

青少年肠道菌群特征及益生菌对其抑郁症影响的研究进展

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[摘要] 青少年肠道菌群定植不稳定, 较成人更加多样化, 而抑郁症与肠道菌群存在关联, 抑郁症患者更易出现肠道内菌群失调。益生菌是指对人体有益的活性微生物, 主要包括酵母菌、益生芽孢菌、丁酸梭菌、乳杆菌、双歧杆菌及放线菌等。药理学研究发现, 益生菌具有稳定肠道菌群、促进消化吸收、提高机体免疫力等多种药理作用。近年来研究表明, 益生菌还具有抗抑郁作用, 可通过微生物群-肠-脑轴及其他途径改善情绪, 并在动物及人体试验中得到证实。该文就近年来青少年肠道菌群特征及益生菌抗抑郁的作用及机制等方面的研究进行综述。

[关键词] 肠道菌群; 益生菌; 青少年; 抑郁症

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Characteristics of intestinal flora and antidepressant effect of probiotics in adolescents: Research progress

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[Abstract] The colonization of the gut microbiota in adolescents is unstable and more diverse than adults. Studies have shown that the intestinal bacterial flora of depression patients is imbalanced, indicating that there is a certain connection between depression and the intestinal flora. Probiotics refers to active microorganisms that are beneficial to the human body, mainly including yeast, probiotic spores, *Clostridium butyricum*, *Lactobacillus*, *Bifidobacterium*, *Actinomyces*, etc. Pharmacological studies have found that it has various pharmacological effects such as stabilizing gut microbiomes, promoting digestion and absorption, and improving immunity. Recent studies have shown that probiotics also has an anti-depressant effect, can improve mood through the microbiota-gut-brain axis and other ways, and has been confirmed by experiments in animals and humans. This article reviews recent studies on the characteristics of adolescent intestinal flora and the antidepressant mechanism of probiotics in adolescents.

[Key words] gut microbiomes; probiotics; adolescent; depression

由于受到快餐式饮食、少动、久坐等不健康生活习惯的影响, 近年来全球青少年的抑郁症发病率明显上升^[1-4]。有研究使用流调中心用抑郁量表(Center for Epidemiologic Studies Depression Scale, CES-D)对175名青少年进行调查发现, 有25.1%的青少年达到中度至重度抑郁^[5], 尤其是女孩, 患病率为男孩的2倍^[6]。不仅如此, 抑郁症患儿还有着更高的自杀倾向。有研究调查了276例抑郁症患者, 发现青少年抑郁症患者自杀未遂发生率为48%, 成年抑郁症患者为26%^[7]。此外, 青少年抑郁症的复发率很高。研究发现, 在重度抑郁的青少年中, 有53%经历了抑郁症的复发, 79%合并其他精神疾患^[7]。

青少年的胃肠道拥有超过100万亿个微生物(如细菌、单细胞真核生物、寄生虫及病毒等), 重达2 kg, 其质量与人类大脑大致相等。胃肠道中微生物

的基因总数超过300万个, 是人类基因组的100倍^[8-9], 它们与宿主共生, 对人体健康至关重要^[10-11]。而青少年的肠道微生物处于不稳定状态, 且比成人更加多样化^[12]。

由于身体发育还未完善, 青少年抗抑郁药的选择受到较大限制^[13-14], 且不良反应较成人多, 如胃肠道反应、QT间期延长、躁动^[15]等, 所以寻找安全有效的抗抑郁药物成为迫切的任务。益生菌作为无毒无害的保健食品, 可通过微生物-肠-脑(microbiota-gut-brain, MGB)轴发挥抗抑郁作用^[16]。益生菌还可通过恢复紊乱的菌群, 从而增加血清素、去甲肾上腺素、脑神经营养因子等神经递质^[17], 而上述递质的减少与抑郁症的发生密切相关^[18]。另外, 益生菌还能降低下丘脑-垂体-肾上腺(hypothalamic-pituitary-adrenal, HPA)轴的异常激活, 改善肠道的通透性^[19-20], 并减轻大脑及外周循环的炎症反应^[21]。本文就近年来关于青少年肠道菌群的特点以及益生菌抗抑郁机制的研究进行综述。

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1 青少年肠道菌群特征

1.1 肠道微生物的定植及发展 肠道细菌在整个生命过程中可根据生理及环境的改变而改变^[12], 大约1/3的肠道菌群是普遍的, 而其他2/3则存在特异性^[8]。在新生儿时期, 通过阴道分娩的胎儿暴露于阴道乳酸菌属中, 故乳酸菌属开始定植于胎儿肠道内, 成为优势菌群^[22]; 而未经阴道分娩的新生儿, 因进食食物的不同其肠道菌群亦有不同的变化^[23]。由于食物及生理环境的改变, 厚壁菌及拟杆菌属成为儿童的优势菌群^[24], 青少年则以双歧菌及梭状芽孢菌属为主^[25]。早期微生物定植与HPA轴的激活有关, HPA轴过度亢进会导致革兰阴性菌属增加, 双歧菌属减少^[24]。随着时间的推移, 菌群逐渐保持稳定, 在成年后以乳酸菌、梭菌、肠球菌、拟杆菌及硬毛菌门(属)为优势菌群, 共占肠道菌群的90%以上^[26-27]。

1.2 分泌机体所需神经递质 肠道菌群能分泌多种神经递质及激素, 如5-羟色胺(5-hydroxytryptamine, 5-HT)、脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)、去甲肾上腺素(noradrenaline, NA)等^[17], 这些信号与抑郁症关系密切, 可通过MGB轴上的迷走神经传递到大脑, 调节人体的正常生理活动^[28]。

2 青少年抑郁症患者肠道菌群变化

2.1 菌群种类的变化 大量证据显示抑郁症人群与健康人群的肠道菌群具有明显差异, 表现为菌群多样性减少^[29], 不同细菌的丰度也出现明显改变^[30]。在门水平上, 与健康人群相比, 抑郁症患者肠道内拟杆菌、协球菌、厚壁菌及变形杆菌门的丰度较低^[31-34], 而硬毛菌及放线菌门丰度较高^[32]。在属水平上, 与健康人群相比, 抑郁症患者体内的双歧杆菌、乳酸杆菌、劳特氏菌、费氏杆菌、毛螺菌属的丰度相对较低^[31-32], 而鲁米诺球菌及霍尔德曼氏菌属的丰度相对较高^[31,35-36]。研究发现, 抑郁症还与某些肠道菌群有密切关系, 如鲁米诺球菌的相对丰度与抑郁程度呈正相关^[35], 而霍尔德曼氏菌丰度与抑郁患者的感知压力水平呈正相关^[31]。与之相反的是, 费卡氏菌、毛螺菌、厚壁菌、协球菌门(属)的丰度及硬毛菌/拟杆菌的比值与抑郁程度呈显著负相关^[27,34,36-38]。某些肠道菌群还具有性别差异, 如双歧杆菌丰度在女性人群中与抑郁程度呈负相关, 而乳酸杆菌丰度在男性人群中与抑郁量表评分呈负相关^[39]。研究发现, 抑郁症患者的皮质醇分泌亢进^[19], 而皮质醇可通过MGB轴直接改变肠道菌群的构成^[40]。另外, 动物实验研究表明改变肠道菌

群也可以引起抑郁样行为, 如把抑郁症患者的粪便移植到无菌小鼠身上, 小鼠会出现少动、求生欲望减少等抑郁样行为^[41]。以上研究均提示抑郁症与肠道菌群相互影响。

2.2 神经递质的变化 肠道微生物也会直接分泌机体所需的多种神经递质^[17], 如双歧杆菌可以分泌色氨酸、多巴胺(dopamine, DA)等神经活性递质^[17]。受抑郁症的影响, HPA轴在压力环境下被激活^[42], 导致肠道菌群紊乱, 减少了5-HT等神经递质的产生^[43], 致使通过MBG轴进入大脑内的神经递质减少。此外, 促肾上腺皮质激素释放因子的释放会激活肥大细胞以释放肿瘤坏死因子(TNF)- α 及蛋白酶, 致使正常的负反馈回路受损, 导致HPA轴对皮质醇刺激产生抗性, 皮质醇的抑制作用减弱, 进一步破坏肠道微生物的平衡, 减少兴奋性递质的产生^[6]。

3 益生菌的抗抑郁作用及机制

3.1 对青少年抑郁症的作用 青少年抑郁症的主要诱因为压力, 包括来自家庭及学校的压力^[1-2]。荟萃分析表明, 除氟西汀、西酞普兰对青少年抑郁症有效外, 大多数抗抑郁药与安慰剂相比无明显优势^[44]。青少年在用药上有很多限制^[13], 不良反应较成人多^[15], 再加上自尊心受损^[45], 自控力较弱^[45], 使其用药依从性差。而益生菌具有良好的耐受性, 即使对患有肝病的病鼠也不会造成不良影响^[5]。此外, 益生菌能通过自我维持的方式改变肠道菌群, 因此不需要长期服药^[27], 这与抗抑郁药的用法明显不同, 因此能提高患者的用药依从性。

大数据研究显示, 益生菌作为治疗手段有最低剂量, 即细菌数量小于 1×10^9 CFU/d时, 治疗效果较差^[46]。既往研究表明, 抑郁症患者口服乳酸菌及双歧菌属[剂量为 $(1 \sim 50) \times 10^9$ CFU/d, 持续2~3个月]可有效缓解抑郁症状^[35,37,47-48], 并能改善冲动性及决策能力^[49], 还可以稳定肠道屏障^[35], 降低肠内致病微生物的通透性^[43], 抑制鲁米诺球菌的生长、HPA轴的激活及炎症反应^[35,50]。另外, 乳酸菌及双歧菌属还可以分泌色氨酸(5-HT的前体)、DA、BDNF等与抑郁症相关的神经递质^[17], 从多个方面缓解抑郁症。

乳酸菌属还能减轻抑郁症造成的认知损害^[48], 抑制潜在病原性细菌、真菌的生长及黏附, 增加双歧杆菌及乳酸杆菌的数量, 还能增强短链脂肪酸的合成, 并积极调节炎性细胞的状态^[48], 从而改善抑郁状态。双歧菌属还能使机体产生积极的行为^[48], 并降低硬毛菌及革兰阴性菌门(属)的丰度, 增加拟杆菌门的丰度^[37,51], 从而恢复紊乱的肠道菌群。有研究发现, 抑郁症患者服用酪酸梭状芽孢杆菌

(2.4×10^9 CFU/d) 2个月后, 其负面情绪、认知及记忆力能力均得到改善^[52]。酪酸梭状芽孢杆菌还能增加大脑中的丁酸浓度^[52], 进而缓解抑郁症^[52]。

益生菌还能通过粪移植直接对肠道起治疗作用。有试验采用粪移植的方法(200 ml/次, 1~3次)治疗抑郁症患者, 结果发现患者的抑郁症状得到缓解, 且肠道内的微生物多样性也得到了恢复^[29-30,53]。粪移植后, 在门水平上疣状病毒及古菌门相对丰度增高, 在属水平上甲烷杆菌及艾克曼氏菌属相对丰度增高^[30]。目前还没有研究证实口服益生菌与粪移植的疗效哪个更好, 这与细菌数量及种类均有密切的关系。有研究发现益生菌对成人及成年大鼠的抗抑郁效果并不明显^[27,54], 可能是因为成人及大鼠的菌群定植已稳定, 紊乱后恢复平衡的能力弱, 而且其脑神经发育已完善, 损伤后的可塑性差。这也说明益生菌的抗抑郁作用有一定的年龄限制。

3.2 抗青少年抑郁的机制 目前用来稳定肠道菌群组成的益生菌主要有乳酸菌及双歧菌属^[8,54]。乳酸杆菌及双歧杆菌均可通过表达甘露糖特异性黏附素黏附于肠黏膜, 并刺激肠道产生肠黏膜桥接蛋白来改善肠道屏障功能^[35,48], 以此来降低肠道对肠内微生物的通透性, 减少细菌毒素入血, 减轻炎症反应, 并抑制致病微生物对肠黏膜桥接蛋白的损害, 间接提升肠道屏障的稳定性^[43]。乳酸杆菌及双歧杆菌还能通过减少迷走神经以及下丘脑对5-羟色胺和多巴胺的神经调节来稳定皮质-纹状体-丘脑-皮质轴, 从而减少患者的冲动行为^[49]。另外, 乳酸菌及双歧菌属还能直接分泌兴奋性神经递质^[17], 后者通过迷走神经直接与受体作用, 产生快乐的感觉^[55], 进而改善负面情绪, 缓解压力。HPA轴对压力应激特别敏感^[42], 当压力减小时, HPA轴激活被抑制, 皮质醇分泌减少, 进而抑制了单核细胞的激活^[50], 降低了炎症反应的水平。

乳酸菌属还可通过降低犬尿氨酸酶的活性, 减少色氨酸转化为犬尿氨酸的比例, 将更多的色氨酸转换为5-HT^[47], 从而缓解抑郁情绪。因此, 犬尿氨酸/色氨酸比例降低可能是抑郁症缓解的机制。此外, 乳酸菌属也可通过抑制慢性低毒炎症的发生来减少犬尿氨酸的产生, 犬尿氨酸水平降低可恢复谷氨酸代谢途径, 促使谷氨酸生成, 促进神经突触的连接, 从而改善认知^[48]。这可能是益生菌影响认知功能的一种潜在机制。

双歧菌属可通过直接增加肠道内双歧杆菌的丰度, 并协同提升梭状芽孢杆菌的丰度, 共同抑制革兰阴性菌属^[51], 减少细菌毒素入血后激活单核细胞、巨噬细胞及小胶质细胞的可能^[44,56], 从而抑制

炎症因子的产生。此外, 双歧菌属还能竞争性抑制硬毛菌属的丰度, 增加拟杆菌门的丰度, 恢复硬毛菌与拟杆菌门(属)的比例^[37], 并利用色氨酸酶与犬尿酸酶的协同作用来改变中枢神经系统单胺酶的活性^[48], 引发机体产生积极的行为。

此外, 酪酸梭状芽孢菌属可引起丁酸浓度变化, 增加大脑中的丁酸浓度, 提高海马神经元存活率并缓解神经紊乱, 从而提高认知及记忆力^[52]。因此, 酪酸梭状芽孢菌属的抗炎及神经保护作用(促进神经突触连接、抗氧化及抗谷氨酸兴奋性中毒)可缓解抑郁症。

4 总结与展望

益生菌的抗抑郁作用主要是通过MGB轴实现的, 在稳定菌群的基础上, 通过迷走神经及其他通路增加神经递质, 减少肠道通透性, 抑制HPA轴激活, 降低炎症反应水平, 进而改善情绪、缓解压力、改善认知及记忆力, 可达到治疗抑郁症的效果。益生菌的不良反应很小, 无须长期规律服药, 能提高患者的依从性。益生菌取材广泛、易得, 药理学机制广泛, 有着良好的应用前景。但是, 目前关于益生菌的作用及其机制研究还较浅显, 益生菌的应用多局限于治疗腹泻等引起的肠道菌群紊乱, 其他方面的临床应用尚处于探索阶段, 因此益生菌抗抑郁的机制以及相关产品的开发仍有待进一步深入研究。

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