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专论与综述

益生菌疗法——抑郁症患者的福音?

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摘　要：近几年，肠道菌群与精神疾病，如孤独症谱系障碍、焦虑症、抑郁症等之间的关系越来越受到重视。本文主要介绍了肠道菌群调控精神行为的现有证据，并总结了益生菌对抑郁症干预作用的现有主要临床前及临床研究结果。虽然目前在这一领域取得了许多令人激动的进展，但仍需要更多深入的研究来促进我们理解肠道菌群与抑郁症二者之间的因果关联，并充分评估益生菌防治抑郁症的潜力。

关键词：肠道菌群，抑郁，益生菌，色氨酸，炎症，HPA 轴

Probiotic therapy——the gospel of people with depression?

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Abstract: In recent years, the relationship between gut flora and psychiatric disorders such as autism spectrum disorder, anxiety, depression, has gained increasing attention. This article mainly introduced the correlation between gut flora and depression, and the existing evidence that whether and how the probiotics might affect depression. Although exciting progress has been achieved in this area, further studies are still needed to promote our understanding about the causality between gut flora and depression, and to fully assess the potential of probiotics to prevent and treat depression.

Keywords: Gut flora, Depression, Probiotic, Tryptophan, Inflammation, HPA axis

抑郁症是一种普遍的、危及生命、高度复发的慢性精神疾病，特征是持久性情绪低落、快感缺失和极其高的自杀率。据 2017 年世界卫生组织统计，抑郁症影响全球超过 3 亿人，每年大约有 80 万人因此自杀 (Http://www.who.int/en/news-room/fact-sheets/detail/depression)，且发病率有逐年上升的趋势。但是，抑郁症的病因和发病机制仍然未知，同其它精神性疾病比较而言，抑郁症往往缺少遗传或生化标志物来帮助进行疾病诊断和防治。当今抑郁症的诊断主要依据 24 项汉密尔顿抑郁量表以及专业医生主观判断来进行，而其干预则主要通过抗抑郁药和心理治疗，但大部分患者病情会反复发作。近些年，肠道菌群与抑郁症之间的密切联系逐渐引起广泛的关注，本文初步探讨肠道菌群在抑郁症发生发展

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中可能扮演的角色。

1 抑郁症的发病假说

消极的环境因素，比如生命早期应激、创伤经历、负面生活事件等均可诱发抑郁症的发生[1]，但并不是所有经历不良事件的人都会患病。基于双胞胎、家族等进行流行病研究统计发现，遗传因素在抑郁发病中占 37%−40%[2]，与抑郁症亲属的血缘关系越近，其患病的几率就越高。报道较多的抑郁相关基因主要有[3-4]：色氨酸羟化酶 2 (Tryptophan hydroxylase 2，TPH2)、5 羟色胺受体(5-Hydroxytryptamine receptor，5-HTR)、多巴胺受体(Dopamine receptor，DR)、多巴胺转运体(Dopamine transporter，DAT)、脑源性神经营养因子(Brain-derived neurotrophic factor，BDNF)、促代谢型谷氨酸受体 5 (Glutamate metabotropic receptor 5，GRM5)、钙结合蛋白 1 (Calcium binding protein 1，CABP1)基因、以及血管相关通路基因等。

研究普遍认为环境与遗传均是抑郁发病的重要病因，机体的应激反应和突触可塑性与抑郁症的易感性密切相关[5]，目前主要有以下几种假说试图解释抑郁症的发病机理。(1) 神经递质失调：主要包括单胺类递质系统中的儿茶酚胺、5-羟色胺(5-Hydroxytryptamine，5-HT)、氨基酸类神经递质和神经肽失调[6]；此假说认为情绪障碍是由于神经递质的产生、释放、周转、功能改变或其受体结构功能改变造成的，目前大多数抗抑郁药的开发均基于该假说。(2) 神经营养的改变：神经营养因子可促进神经突触建立、维持神经元存活，其缺乏会诱导大脑结构萎缩和抑郁症[7]。BDNF 表达改变，被广泛用作抑郁症的相关生物标志物[8]。(3) 神经内分泌紊乱：抑郁与下丘脑-垂体-肾上腺(Hypothalamus-pituitary-adrenal，HPA)轴活性有密切联系[9]，特别是机体暴露于应激源时，HPA 轴的过度激活是抑郁发生的重要原因[10]。(4) 炎症反应假说：细胞因子对于大脑发育和功能的正常行使都是至关重要的[11]，抑郁患者血清促炎因子 IL-6、TNF-α 水平常有显著增加，且脑内小胶质细胞出现异常活化[12]。文献[13-14]报道和我们的前期研究均发现，炎症因子可通过影响 HPA 轴活性、神经递质水平、神经营养途径等参与抑郁的发生发展，而抗炎药物能显著改善慢性应激动物的抑郁样行为[15-16]；神经炎症成为近年来抑郁治疗领域的新靶标。

2 肠道菌群与抑郁症的相关性

人体胃肠道大约含有 1 000 种细菌[17]，基因总数超过人体自身基因数目的 100 倍[18]，号称人体“第二基因组”。每个人都有独特的肠道菌群指纹，从胎儿期至出生后 3−5 年，受分娩方式、饮食、遗传等因素的影响，人类肠道菌群的多样性不断增加并最终形成较为稳定的结构；成年时期的肠道菌群主要由拟杆菌门(*Bacteroidetes*)和厚壁菌门(*Firmicutes*)组成，与人体生理活动保持着动态平衡，但感染、生活方式、抗生素使用等仍可使肠道微生态失调[19]。

肠脑轴(Gut-brain axis)是机体胃肠道与大脑之间藉由内分泌、免疫和神经系统紧密联系的双向交流系统。研究发现肠道菌群及其介导产生的细胞因子和代谢产物可通过以下肠脑轴途径直接或间接的参与机体认知和情绪行为的调控[20-22]。(1) 维持肠屏障：正常的肠道菌群结构可竞争拮抗有害菌的定殖，而肠道菌群失调(如应激、抗生素的使用)会破坏肠屏障，增加肠通透性，诱发免疫反应，引起系统炎症细胞因子(如 IL-6、IL-10 等)或细菌有毒成分入血增加，后者可直接或通过作用 HPA 轴间接影响神经行为[23-26]。(2) 参与神经递质合成：肠道共生菌已被证实参与肠道多种神经递质(如 γ-氨基丁酸、血清素、儿茶酚胺、组胺等)的生物合成，而其中与抑郁最密切相关的就是血清素，即 5-HT[27]。结肠内的部分菌种不仅可代谢未消化的蛋白质为机体提供 5-HT 的前体——色氨酸，还可通过调控犬尿氨酸代谢通路改变外周血中相关产物的含量，对情绪行为产生影响[28-29]。(3) 细菌代谢产物的作用：研究最多的主要包括革兰阴性菌的胞壁成分脂多糖(Lipopolysaccharide，LPS)以及结肠菌群通过发酵未消化的碳水化合物产生的一系列短链脂肪酸(Short chain fatty acids，SCFAs)。LPS 入血后可进入

中枢神经系统激活小胶质细胞，通过神经炎症影响情绪行为[30-31]；SCFAs 具有组蛋白去乙酰化酶抑制剂的活性，不仅可影响肠道能量代谢[32]，还可通过血脑屏障直接或间接影响脑内线粒体功能、神经递质产生及免疫反应等[33-34]。(4) 刺激迷走神经：迷走神经刺激法是美国食品与药品监督管理局公认的一种针对难治性抑郁症的方法[35]；在一系列动物实验中均发现，LPS 或肠道细菌对情绪行为的影响依赖完整的迷走神经，这可能与细菌产生的神经递质对迷走神经的刺激密切相关[36]。

近年许多临床研究和动物实验均发现，情绪反应与肠道菌群的改变存在显著相关性。抑郁症患者粪便菌群多样性减少[37-38]；与健康对照相比，抑郁症患者粪便菌群中来自放线菌门、拟杆菌门和厚壁菌门的部分菌种含量发生显著改变[39-40]。成年 SD (Sprague Dawley)大鼠肠道菌群被抗生素破坏后，在强迫游泳试验中表现出抑郁样行为[41]。以抗生素耗竭大鼠的肠道菌群后移植抑郁症患者的粪便菌群，可诱发大鼠产生抑郁样行为，并出现色氨酸代谢的显著改变[40]。与无特定病原体(Specific-pathogen-free，SPF)小鼠相比，无菌(Germ-free，GF)小鼠脑内的神经化学通路(如 5-HTR、BDNF 表达)显著不同[42]，并且在强迫游泳试验中表现出一定的焦虑样行为；给 GF 小鼠移植抑郁症患者的粪便菌群后，其出现抑郁样行为[40]。围产期低剂量青霉素处理会导致新生小鼠肠道菌群组成、血脑屏障的完整性和大脑细胞因子以及神经行为的长期变化，而补充鼠李糖乳杆菌(*Lactobacillus rhamnosus* JB-1)可以减弱青霉素的某些有害影响[43]。由此可见，肠道细菌对大脑神经突触的发育及功能至关重要[44]；而通过粪菌移植或使用益生菌、益生元来调节肠道菌群组成被认为具有潜在的改善异常情绪行为的作用[26]。

3 益生菌对抑郁症的作用研究

益生菌(Probiotic)指的是适量使用可促进宿主健康的活微生物，有单株和复合制剂。传统益生菌主要来自双歧杆菌属(*Bifidobacterium*)、乳杆菌属(*Lactobacillus*)和其它一些乳酸菌(Lactic acid bacteria，LAB)或酵母菌(Yeast)等。益生菌被人广为了解的是其对宿主体重、脂质代谢和免疫反应的调节活性，但近年来随着对肠脑轴研究的关注和深入，也涌现出很多关于益生菌对人体精神状态、认知功能等方面的作用研究。

Aizawa 等发现重度抑郁症(Major depressive disorder，MDD)患者粪便中双歧杆菌的含量较健康人群显著减少(P=0.012)，乳杆菌含量也有减少趋势(P=0.067)[45]。如表 1 所示，一系列使用益生菌(主要来自双歧杆菌属和乳杆菌属)的动物及人体试验研究结果提示，口服益生菌具有一定的抗抑郁作用。但若将近 50 年内进行的临床相关研究进行荟萃分析(Meta analysis)，那么益生菌制剂对于情绪并无显著的改善作用[57]。当然，不同研究对于入组人员的基本情况、选用益生菌种类和剂量的差异等因素都有可能影响评估结果，因此将益生菌制剂作为 MDD 的主要疗法还有待进一步的研究。

目前，关于益生菌抗抑郁的作用机制研究主要集中在其刺激迷走神经、减弱机体 HPA 轴反应、调节色氨酸代谢和抑炎作用方面。例如，Bravo 等发现，口服鼠李糖乳杆菌 JB-1 可引起健康成年雄性 BALB/c 小鼠大脑海马、杏仁核等不同区域 γ-氨基丁酸(Gamma-aminobutyric acid，GABA)受体表达改变，显著降低应激诱发的皮质酮水平，并改善应激动物的焦虑和抑郁样行为；然而切断小鼠迷走神经后，JB1 的作用消失[47]。Liang 等发现，*Lactobacillus helveticus* NS8 改善了慢性应激诱导的大鼠抑郁行为，并减少了应激大鼠血浆皮质酮和促肾上腺皮质激素水平的升高，缓解了血浆抗炎因子 IL-10 水平的降低[50]。Liu 等发现，*Lactobacillus plantarum* PS128 处理可缓解 GF 小鼠的焦虑样行为，并显著增加脑内纹状体的多巴胺和血清素水平[58]。Akkasheh 等发现，补充混合益生菌(*Lactobacillus acidophilus*、*Lactobacillus casei*、*Bifidobacterium bifidum*)可改善抑郁患者的精神症状、降低其胰岛素抵抗和外周炎症相关因子——血清 C 反应蛋白的水平[56]。

表 1　益生菌在临床前及临床试验中的潜在抗抑郁作用

Table 1　Potential antidepressant effects of probiotic in preclinical and clinical trials

益生菌种类、剂量 Probiotics, dose (CFU/d)	对象及处理因素 Object and processing factors	结果 Results	参考文献 References
Bifidobacterium infantis 35624, 10^{10}	母婴分离(Maternal separation，MS)大鼠模型；MS 鼠仔给予益生菌或溶剂灌胃 45 d Maternal separation rat model; MS pups were given probiotics or solvents for 45 days	抑郁行为↓ 部分纠正了 MS 引起的外周血细胞免疫反应和中枢神经递质水平的异常 Depression behavior ↓ Partially corrected the peripheral blood cell immune response and abnormalities of central neurotransmitter levels caused by MS	[46]
Lactobacillus rhamnosus JB-1, 10^{9}	成年雄性 BALB/c 小鼠；益生菌或溶剂连续灌胃 28 d Adult male BALB/c mice; Probiotics or solvents were administered continuously for 28 days	不同脑区的 GABA 受体表达改变 应激诱发 CORT 水平和焦虑、抑郁行为↓ The expression of GABA receptors in different brain regions was changed CORT levels, anxiety and depression behaviors induced by stress↓	[47]
Lactobacillus acidophilus (as LAB or LAB FB), 10^{7}	慢性疲劳综合征(Chronic fatigue syndrome)大鼠模型；造模 28 d，造模最后 7 d 每天给予益生菌灌胃 Chronic fatigue syndrome rat model; Modeling for 28 days, giving probiotics per day for the last 7 days of modeling	抑郁行为↓ 脑内氧化-硝化应激相关标志物↓ TNF-α↓ Depression behavior ↓ Intracerebral oxidative-nitrification stress-related markers↓ TNF-α↓	[48]
*Bifidobacterium longum*1714/ *Bifidobacterium brebe* 1205, 10^{9}	BALB/c 小鼠(天生焦虑的小鼠品系)；益生菌连续灌胃 21 d BALB/c mice (Naturally anxious mouse strains); Probiotics continuously administered for 21 days	*B*. *longum*: 焦虑、抑郁行为↓ *B*. *breve*: 焦虑行为↓ CORT 水平无显著差异 *B*. *longum*: Anxiety, depression behavior↓ *B*. *breve*: Anxiety behavior↓ There was no significant difference in CORT level	[49]
Lactobacillus helveticus NS8, 10^{9}	慢性束缚应激大鼠模型与对照；造模 21 d 期间，每天益生菌灌胃 Chronic restraint stress rat model and control; Probiotics continuously administered for 21 days	焦虑、抑郁行为↓ 非空间记忆↑ Anxiety, depression behavior↓ Non-spatial memory↑	[50]
Lactobacillus plantarum PS128, 10^{9}	幼年应激(Early life stress, ELS)小鼠与正常幼鼠；连续益生菌灌胃 28 d Early life stress mice and control; Probiotics continuously administered for 28 days	正常幼鼠的焦虑行为↓ ELS 小鼠的 CORT、抑郁行为↓ 脑内神经递质 5-HT、DA↑ Anxious behavior of the control group↓ The CORT, depression behaviors of ELS mice↓ Brain neurotransmitter 5-HT, DA↑	[51]
Bifidobacterium bifidum W23/ *Bifidobacterium lactis* W52/ *Lactobacillus acidophilus* W37/ *Lactobacillus brevis* W63/ *Lactobacillus casei* W56/ *Lactobacillus salivarius* W24/ *Lactococcus lactis* (W19 and W58)	雄性 SD 大鼠正常饮食/高脂饮食 10 周；后 5 周连续灌胃复合益生菌或溶剂对照 Male SD rats had a normal diet/high-fat diet for 10 weeks; Continuous administration of probiotics or solvent in the last 5 weeks	抑郁行为↓ 海马区 HPA 轴调控相关因子的转录水平(Crh-r1, Crh-r2 和 Mr)↓ 外周血单个核细胞的免疫反应水平改变 Depression behavior↓ Transcriptional level of HPA axis regulation related factors (Crh-r1, Crh-r2 and Mr) in hippocampus↓ Changes in immune response levels in peripheral blood mononuclear cells	[52]

(待续)

(续表 1)

Lactobacillus casei Shirota (LcS), 24×10^9	双盲试验：39 位慢性疲劳综合征患者，年龄在 18−65 岁之间，随机分别接受益生菌或安慰剂，持续 8 周 Double-blind trial: 39 patients with chronic fatigue syndrome between the ages of 18 and 65, randomized to receive probiotics or placebo for 8 weeks	益生菌制剂可改善焦虑，但对抑郁无显著影响(BAI 评分显著降低，而 BDI 评分无显著差异) Probiotics improved anxiety but had no significant effect on depression (BAI scores were significantly reduced, while BDI scores were not significantly different)	[53]
Lactobacillus helveticus R0052/ *Bifidobacterium longum* R0175, 3×10^9	双盲试验：55 位健康志愿者，年龄在 30−60 岁之间，随机分别接受益生菌或安慰剂，持续 30 d Double-blind trial: 55 healthy volunteers between the ages of 30 and 60, randomized to receive probiotics or placebo for 30 days	益生菌制剂可缓解志愿者的心理压力(HSCL-90/HADS/CCL 评分) 尿液游离皮质醇含量↓ Probiotics relieve psychological stress in volunteers (HSCL-90/HADS/CCL score) Urine free cortisol levels↓	[54]
Bifidobacterium bifidum W23, *Bifidobacterium lactis* W52, *Lactobacillus acidophilus* W37, *Lactobacillus brevis* W63, *Lactobacillus casei* W56, *Lactobacillus salivarius* W24, *Lactococcus lactis* (W19 and W58), 5×10^9	三盲试验：40 位健康青少年随机分别接受益生菌复合补充剂或安慰剂，持续 4 周 Three-blind trial: 40 healthy adolescents were randomized to receive probiotic supplements or placebo for 4 weeks	复合益生菌制剂可减少对于悲伤情绪的负面想法 Probiotics reduce negative thoughts about sadness	[55]
Lactobacillus acidophilus/ *Lactobacillus casei*/ *Bifidobacterium bifidum*, 2×10^9	双盲试验：40 位重度抑郁症患者，年龄在 20−55 岁之间，随机给予益生菌复合制剂或安慰剂，持续 8 周 Double-blind trial: 40 patients with major depression, between the ages of 20 and 55, randomized to a probiotic combination or placebo for 8 weeks	改善抑郁(BDI 评分降低) Improved depression (decreased BDI score)	[56]

4 展望

当今大众对于益生菌的了解和使用还比较局限于很小范围内的微生物(如双歧杆菌、乳杆菌)。但随着对肠道微生物菌群组成和功能的认识加深，益生菌将从功能性食品向药物这个方向进行开发，也被称为下一代益生菌(Next-generation probiotics)[59]。这些非传统益生菌，如 *Faecalibacterium prausnitzii*[60]、拟杆菌属(*Bacteroides*)[61]近年来也被发现具有潜在的抗抑郁作用，但还有待更多的临床试验去证实。

在我们的前期研究中，发现低聚果糖(Fructo-oligosaccharide，FOS)可显著增加慢性应激小鼠肠道内多种益生菌的含量，并显著改善应激小鼠的抑郁样行为[62]。低聚果糖和低聚半乳糖是常被使用的益生元(Prebiotic)，作为可被宿主微生物选择利用的膳食纤维，益生元可广泛调节肠道菌群结构，具有潜在的改善焦虑、抑郁的作用[63]。将益生元和益生菌联合使用，或可进一步促进微生态制剂对抑郁症的防治效果。当今社会，抑郁症患者的数量呈上升趋势，而青壮年是抑郁症患者的主体，这给个人、家庭甚至整个社会都带来沉重的负担。尽管肠道细菌与人体情绪认知之间的因果关系及作用机制还有待进一步阐明，但益生菌/益生元疗法仍为抑郁症的防治带来了新的前景。

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