受到抑制的缘故[47,48]。同时, 异丙嗪和丙咪嗪也被证明能通过干扰质粒复制来抑制大肠杆菌和小肠结肠炎耶尔森菌的生长[49,50]。此外, 典型 (第一代) 抗精神病药也对各类菌表现不同的抗菌活性。包括硫利哒嗪[51]、氟奋乃静[52]、三氟拉嗪[53]、丙氯拉嗪[54]和氯丙嗪[55]等。

因此, 口服类神经精神疾病治疗药物的使用与肠道菌群组成的改变息息相关。众多动物模型上的研究阐明了两者具有潜在联系。例如非典型抗精神病药物 (atypical antipsychotics, AAP) 奥氮平可诱导给药后3周的大鼠肠道微生物群发生特定的改变,包括硬毛菌、放线菌, 变形杆菌和拟杆菌等多个菌门[56]。阿立哌唑是另一种AAP药物, 在以每天20 mg·kg$^{-1}$的剂量给予大鼠4周后, 可诱导其微生物群组成发生明显的变化, 包括梭菌属, 瘤胃梭菌属等各类菌的相对丰度增加[57]。此外, 一项探究抗抑郁药影响小鼠肠道菌群的研究进一步证明了这一联系。Iva等[58]长期给予小鼠服用5种抗抑郁药物中的任一种 (氟西汀、艾司西酞普兰、文拉法辛、度洛西汀或地斯帕明) 后, 发现其肠道菌丰度有所降低, 而$\beta$多样性增加; 属水平上降低了抑郁样行为相关的瘤胃球菌属丰度, 进一步研究发现黄化瘤胃球菌 (*Ruminococcus flavefaciens*) 会降低度洛西汀的功效, 这为肠道菌群的抗抑郁作用提供了证据。

临床上的研究则进一步证明了两者的关系。Ticinesi等[59]曾对76名老年住院患者的粪便菌群进行分析, 发现各类抗精神病药的使用均能改变患者肠道菌群的组成。另一项横断式设计的研究通过16S核糖体测序分析了100多名双相情感障碍服药患者和对照患者的粪便样本, 旨在研究AAP的服用对肠道菌群的影响。其中所研究的AAP包含了氯氮平、奥氮平、利培酮、喹硫平、阿塞尼平、齐拉索酮、卢拉西酮、阿立哌唑、帕潘立酮和伊潘立酮等各类药物。结果表明, 两组女性患者的肠道菌群被显著区分, 即经AAP治疗的女性患者显示出更低的肠道微生物多样性, 特别是*Lachnospiraceae*、*Akkermansia*和*Sutterella*菌科的丰度差异显著; 而男性患者则没有明显的区别[60]。同样, 一项针对精神病患者的横断式队列研究中也观察到了AAP对肠道菌群的部分影响。尽管使用AAP的对照组患者组与未使用AAP的对照组之间没有检测到肠道菌群的显著变化, 但服用APP后患者的*Alistipes*菌属有所增加。与

此同时AAP治疗组女性患者的肠道菌群多样性也有所降低[61]。Bahr等[62]则更细致的调查了利培酮对肠道菌群组成的影响。与对照组相比, 接受利培酮治疗的儿童患者肠道微生物组发生了改变, 即拟杆菌门和厚壁菌门的丰度有显著降低, 而这可能与患者的体重增加密切相关。而纵向观察研究发现在随后12个月的利培酮治疗中, 拟杆菌门与厚壁菌门的比例则逐步降低。尽管可能存在样本量小等缺陷, 但这些研究初步证明了长期使用利培酮等APP的患者肠道微生物组会产生更加独特的改变。在抗抑郁药方面, 一项对老年受试患者的调查研究表明, 服用抗抑郁药与肠道菌群结构的变化密切相关[63]; 而另一项针对肠道菌群结构的不同群体水平分析也得到了同样的结果[64]。一项针对临床290例重度抑郁症患者代谢组学的研究更是带给了人们深入的思考。口服西酞普兰/艾司西酞普兰后, 体内更多地产生了吲哚和酚酸等肠道菌群相关的代谢产物; 而伴随着患者对药物效应存在高低, 肠道菌群相关的代谢物差异更为显著[65]。

一些成瘾性的药物在发挥药效的同时也改变了肠道菌群结构。氯胺酮是一种非竞争性的*N*-甲基-*D*-天冬氨酸 (*N*-methyl-*D*-aspartate, NMDA) 拮抗剂, 作用于NMDA受体中的苯环利定结合位点[66], 因近期发现了快速持久的抗抑郁作用而备受瞩目[67]。低剂量的氯胺酮显著增加了大鼠乳酸杆菌和*Turicibacter*属的丰度水平, 并改善了其抑郁样行为[68]。而在一项脂多糖诱导的抑郁小鼠模型实验中, 氯胺酮显著降低了其强迫游泳试验中所增加的不动时间, 改善了肠道菌*α*多样性, 并发现肠道菌中放线菌门和肠杆菌属可能是氯胺酮抗抑郁功效的潜在生物标志物[69]。此外, (*R*)-氯胺酮比 (*S*)-氯胺酮具有更强的抗抑郁作用。Yang等[70]发现尽管氯胺酮的两种对映异构体均可改善慢性社会挫败应激小鼠的抑郁样行为并恢复其肠道*Butyricimonas*等菌属的水平, 但 (*R*)-氯胺酮效用更强。这一结果解释了氯胺酮不同对映体发挥更强抗抑郁作用的部分原因。因此, 神经精神疾病治疗药物的使用与个体肠道菌群的变化密切相关。

## 3 肠道菌可能引起药物的不良反应

许多精神疾病治疗药物长期服用可通过肠道菌群产生不良反应。奥氮平是一种新的非典型神经安定药, 能与多巴胺受体、5-HT受体和胆碱能受体结合, 并具有拮抗作用。Morgan等[71]给予小鼠奥氮平后, 小鼠的体重明显增加, 但无菌条件下该效应并不存在; 而重新恢复其肠道菌群后该效应又很快出现, 表明肠道菌群可能是奥氮平诱导的体重增加和相关的代谢综合征的关键因素。抗生素对奥氮平诱导的体重增加效应更是进一步证明了上述结果。一项奥氮平与抗生素联合给药的实验中, 雌性大鼠的体重增加, 子宫脂肪沉积, 血浆游离脂肪酸水平也显著提高[72]。利培酮用于治疗急性和慢性精神分裂症, 其对体内肠道菌群也有着类似的影响。在2个月内每天给予雌性小鼠利培酮80 μg可表现出明显的体重增加, 这与肠道菌群改变后继发的能量代谢减少有关; 有趣的是, 将上述小鼠的粪便移植到幼鼠体内后, 其总静息代谢率下降了16%, 这种现象可能来源于幼鼠的厌氧代谢受到了抑制[73]。氟西汀为临床广泛应用的选择性5-HT再摄取抑制剂 (SSRI), 可选择性地抑制5-HT转运体, 阻断突触前膜对5-HT的再摄取, 延长和增加5-HT的作用, 从而产生抗抑郁作用。Lyte等[74]则发现氟西汀能选择性抑制雄性CF-1小鼠肠道中有益的菌群, 如约氏乳酸杆菌和拟杆菌S24-7, 进而产生负面的体重影响。Fung等[75]观察到肠道中5-HT可与肠道菌群中的一种产孢细菌 (*Turicibacter sanguinis*) 相互作用, 即*T. sanguinis*可摄取5-HT, 5-HT可降低*T. sanguinis*的产孢因子及膜转运蛋白的表达。有趣的是, 这些均可被氟西汀所抑制, 同时氟西汀可调节*T. sanguinis*的基因表达和肠道中的定殖, 从而影响了小鼠的脂质代谢。

怀孕后使用精神活性药物更易对后代产生负面影响。Liu等[76]发现怀孕后的大鼠使用丙戊酸钠可能影响后代的肠道菌群, 并使后代产生类似自闭症的症状。施用丙戊酸的母体小鼠也会产生相似的结果, 表现为子代的拟杆菌门、厚壁菌门及脱硫弧菌目的丰度改变[77], 这与自闭症儿童肠道菌群的变化相似; 而雄性后代的社交行为更少, 这可能影响了肠道内*Alistipes*和*Erysipelotrichales*等多个菌属, 继而改变了肠道内5-HT的水平[78]。此外, 在孕期和哺乳期时使用氟西汀进行抗抑郁治疗也可能改变肠道菌群的组成和功能。Anouschka等[79]发现氟西汀改变了大鼠从妊娠期到哺乳期期间粪便中几种关键氨基酸的浓度, 并与普氏杆菌和拟杆菌的相对丰度负相关。而这可能对母体和后代产生不良影响。

此外, 怀孕后使用硝西泮和氯硝西泮可被肠道硝基还原酶介导代谢, 产生相应的7-氨基代谢产物, 从而对胎儿产生致畸作用。Elmer等[80]给予无菌大鼠放射性标记的氯硝西泮并在其粪便菌群定殖前后对氯硝西泮的硝基还原代谢物产量进行了定量。结果表明, 菌群定殖后, 硝基还原代谢物产量从15%显著增加到77%。而硝西泮还原为7-氨基硝西泮和7-乙酰氨基硝西泮的代谢过程也是由梭菌属、拟杆菌属和优杆菌属等人体肠道中的厌氧细菌所介导。特别是其中的梭状芽孢杆菌, 具有高度特异性的硝基还原酶活性[81]。此

外, Takeno 等[82]采用 300 mg·kg$^{-1}$的硝西泮给予怀孕大鼠口服, 其硝基还原代谢物产量在抗生素的作用下从30%下降到2%, 暗示了抗生素可能降低硝基还原酶的活性。综上, 硝西泮等苯二氮䓬类衍生物需要经硝基还原酶激活才能产生致畸作用, 而肠道菌群是其发生还原代谢转化的主要场所。

## 4 肠道特征菌及代谢物对药物疗效的调节作用

尽管已知的神经精神疾病治疗药物是作用在中枢神经系统的各个靶点, 并能透过血脑屏障更多暴露至脑内, 但是仍不能阐明其药效和作用机制, 而更多研究则关注到了肠道菌群的作用。近期多项研究[83-85]表明肠道菌群失调与AD进展之间存在着密切的联系, 提示了肠道菌群可能参与了AD中小胶质细胞的活化和神经炎症的调控。Wang 等[86]对 AD 小鼠模型研究后发现, 在AD进展过程中, 肠道菌群组成的改变会导致苯丙氨酸和异亮氨酸的累积显著增加, 从而刺激促炎性1型辅助T细胞 (pro-inflammatory T helper 1, Th1) 的分化和增殖; 而脑浸润的外周Th1免疫细胞与M1小胶质细胞激活相关, 促使了AD相关的神经炎症发生。这一结果也由AD引起的轻度认知障碍患者中得到证实, 从这两个独立的病例中均观察到血中苯丙氨酸和异亮氨酸浓度的升高以及Th1细胞的升高。给药后通过改善肠道菌群的失调, 抑制了相关的苯丙氨酸/异亮氨酸蓄积, 从而控制神经炎症并逆转认知障碍。这一研究突出了肠道菌群失调与AD进展中神经炎症之间的潜在联系, 并提出了通过重塑肠道菌群治疗AD的新策略。

肠道菌群还能逆转精神疾病治疗药物对机体的损害。临床研究发现, 氟哌啶醇可引起轴突的损伤, 而肠道菌群可代谢产生丙酸酯等SCFAs, 逆转pCREB-NPY介导的损伤机制, 进而预防轴突病变[87]。肠道菌群已成为治疗神经精神疾病的重要领域之一。

## 5 基于“肠–脑”代谢通路的天然药物体内过程的研究

肠道菌群则更多的参与到中药的作用机制研究, 特别是具有潜在神经精神疾病治疗活性的天然药物。作为中国经典的方剂, 逍遥丸 (散) 具有疏肝解郁等抗抑郁作用。Zhu 等[88]观察到口服逍遥散21天后通过调节抑郁大鼠肠道菌群的结构而改善了其抑郁症样的行为, 并分别从门属等不同水平改变了肠道菌丰度。其中, 白芍、柴胡、当归、甘草、白术、薄荷等均能产生一定的抗抑郁作用。譬如柴胡可通过增加神经生长因子和脑源性神经营养因子改善抑郁症[89], 并且其关键成分柴胡皂苷A可促进海马中的脑源性神经营养因子 (brainderived neurotrophic factor, BDNF)-酪氨酸激酶受体B (tyrosine kinase receptor B, TrkB) 信号通路 (BDNF-TrkB) 信号传导, 减轻绝经后CUMS小鼠的抑郁样行为[90]。当归中的多种活性成分[91], 包括阿魏酸[92]等有机酸类、丁烯基苯酞[93]等苯酞类以及法卡林二醇等多炔类成分[94]均有不同程度的抗抑郁作用。甘草则是通过甘草苷[95]、异甘草苷[96]等成分发挥抗抑郁功效。另外, 白术中的白术内酯I、III[97]以及薄荷中的左旋薄荷酮[98]也在细胞和动物水平初步展现了其较强的抗抑郁能力。上述研究均表明逍遥丸 (散) 的多成分特点决定了其能够通过多靶点、多系统、多层次以调节抑郁症状。

作为逍遥丸 (散) 中的主要成分, 白芍具有良好的安全性, 白芍常用于血虚萎黄、月经不调、自汗、盗汗、胁痛、腹痛、四肢挛痛、头痛眩晕。现代药理学表明白芍具有镇痛、抗炎、抗惊厥和免疫调节等多种药理活性[99,100]。芍药苷和芍药内酯苷是从白芍中分离得到的单萜苷类化合物。近年来发现芍药苷和芍药内酯苷有良好的抗抑郁活性[101-104]。尽管芍药苷和芍药内酯苷口服后在体内吸收快, 但是吸收差, 生物利用度低[105,106]。肠道菌群则帮助解释了白芍活性成分如何发挥药效。Zhao 等[107]在体内外均鉴定出苯甲酸为芍药内酯苷 (白芍的有效成分) 在肠道中的特征代谢产物。苯甲酸可以穿过血脑屏障, 并且作为脑中 *D*-氨基酸氧化酶的抑制剂, 可以改善脑功能并在体内发挥抗抑郁活性; 另一方面, 肠道中的羧酸酯酶是芍药内酯苷发生水解而代谢转化为苯甲酸的关键酶 (图1)。同样, 其异构体芍药苷作为逍遥丸的重要成分, 也通过相同的肠道菌代谢机制来发挥药效, 但起关键作用的羧酸酯酶亚型有所差异[106]。此外, 这两项研究揭示了肠道菌群与天然药物在神经精神疾病的发病机制和治疗机制上起着互为因果的作用。

小檗碱 (berberine, BBR) 是一种从黄连和刺檗等中草药中分离出来的天然化合物, 在中国已被用于治疗腹泻患者的非处方药 (OTC)。自2004年以来, 蒋建东课题组等已经确认BBR是一种安全有效的治疗高脂血症和2型糖尿病的药物, 其机制新颖[108]。在过去的十年中, BBR降低血脂和血糖的临床疗效得到了广泛的证实[108-111]。此外, 多个研究团队报道了BBR对脑功能是有益的[112-115]。由于BBR口服后在肠道中吸收不佳[116-118], 并在肠道中的浓度很高, 揭示了BBR与肠道菌群之间可能的相互作用, 以及BBR可能具有连接肠道菌群和中枢神经系统的化学机制。由于肠道菌中含有丰富的代谢酶[119], 这与脑中重要的神经递质左旋多巴可能存在密切的关系。中国医学科学院药物研究所的研究团队发现小檗碱是肠球菌中酪氨酸羟化酶

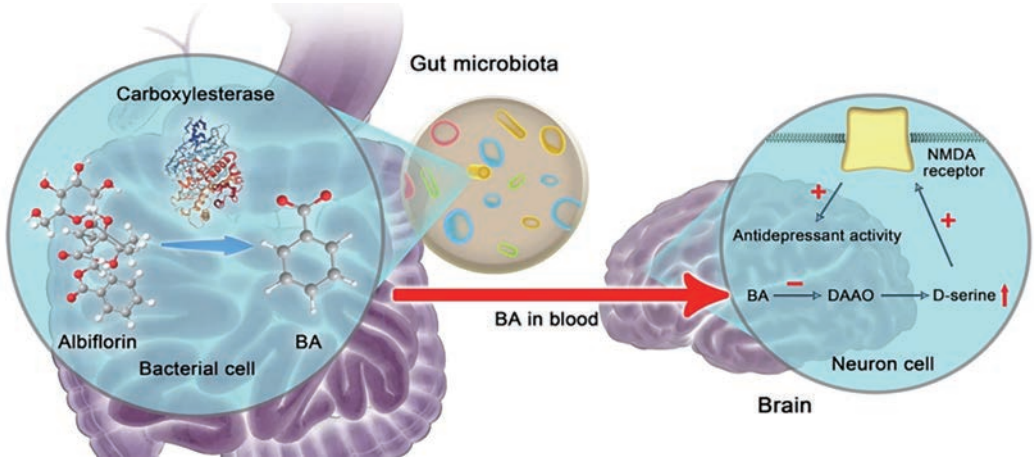


**Figure 1** Gut-brain axis metabolic pathway regulates antidepressant efficacy of albiflorin [107]. NMDA: *N*-Methyl-*D*-aspartate; DAAO: *D*-Amino acid oxidase; BA: Benzoic acid

的激动剂, 并可能导致肠道中左旋多巴的产生 (尚待发表)。研究者对小鼠经口给予小檗碱后发现, 小檗碱可经肠道菌群中硝基还原酶产生二氢小檗碱, 这一过程提供了氢自由基并促进二氢生物蝶呤生成四氢生物蝶呤。由于四氢生物蝶呤可增强酪氨酸羟化酶的活性, 从而加速肠道菌群产生左旋多巴。而肠道菌群产生的左旋多巴通过循环系统进入大脑, 并转化为多巴胺, 改善了帕金森病中多巴胺缺乏的主要病理表现[120]。为了验证小檗碱激活“肠−脑”轴的作用, 研究者利用粪菌移植手段将粪肠球菌以及屎肠球菌分别定殖到了帕金森病小鼠的肠道中, 显著提高了小鼠大脑中的多巴胺水平, 改善了其帕金森病的症状, 并且小檗碱与粪菌移植联用具有更好的治疗效果。这一研究提供了天然药物通过“肠−脑”轴通路改善大脑神经精神疾病的直接证据。

黄酮醇类物质也具有类似的作用机制, 并被体内外研究证实具有抗焦虑活性[121]。Cica 等[122]比较了不同给药途径对山柰酚、槲皮素和杨梅素等黄酮醇类化合物的代谢影响。结果发现, 仅在口服后才检测到特定的代谢产物对羟基苯乙酸 (*p*-HPAA) 和 3,4-二羟基苯基乙酸 (DOPAC), 并对小鼠产生抗焦虑效应; 而腹腔注射后未观察到抗焦虑作用。有趣的是, 当上述代谢产物 *p*-HPAA 和 DOPAC 腹腔注射小鼠后展现了抗焦虑活性, 并且抗生素恩诺沙星可抑制肠道菌群的代谢转化, 从而使抗焦虑作用消失。

多种天然药物提取物也能通过肠道菌群发挥治疗神经精神疾病的药效。已有报道从巴戟天提取的菊粉型低聚寡糖 (inulin-type fructo-oligosaccharides, FOSs) 被证明具有抗抑郁作用, 并被国家食品药品监督管理局批准为处方中药治疗轻度至中度抑郁症。Chi 等[123]观察到 FOSs 减轻了 CUMS 大鼠抑郁症样行为并恢复了肠道菌群的生态平衡, 包括蓝藻细菌等菌门丰度增加, 并且该类细菌可分泌 $H_2S$ 等抗抑郁代谢产物; 而肉苁蓉提取物则是通过肠道菌群影响了神经活性代谢物 SCFAs 的产生, 进而恢复抑郁大鼠脑内 5-羟色胺和 BDNF 的表达, 改善了抑郁样行为症状[124]。文冠果壳苷也是通过调节 AD 大鼠肠道菌群改善了相关的 AD 症状。其中包括多个门属水平的丰度变化, 特别是厚壁菌门与拟杆菌门的比例改变; 同时肠道菌群的变化与氨基酸、溶血磷脂酰胆碱、二氢鞘氨醇、植物鞘氨醇、肌苷和次黄嘌呤等内源性代谢物显著相关[125]。此外, 迷迭香[126]、黄连[127]等天然药物提取物也能重塑肠道菌群结构改善神经精神疾病。

## 6 总结与展望

长久以来, 肠道在维持体内稳态方面发挥着不可忽视的作用, 特别是在过去的十多年间, 肠道菌群的深入研究使人们认识到肠道、肠道菌群与大脑这三者之间的相互作用。在神经精神疾病的生物学和生理学基础的领域中, “肠−脑”轴越来越受到关注。尽管如此, 多数研究只是看到了菌群的变化, 而并未深入探索菌群变化究竟是病因还是结果; 此外, 隔绝菌群等影响因素来验证研究结果依然困难重重, 无论是通过抗生素构建的相对无菌动物模型还是真正的无菌动物, 均存在各自的局限性。因此, 针对肠道菌群与药物, 尤其是神经精神疾病治疗药物的研究还需要更多关键技术上的突破, 这些技术涉及了肠道菌介导的药物代谢−药效研究领域的多学科交叉的前沿技术, 包括宏基因组测序技术、多组学与生物信息学技术、粪菌移植技术、肠道菌内源性代谢产物鉴定与定量分析技术等的运用与普及。此外, 菌群研究的一大难题就是如何定义健康

的肠道菌群。由于个体间肠道菌群结构的差异, 使得统一肠道菌群的研究方法具有挑战性。然而, 也正是因为肠道菌的个体差异, 将可能导致神经精神类药物依赖肠道菌的临床个性化治疗新策略[128]。

考虑到饮食疗法一直被用作精神障碍治疗的辅助治疗方法[129-131], 食物将在未来预防和治疗精神疾病中发挥重要作用[132]。将饮食疗法与其他干预措施相结合, 如药物治疗, 心理疗法和运动等, 已显示出一些良好的功效[133,134]。今后“肠–脑”轴研究应集中在如何利用粪菌移植、益生菌、益生元以及健康饮食来改善肠道菌群, 从而调节“菌群–肠–脑”轴功能并治疗神经精神疾病; 另一方面, 肠道菌群个体化差异与药物的相互作用也是未来的研究重点, 通过探索肠道菌越来越多的生物标志物 (特征菌或代谢酶等), 以实现药物在临床上对疾病尤其对慢病患者的个性化治疗。

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