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综 述

应激对肠道菌群的影响及机制研究进展

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摘 要：应激是机体受到各种因素刺激时所出现的全身非特异性反应，可对全身各个系统产生影响。肠道菌群是肠道微生态的重要组成部分，对维持机体健康发挥重要作用。应激通过影响肠道黏膜屏障功能、肠道免疫功能、胃肠道运动功能等引起肠道菌群紊乱。本文就应激对肠道菌群的影响及机制的研究进展进行综述。

关键词：应激；肠道菌群；益生菌
中图分类号：R338

Progresses on the effects and mechanisms of stress on gut microbiota

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Abstract: Stress is the non-specific systemic response that occurs when the body is stimulated by various factors, and it can affect multiple systems of the body. Recent studies have shown that gut microbiota is an essential part of human microecology, and plays a pivotal role in keeping the body healthy. Stress can result in gut dysbiosis by affecting the function of intestinal mucosal barrier, intestinal immune and gastrointestinal motility. This article reviewed the alteration of gut microbiota caused by stress and the possible mechanisms involved.

Key words: stress; gut microbiota; probiotics

应激是指机体受到内、外环境因素及社会、心理因素刺激时所出现的全身非特异性适应反应，典型表现包括焦虑、恐惧、血糖升高、血压上升、心率加快、呼吸加速等。在应激反应中，蓝斑 - 交感 - 肾上腺髓质系统和下丘脑 - 垂体 - 肾上腺皮质 (hypothalamic-pituitary-adrenal, HPA) 轴激活。适度的应激可以调动全身多个系统，达到抵御风险、储存能量等目的，但是应激持续时间过长或强度过大，则会出现不同程度的躯体、内脏或 / 和心理障碍，增加个体对疾病的易感性 [1]，应激还可引起肠道菌群紊乱 [2]。

肠道内微生物数量巨大，人类肠道细菌数可达 10^{14}。在脊椎动物的肠道菌群中，厚壁菌门与拟杆菌门所占比例最高，变形菌门、梭杆菌门、放线菌门、疣微菌门、螺旋体门等所占比例不足 10% [3]。肠道菌群紊乱存在于多种消化系统疾病，如肠道肿瘤、肠道炎症性疾病、功能性胃肠病等 [4–6]，肠易激综合征 (irritable bowel syndrome, IBS) 患者不仅存在肠道菌群紊乱 [7]，其粪便中的菌群代谢产物 —— 短链脂肪酸水平也发生变化 [8]。此外，肠道菌群可对神经、内分泌、免疫等多个系统产生影响 [9–11]，“菌群 - 肠 - 脑轴”(flora-gut-brain axis) 概念的提出进一步强调了菌群与中枢神经系统的密切联系。机体的正常功能依赖于肠道菌群的动态平衡。本文就应激对肠道菌群的影响及其相关机制进行综述。

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1 应激对肠道菌群的影响

许多研究表明，应激可以造成机体肠道菌群紊乱 (表 1)。大鼠在胎儿期接受的外界应激可以对其成年阶段产生影响，包括 HPA 轴对刺激的过度激活、血压升高、胃肠道神经功能障碍、认知功能受损，肠道菌群中乳酸杆菌属 (*Lactobacillus*) 丰度趋势性降低，颤杆菌属 (*Oscillibacter*)、厌氧棍状菌属 (*Anaerotruncus*)、消化球菌属 (*Peptococcus*) 丰度显著升高 [12]。另一项研究表明，雌性 C57BL/6 小鼠在孕期接受慢性束缚应激后，不仅其自身粪便菌群的 β 多样性发生显著改变，应激还使胎盘组织和胎儿期小鼠的脑组织炎症因子白细胞介素 -1β (interleukin-1β, IL-1β) 含量明显增加，胎盘脑源性神经营养因子 (brain-derived neurotrophic factor, BDNF) 浓度显著下降；子代雌性小鼠成年后 (60~70 日龄) 杏仁核 BDNF 显著下降，焦虑行为显著增加，粪便中拟杆菌门、厚壁菌门、双歧杆菌科 (Bifidobacteriacea) 丰度显著降低，菌群 β 多样性明显改变 [13]。恒河猴孕期受到一段时间的噪声应激后，其子代在 24 周内直肠内容物中乳酸杆菌和双歧杆菌的含量显著降低 [14]。上述研究提示，应激引起的不良反应可在亲代和子代中传递，影响子代的神经发育和焦虑状态等，肠道菌群可能在其中发挥作用，具体机制仍需进一步的研究进行验证。

生命早期的心理、社会应激同样会对个体产生长期的影响。哺乳期母婴分离动物模型常用于研究早期应激对机体的影响，母婴分离动物可表现出行为能力缺陷、内脏敏感性升高、血浆皮质酮含量升高、脑去甲肾上腺素含量降低、免疫反应增强等特点 [15, 16]。母婴分离大鼠盲肠中拟杆菌属 (*Bacteroides*)、梭菌属 (*Clostridium*) 含量升高，乳酸杆菌、双歧杆菌含量降低 [17]。Hantsoo 等人 [18] 的一项临床研究显示，严重的早期不良生活经历可使孕妇肠道菌群中普雷沃氏菌属 (*Prevotella*) 丰度升高，考拉杆菌属 (*Phascolarctobacterium*) 丰度降低，且部分菌属丰度与炎症因子水平存在显著相关性，如血清白细胞介素 -6 (interleukin-6, IL-6) 水平与拟杆菌属丰度呈正相关，与梭菌目 (Clostridiales)、毛螺菌科 (Lachnospiraceae)、小类杆菌属 (*Dialister*)、肠杆菌科 (Enterobacteriaceae) 丰度呈负相关。

给予成年期小鼠慢性束缚应激后，其盲肠菌群丰富度和多样性显著降低，紫单胞菌科 (Porphyromonadaceae) 丰度也明显降低，应激可通过影响菌群结构促进致病菌的肠道定植 [19]。慢性社交失败应激 (social disruption stress, SDR) 可导致小鼠盲肠内容物菌群多样性显著降低，其中拟杆菌属、乳杆菌属相对丰度降低，梭菌属相对丰度升高，且菌群多样性的降低与大鼠的行为学改变具有相关关系。此外，小鼠应激后在不同时间采集样本，其肠道菌群也存在差异，如菌群多样性在应激后 15 h 显著低于应激结束时，罗斯氏菌属 (*Roseburia*) 丰度在应激后 15 h 显著高于应激结束时。应激后血清中的炎症因子 IL-6、单核细胞趋化蛋白 -1 (monocyte chemotactic protein-1, MCP-1)、肿瘤坏死因子 -α (tumor necrosis factor-α, TNF-α)、γ- 干扰素 (interferon-γ, IFN-γ) 表达显著上升，其中 IL-6、MCP-1 含量与部分菌属存在显著相关性 [20]。另一项研究也证明受到 SDR 的小鼠粪便菌群多样性显著降低，宏基因组分析显示，菌群的功能基因发生变化，其中与丙酸、丁酸甲酯代谢，与酪氨酸、色氨酸合成有关的通路基因表达水平降低，丙酸、丁酸可对肠道微生态发挥有益作用，酪氨酸、色氨酸可作为多巴胺、5- 羟色胺 (5-hydroxytryptamine, 5-HT)、去甲肾上腺素、褪黑素等神经递质的前体物质 [21]。接受连续 10 天避水应激的大鼠粪便菌群结构和功能发生改变，普雷沃氏菌科 (Prevotellaceae)、红蝽杆菌科 (Coriobacteriaceae) 丰度显著升高，消化球菌科 (Peptococcaceae) 和韦荣氏球菌科 (Veillonellaceae) 丰度显著降低，同时丁酸酯代谢水平显著降低，丁酸对维持肠道健康有重要作用 [22]。由于黏膜附近的微生物与局部免疫成分发生相互作用的可能性更大，Galley 等人 [23] 研究了急性 SDR 对小鼠结肠黏膜相关菌群的影响，结果表明，应激显著改变了结肠黏膜相关菌群的结构，β 多样性明显改变，乳酸杆菌属相对丰度明显下降，说明单次 SDR 即可对菌群产生影响，同时证明了应激对菌群的作用并不依赖于饮食等因素的改变。这一领域的研究主要集中于动物模型，不过，也有研究证明了应激会改变人类的肠道菌群构成，如大学生在考试时粪便乳酸杆菌相对含量显著降低 [24]；军事训练可以增加粪便菌群的香农指数 (Shannon index)，拟杆菌门丰度降低，厚壁菌门丰度升高，同时伴有肠黏膜通透性的增加 [2]。

应激对肠道菌群的影响在不同研究中具有较大的异质性，研究对象、造模方式、取样部位的差异均会对结果产生影响。不过，应激引起的菌群 α 多样性降低，乳酸杆菌、双歧杆菌丰度降低在多项研

表 1. 应激对肠道菌群的影响

Table 1. Effects of stress on gut microbiota

Stressor	Species	Stress exposure	Samples	Detection method	Microbiota alteration	References
Prenatal restraint stress	SD rats	Embryonic day 14–20	Stool, male offspring at 4 months of age	16S rRNA gene 454 sequencing	*Oscillibacter*↑ *Anaerotruncus*↑ *Peptococcus*↑	[12]
Prenatal restraint stress	C57BL/6 mice	Embryonic day 10–16	Stool, female offspring at 60–70 days of age	16S rRNA gene Illumina MiSeq sequencing	Firmicutes↓ Bacteroidetes↓ Bifidobacteriacea↓ S24-7↓ β-adversity changed significantly	[13]
Prenatal acoustical startle stress	Rhesus monkey	6 weeks during pregnancy	Rectal contents, offspring at 24 weeks of age	Bacteria culturing	Lactobacilli↓ Bifidobacteria↓	[14]
Neonatal maternal separation	Wistar rats	Postnatal day 2–14, 3 h daily	Cecal contents, male rats of 8 weeks	T-RFLP	Bacteroides↑ Clostridium cluster XI↑ Bifidobacterium↓ Lactobacillales↓	[17]
Adverse childhood experiences	Adult pregnant women	—	Stool	16S rRNA gene Illumina MiSeq sequencing	*Prevotella*↑ Erysipelotrichaceae↓ *Phascolarctobacterium*↓	[18]
Restraint stress	Male CD-1 mice aged 6–8 weeks	7 days, 14 h daily	Cecal contents	16S rRNA gene 454 sequencing	α-diversity↓ *Porphyromonadaceae*↓	[19]
Social disruption stress	Male CD-1 mice aged 6–8 weeks	6 days, 2 h daily	Cecal contents	bTEFAP	α-diversity↓ *Bacteroides*↓ Lactobacillus↓ Clostridium↑	[20]
Social defeat stress	Male C57BL/6 mice aged 8 weeks	10 days	Stool	16S rRNA gene Illumina MiSeq sequencing	α-diversity↓ Coriobacteriaceae↓	[21]
Water avoidance stress	Male SD rats aged 6–7 weeks	10 days, 1 h daily	Stool	16S rRNA gene Illumina MiSeq sequencing	Prevotellaceae ↑ Coriobacteriaceae↑ *Prevotella*↑ Peptococcaceae↓ Veillonellaceae↓	[22]
Social disruption stress	Male C57BL/6 mice aged 6–8 weeks	2 h	Colonic tissue	16S rRNA gene 454 sequencing	β-diversity changed significantly Porphyromonadaceae↓ Lactobacillaceae↓ Parabacterioides↓	[23]
Exam	Undergraduate students	1 week	Stool	Bacteria culturing	Lactic acid bacteria↓	[24]
Military training	Norwegian army soldiers	4 days	Stool	16S rRNA gene Illumina MiSeq sequencing	α-diversity↑ Bacteroidetes↓ Firmicutes↑	[2]

↑, increase; ↓, decrease; T-RFLP, Terminal Restriction Fragment Length Polymorphism Analysis; bTEFAP, bacterial tag encoded FLX amplicon pyrosequencing; SD, Sprague-Dawley.

究结果中是一致的。

2 应激影响肠道菌群的可能机制

2.1 应激影响肠道黏膜屏障功能

应激可以引起肠道屏障功能受损从而影响菌群的定植或移位 (图 1)，例如，母婴分离、避水应激均可增加大鼠肠黏膜通透性 [25, 26]；早期断奶可使猪空肠通透性升高，空肠紧密连接蛋白 occludin、claudin-1、ZO-2、ZO-3 表达降低，促肾上腺皮质激素释放激素 / 因子 (corticotropin releasing hormone/factor, CRH/CRF) 表达升高 [27]；小鼠接受慢性 SDR 或束缚应激可增加细菌向肠系膜淋巴结、腹股沟淋巴结和肝脏的移位 [28]；小鼠在口服一种肠道病原菌柠檬酸杆菌 (*Citrobacter rodentium*) 的同时接受慢性束缚应激，可增加肠道病原菌水平、加剧肠黏膜病理情况、加重焦虑程度，促进细菌向脾的移位 [29]。

应激时 HPA 轴的激活参与肠道屏障的损伤过程。研究表明，应激可通过引起 CRH 升高，肥大细胞活化，肠上皮通透性升高，从而引起肠道细菌的移位 [30]；皮质酮水平升高可以通过降低 claudin-1、occludin、ZO-1 的表达增加肠黏膜的通透性 [31]。CRH 1 型和 2 型受体 (CRHR1, CRHR2) 在应激所致的肠黏膜屏障损伤中发挥不同的作用，在母婴分离小鼠中，CRHR1 可介导结肠炎症和黏膜损伤，引起菌群结构改变，CRHR2 则通过促进肠上皮细胞的增殖和分化，介导肠上皮修复 [32]。慢性拥挤应激可以上调 Wistar-Kyoto 大鼠结肠 CRF1 的表达水平 [33]；急性束缚应激后，CRF2 缺陷小鼠表现出血清组胺水平和结肠通透性升高，体外实验证明，肥大细胞表达的 CRF2 可以抑制细胞脱颗粒 [34]。肥大细胞在肠黏膜屏障损伤过程中发挥重要作用，研究证明，人在进行公共演讲或外周应用 CRH 后十二指肠的通透性升高，这种改变可以被肥大细胞稳定剂色甘酸二钠所阻断 [35]；猪在接受早期断奶后，回肠和结肠组织中类蛋白酶阳性肥大细胞数量显著增加 [36]。此外，应激可上调蛋白酶活化受体 2 (proteinase-activated receptor 2, PAR2) 和神经生长因子 (nerve growth factor, NGF) 的表达，激活瞬时感受器电位香草酸受体 1 (transient receptor potential vanilloid receptor 1, TRPV1)，并磷酸化激活细胞外信号调节蛋白激酶 1/2 (extracellular signal-regulated protein kinase 1/2, ERK1/2) 信号通路，而该作用具有肥大细胞依赖性 [37]。肥大细胞表达的 CRF 受体在肠 - 脑轴联系中具有重要的桥梁作用，CRF 可以促进肥大细胞释放类胰蛋白酶和 TNF-α，增加肠上皮通透性，同时减少紧密连接蛋白 occludin 的表达 [38]。

2.2 应激影响肠道免疫功能

应激可通过调节肠道免疫状态影响肠道菌群

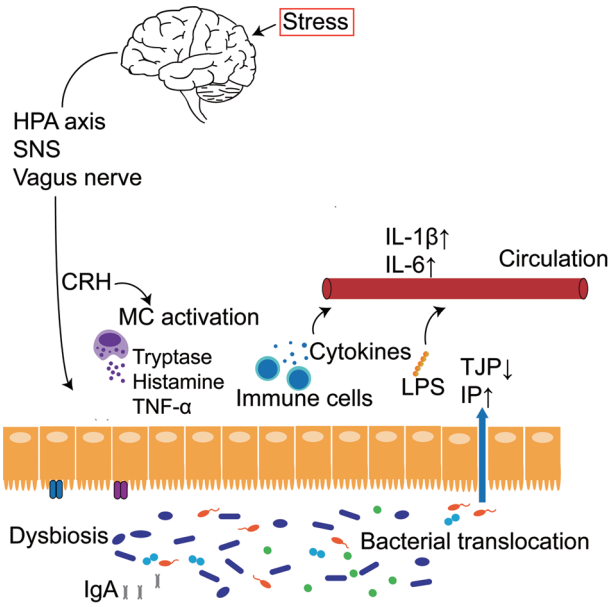

图 1. 应激影响肠道菌群可能机制的示意图

Fig. 1. Possible mechanisms of stress on gut microbiota. SNS, sympathetic nervous system; HPA: hypothalamic-pituitary-adrenal; CRH, corticotropin releasing hormone; LPS, lipopolysaccharide; MC, mast cell; TJP, tight junction protein; IP, intestinal permeability; ↑, increase; ↓, decrease.

(图 1)。在正常状态下，免疫系统始终对肠道菌群起“监视”作用并与其保持相对稳定。其中，肠道分泌型 IgA 可以与肠道内的病原微生物结合，有利于宿主对它的清除，IgA 的缺乏可能使厌氧菌，尤其是厚壁菌门中的分节丝状菌 (segmented filamentous bacteria, SFB) 大量繁殖 [39]；另一项研究表明，在 IgA 缺陷的小鼠中，血清脂多糖 (lipopolysaccharide, LPS) 浓度显著升高，空肠菌群结构发生变化，表现为梭菌科(Clostridiacea)含量降低，副球菌属(*Paracoccus*)含量升高 [40]。应激可以影响肠道免疫细胞的数量和功能。Martínez-Carrillo 等人 [41] 研究显示，小鼠慢性束缚应激可以下调肠黏膜派尔集合淋巴结 (Peyer patch, PP) 淋巴细胞的总数以及 IgA^+ 浆细胞的数量，小鼠皮下注射儿茶酚胺或糖皮质激素也可以降低 PP 结中 T 细胞、B 细胞、浆细胞的数量。Jarillo-Luna 等人 [42] 的研究显示，Balb/c 小鼠在慢性束缚应激后，小肠肠腔总 IgA 浓度显著下降，空肠固有层 IgA^+ 细胞数量无明显变化，对小鼠进行肾上腺切除或交感神经阻断后，应激小鼠的肠腔总 IgA 水平有所改善，给小鼠注射地塞米松或肾上腺素后，肠腔 IgA 水平和 IgA^+ 细胞数量均出现显著下降。不过也有研究呈现出不同结果，Wistar 大鼠在接受慢性束缚应激后，十二指肠和空肠的肠腔 IgA 浓度和 IgA mRNA 水平显著升高，在应激条件下对大鼠进行肾上腺切除则可以显著降低肠腔 IgA 浓度和 IgA mRNA 的表达 [43]，提示应激对肠道免疫的调节受多种因素影响，如应激的持续时间、强度、应激对象等，具体原因有待进一步实验进行探究。一项 Meta 分析探讨了人在经历急性应激后炎症因子水平的变化，结果表明，应激可以显著增加循环血液 IL-6、IL-1β 的含量 [44]。细胞实验证明，去甲肾上腺素可显著提高胃上皮细胞 IL-6 的表达水平 [45]。乙酰胆碱是迷走神经的主要神经递质，人巨噬细胞在受到 LPS 刺激时，乙酰胆碱可显著降低 TNF、IL-1β、IL-6、IL-18 等炎症因子的释放，减轻炎症反应 [46]。当应激持续发生时，交感神经系统持续激活，而副交感神经系统活性降低，炎症因子释放增加，引起机体的持续炎症状态。肥大细胞缺陷型大鼠对恶唑酮诱导的结肠炎易感性明显降低，肥大细胞稳定剂曲尼斯特可显著降低野生型结肠炎大鼠模型体内的炎症因子水平 [47]。

多种模式识别受体 (pattern recognition receptors, PRR) 可以通过对细菌成分的感知调节肠道菌群结构 [11]。存在于肠上皮细胞的模式识别受体 Toll 样受体 5 (Toll-like receptor 5, TLR5) 可以识别细菌的鞭毛蛋白，在肠上皮细胞 *TLR5* 基因敲除的小鼠中，肠道菌群结构发生变化，结肠黏膜的细菌总量显著增加，粪便上清中鞭毛蛋白和 LPS 活性显著升高，肠黏膜可表现为低度炎症，更易发生结肠炎，应用抗生素可以减轻肠道炎症，降低粪便 LPS 和鞭毛蛋白含量 [48]。关于应激对肠黏膜 TLR 的调控作用，现有研究较少。一项研究表明，小羊在受到早期断奶应激的情况下，回肠黏膜 TLR5 的 mRNA 水平显著升高 [49]。有关应激、TLR、肠道菌群三者之间的相互关系还需要更多的研究去探索和验证。炎症小体 NLRP6 (NOD-like receptor family pyrin domain containing 6) 对维持肠道菌群稳态有重要作用，结肠上皮细胞 *NLRP6* 基因缺陷的小鼠出现肠道菌群紊乱，其中粪便菌群中的普雷沃氏菌科和 TM7 门相对丰度上升，菌群变化使小鼠对葡聚糖硫酸钠 (dextran sulfate sodium, DSS) 所致结肠炎和肠道感染更加易感，这种倾向可通过菌群在个体之间相互传递 [50]。另有研究证明，C57BL/6 小鼠接受避水应激后 CRH 分泌增加，CRH 可下调 NLRP6 的表达，从而引起肠道菌群改变，增加肠道炎症的易感性 [51]。

2.3 应激影响胃肠道运动功能

在应激状态下，胃肠运动会受到影响，可表现为小肠传输减弱 [52]，结肠动力增强 [53]，胃肠动力改变引起的肠道环境变化可显著影响菌群结构 [54]。粪便成形度可以反映结肠传输情况，一项关于粪便成形度与肠道菌群关系的临床研究显示，随着粪便成形度的降低，肠道菌群物种丰富度下降，厚壁菌门和拟杆菌门丰度之比降低；肠道菌群的主要菌种构成与粪便成形度有关，普雷沃氏菌属与粪便成形度低有关，而瘤胃菌科 (Ruminococcaceae)、拟杆菌属与粪便成形度高有关，结肠传输时间越长，甲烷短杆菌属 (*Methanobrevibacter*)、艾克曼菌属 (*Akkermansia*) 相对丰度越高 [55]。另有一项临床研究也表明，粪便菌群 α 多样性、可操作分类单元 (operational taxonomic units, OTUs) 丰富度与结肠传输时间呈正相关，肠道菌群 β 多样性与结肠传输时间显著相关，结肠传输时间越长，瘤胃菌科、克里斯滕森菌科 (Christensenellaceae)、甲烷短杆菌属丰度越高，普拉梭菌 (*Faecalibacterium prausnitzii*)、瘤胃菌科、毛螺菌科 (Lachnospiraceae) 丰度越低 [56]。分别使用聚乙二醇或洛哌丁胺处理小鼠，小鼠胃肠传输时间改

变的同时，肠道菌群 β 多样性也发生显著变化 [54]。胃肠动力受损还与小肠细菌过度生长有关 [57]。

3 调节肠道菌群对应激效应的干预作用

上述研究证明，不仅胎儿期和生命早期接受的应激可对肠道菌群产生较为持久的影响，成熟期的应激也对肠道菌群产生即时和持续的影响，因此，在生命的各个阶段均不能忽视应激对个体的影响，应尽早规避和干预。

益生菌干预可以改善应激引起的不良影响。动物实验表明，无菌小鼠存在 HPA 轴的过度激活，给予无菌小鼠婴儿双歧杆菌 (*Bifidobacterium infantis*) 灌胃可以改善 HPA 轴过度激活，而肠致病性大肠埃希菌则会加剧应激带来的不良影响，说明细菌对应激的调节作用依赖于移植的微生物种类 [58]。研究表明，在大鼠受到避水应激的同时给予产丁酸菌 (*Roseburia hominis*) 灌胃，可降低血清 CRH 浓度，提高结肠紧密连接蛋白表达水平，改善内脏高敏感，说明该细菌可能通过其代谢产物丁酸改善应激大鼠 HPA 轴的过度激活，维持肠黏膜屏障的稳定 [22]。Banasiewicz 等人 [59] 也证明了口服丁酸可以显著减轻 IBS 患者的腹痛症状，提示产丁酸菌对改善应激引起的 CRH 水平紊乱与胃肠功能障碍具有较大的研究价值。给予避水应激的小鼠预先使用瑞士乳杆菌 R0052 (*Lactobacillus helveticus* R0052) 和长双歧杆菌 R0175 (*Bifidobacterium longum* R0175) 灌胃，可以显著降低压力诱导的 HPA 轴、自主神经系统过度激活，减轻脑小胶质细胞的活化，改善神经细胞发育，保护肠黏膜屏障 [60]。乳酸杆菌、双歧杆菌还可对应激动物模型产生抗焦虑、抗抑郁作用 [16, 61, 62]。Bravo 等人研究显示，鼠李糖乳杆菌 JB-1 (*Lactobacillus rhamnosus* JB-1) 不仅可降低应激小鼠的皮质酮水平，改善焦虑和抑郁样行为，还可引起大脑不同区域的 γ- 氨基丁酸 (γ-aminobutyric acid, GABA) 受体 mRNA 表达水平改变，在给予小鼠膈下迷走神经切断术后，该细菌的抗抑郁、抗焦虑作用被抵消，GABA 受体表达也有相应变化，说明肠道菌群可通过迷走神经与大脑产生联系，提示了菌群在肠 - 脑轴中的重要作用 [63]。益生菌还可以改善应激导致的胃肠动力紊乱，在应激后的小鼠肠道离体模型中给予鼠李糖乳杆菌 JB-1 刺激，可显著改善回肠和结肠的运动 [64]。此外，在一项双盲、安慰剂对照、平行分组的临床研究中，172 名学生根据性别、年龄、身体质量指数 (body mass index, BMI)、总体健康评分、焦虑评分、唾液皮质醇含量分为两组，分别在考试之前的 8 个星期内每天饮用含干酪乳杆菌代田株 (*Lactobacillus casei* strain Shirota) 的发酵乳或与其味道一样的牛乳饮品，结果显示，相比于对照组，益生菌干预明显降低了学生考试时唾液皮质醇的含量，同时躯体症状、感冒症状、腹部症状也有显著改善 [65]。本研究组研究也显示，腹泻型 IBS 与抑郁共病患者口服益生菌 (乳酸杆菌、双歧杆菌和粪球菌) 不仅可以显著改善腹部症状，还可显著降低外周血 MCP-1 及 IL-1β 水平 [66]。上述研究均证明了益生菌对应激具有有效的干预作用，但是具体的分子机制还需要进一步的实验进行探究。

此外，益生元作为一种膳食补充剂，可促进益生菌的生长。有研究表明，低聚果糖和低聚半乳糖可以显著改善慢性应激小鼠的肠道菌群紊乱状况，降低血浆皮质酮和炎症因子水平，改善抑郁和焦虑样行为 [67]。利福昔明作为一种肠道不吸收型抗生素，可用于治疗功能性胃肠病。动物实验证明，口服利福昔明可以改变避水应激大鼠的回肠菌群结构，显著升高乳杆菌科丰度，同时改善大鼠的肠黏膜炎症、屏障功能与内脏高敏感 [26]。

4 结语

近年来的诸多研究均证明了肠道菌群对维持机体稳态的重要作用，肠道菌群数量庞大，组成成分复杂，受到的干扰因素众多。应激通过 HPA 轴、自主神经系统对肠道菌群产生作用的同时，肠道菌群也通过神经、免疫、内分泌等途径对应激反应做出全身的调节与适应性改变，未来的研究需要进一步关注菌群 - 肠 - 脑轴在整体健康中的作用，深入挖掘应激导致肠道菌群紊乱的机制，以期找到更有效的干预方式。

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