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抑郁症与肠道通透性相互作用机制的研究进展*

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【摘要】 肠道屏障是由多层防御屏障组成的复合结构，能阻挡肠道、外来菌群及其代谢产物向人体内环境转移。肠道屏障的完整性可用肠道通透性来评价，在抑郁症患者中可观察到肠道通透性升高的现象。一些研究证明，抑郁症与肠道屏障存在相互作用，本文将对由抑郁症患者体内低度炎症、迷走神经功能障碍、下丘脑-垂体-肾上腺轴紊乱引起的肠道通透性改变机制，及肠道屏障破坏引起肠道微生物易位导致的抑郁症发病机制进行综述。此外，我们还将探讨抗抑郁药物改善抑郁患者肠道通透性及益生菌改善抑郁症的潜在作用机制。

【关键词】 肠道通透性　　抑郁症　　机制

Latest Findings on the Interaction Mechanism Between Depressive Disorder and Intestinal Permeability

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【Abstract】 The intestinal barrier, a complex structure consisting of multiple layers of defense barriers, blocks the transfer of intestinal and foreign bacteria and their metabolites into the internal environment of the human body. Intestinal permeability can be used to evaluate the integrity of the intestinal barrier. Increased intestinal permeability has been observed in patients with depressive disorder. Some studies have reported an interaction between depressive disorder and intestinal barrier. Herein, we reviewed reported findings on the mechanisms of how systematic low-grade inflammation, vagal nerve dysfunction, and hypothalamic-pituitary-adrenal axis dysfunction cause changes in intestinal permeability in patients with depressive disorder and the pathogenic mechanism of how bacterial translocation caused by damaged intestinal barrier leads to depressive disorder. In addition, the potential mechanisms of how antidepressants improve intestinal permeability and how probiotics improve depressive disorder have been discussed.

【Key words】 Intestinal permeability　　Depressive disorder　　Mechanism

抑郁症是一种以情绪低落、兴趣减退为核心症状的常见精神疾病，据报道，目前全球约有2.6亿人罹患抑郁症，抑郁症已成为最常见的致残疾病之一[1]。现抑郁症的发病机制学说包括单胺类神经递质失衡学说、氧化应激障碍学说、“微生物-肠-脑”轴学说等[2-3]，其中抑郁症“微生物-肠-脑”轴学说的一个核心环节是肠道通透性的改变。抑郁症与肠道通透性改变通过炎症、迷走神经、应激系统这三条途径产生联系。本文将对二者相互作用机制及抗抑郁药物和改善肠道通透性药物潜在的相互治疗价值进行综述。

1　肠道屏障与肠道通透性概述

功能完好的肠道屏障能够选择性地吸收营养物质，防止病原微生物或其代谢产物入侵。肠道屏障主要由三层结构组成。第一层为消化液和肠道菌群层，外来微生物首先受到胃酸、胆汁、胰液等消化液的降解和肠道共生细菌竞争抑制。第二层则包含了水、IgA以及糖萼，可以阻止病原体黏附于肠道上皮。第三层则为相互紧密连接的肠道上皮细胞。上皮细胞层下的固有层中存在大量免疫细胞，可通过分泌免疫球蛋白及细胞因子起到免疫作用[4]。

肠道通透性的定义是在没有载体系统协助的情况下，肠道对中等大小的亲水分子沿浓度梯度的通透程度[5]。肠道通透性的改变在多种疾病中被发现，如胃肠道疾病中的炎症性肠病[6]和肠易激综合征[7]以及非胃肠道疾病中的多发性硬化以及帕金森病等[8]。在中枢神经系统疾病中观察到了肠道通透性的改变，所以二者间存在关联，其中的通路或许是参与构成“微生物-肠-脑”轴的重要组成部分。

2　抑郁症患者肠道通透性标志物概述

常用于衡量肠道通透性的指标有连蛋白（zonulin）、肠型脂肪酸结合蛋白（intestinal fatty acid-binding protein, I-FABP）、脂多糖（lipopolysaccharide, LPS）与脂多糖结合蛋白（lipopolysaccharide binding protein, LBP）、肠道革兰阴性菌的免疫球蛋白IgM、IgA，以及甘露醇乳果糖比值

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(lactulose/mannitol ratio, LMR)。利用这些肠道通透性标志物,研究者们也在抑郁症患者中看到了肠道通透性改变。既往研究证明,I-FABP[9-11]、LBP[9-10]、zonulin[12]、肠道革兰阴性菌的免疫球蛋白IgM和IgA[13-14]在抑郁症患者体内明显高于健康对照者;而在LMR[15]的相关研究中,研究者则未发现抑郁症患者与健康对照者间的显著差距。抑郁症患者肠道通透性的临床研究详细信息均展示在表1中。

3 抑郁症与肠道通透性的相互作用机制

中枢神经系统的行为、情绪和认知,与胃肠道的功能及微生态通过"微生物群-肠-脑"轴这一途径相互联系。肠道屏障是肠道与中枢神经系统建立联系的门户。如前文所述,在抑郁症患者中观察到了肠道通透性的增高,而其升高的机制可主要归纳为3种:炎症反应机制、迷走神经调节机制和应激机制(图1)。

表 1 抑郁症患者肠道通透性临床研究概况

Table 1 Overview of clinical studies on intestinal permeability in MDD patients

Intestinal permeability biomarker	Reference	Experimental group	Control group	Test sample	Test method	Results
Zonulin	ALVAREZ-MON, 2019[9]	MDD (n=22)	HC (n=14)	Serum	ELISA	No significant difference
	ALVAREZ-MON, 2021[10]	MDD (n=30)	HC (n=20)	Serum	ELISA	No significant difference
	OHLSSON, 2019[11]	MDD (n=13)	HC (n=17)	Plasma	ELISA	No significant difference
	WU, 2023[12]	MDD (n=50)	HC (n=40)	Plasma	ELISA	Higher in MDD
Intestinal fatty acid-binding protein (I-FABP)	ALVAREZ-MON, 2019[9]	MDD (n=22)	HC (n=14)	Serum	ELISA	Higher in MDD
	ALVAREZ-MON, 2021[10]	MDD (n=30)	HC (n=20)	Serum	ELISA	Higher in MDD
	OHLSSON, 2019[11]	MDD (n=13)	HC (n=17)	Plasma	ELISA	No significant difference
Lipopolysaccharide-binding protein (LBP)	ALVAREZ-MON, 2019[9]	MDD (n=22)	HC (n=14)	Serum	ELISA	Higher in MDD
	ALVAREZ-MON, 2021[10]	MDD (n=30)	HC (n=20)	Serum	ELISA	Higher in MDD
IgM and IgA against gram-negative enterobacteria	MAES, 2008[13]	MDD (n=28)	HC (n=23)	Serum	ELISA	Higher in MDD
	MAES, 2012[14]	Depression (n= 112)	HC (n=28)	Serum	ELISA	Higher in depressive disorder
Lactulose/Mannitol ratio (LMR)	CALARGE, 2019[15]	MDD (n=16)	HC (n=14)	Urine	Liquid chromatographic analysis	No significant difference

MDD: major depressive disorder; HC: healthy control; ELISA: enzyme-linked immunosorbent assay; LAL: limulus amebocyte lysate.

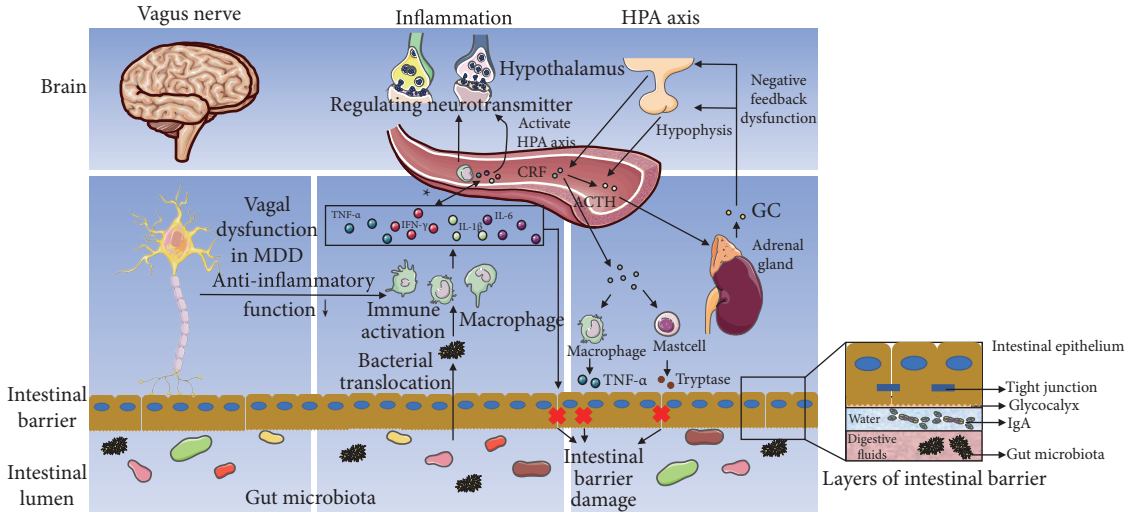

图 1 抑郁症与肠道通透性相互作用机制

Fig 1 The interaction mechanism between major depressive disorder and intestinal permeability

HPA: hypothalamic-pituitary-adrenal; CRF: corticotropin releasing factor; ACTH: adrenocorticotropic hormone; GC: glucocorticoid; IFN-γ: interferon-γ; IL-1β: interleukin-1β; IL-6: interleukin-6; TNF-α: tumor necrosis factor-α. * The bidirectional arrow indicates that the low-grade inflammation of the whole body in patients with depressive disorder may come from the intestinal tract, or may be caused by other factors acting on intestinal barrier. We created the figure by using images provided by Servier Medical Art (http://smart.servier.com). Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/).

3.1　炎症反应机制

抑郁症被视为一种炎症性疾病。现在有大量数据表明, 抑郁症与慢性低度炎症反应、细胞免疫的激活和代偿性抗炎反射系统的激活有关[16-17]。

肠道通透性增加是抑郁症炎症的可能源头之一。抑郁症炎症产生源头可能是应激、饮食、肥胖等因素, 肠道通透性增加、肠道微生物易位也是可能的源头之一[18]。肠道通透性增加会引起肠道微生物及其代谢产物进入血液, 从而激活免疫系统, 活化各种免疫细胞, 导致促炎细胞因子分泌增加, 如肠道细菌的内毒素脂多糖通过CD14激活toll样受体(toll-like receptor, TLR)最终活化单核细胞, 分泌白细胞介素-6(interleukin-6, IL-6)、白细胞介素-2(interleukin-2, IL-2)等促炎症细胞因子[19-20], 造成全身轻度炎症[21]。在脑部, 这些炎症因子通过对神经递质的合成、代谢、再摄取、受体表达等途径产生影响, 造成抑郁症状的出现[22-25]。

肠道既可能是抑郁症患者全身低度炎症的源头, 也是炎症反应的靶点, 即患者体内的炎症也能引起肠道屏障结构的破坏。抑郁症患者与健康对照相比, 血清内各种炎症因子含量更高, 包括干扰素γ(interferon-γ, IFN-γ)、白细胞介素-1β(interleukin-1β, IL-1β)、IL-6和肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)等[26], 上述炎症因子都对肠道通透性有一定影响。TNF-α能诱导Caco-2细胞模型紧密连接通透性增加, 这一过程与肌球蛋白轻链激酶(myosin light chain kinase, MLCK)表达增加有关, MLCK表达增加会引起肌球蛋白轻链(myosin light chain, MLC)磷酸化增加, 导致紧密连接蛋白分布改变和屏障功能损伤[27]。IFN-γ和IL-1β也可能通过MLCK-MLC通路诱导紧密连接结构损害[28-29], IFN-γ还可诱导上皮细胞胞饮作用内吞分解紧密连接蛋白[30]。IL-6升高后结肠上皮细胞中紧密连接蛋白下调, 可能机制的是IL-6 增加了紧密连接基因启动子处的组蛋白H3K9甲基化[31]。

3.2　迷走神经调节机制

抑郁症患者的迷走神经功能存在一定障碍。有研究表明, 抑郁症患者表现出副交感神经反应性降低[32-33]。这说明抑郁症患者的副交感神经系统功能受到抑制, 这一改变也会影响肠道通透性。有动物实验表明, 刺激迷走神经对肠道屏障有改善作用[34]。抑郁症患者迷走神经障碍会影响肠道紧密连接蛋白的表达。迷走神经可通过其抗炎作用, 降低炎症水平, 改善细胞间紧密连接蛋白的表达。有研究表明[35], 抑郁样行为小鼠模型的迷走神经抑制促炎巨噬细胞作用减弱, 肠道的炎症易感性增加, 其肠道通透性增加。这一作用是通过抑制迷走神经胆碱能抗炎通路(cholinergic anti-inflammatory pathway, CAP)实现的。此通路中, 传出迷走神经与肠神经相互作用, 肠神经释放的乙酰胆碱与巨噬细胞的α7型烟碱型乙酰胆碱受体结合, 抑制肠道肌层的巨噬细胞释放TNF-α, 从而引起紧密连接蛋白分布改变和屏障功能损伤[36-38]。

暂未发现直接证据表明肠道通透性改变可通过迷走神经通路引起抑郁症。肠道菌群产生的神经递质可通过传入迷走神经向中枢发出信号[39], 但这与肠道屏障的直接关系较弱。

3.3　应激机制

大多数抑郁症患者的应激系统异常, 下丘脑-垂体-肾上腺(hypothalamic–pituitary–adrenal, HPA)轴处于紊乱状态。超过40% ~ 60%的抑郁症患者会出现高皮质醇血症[40]或HPA系统的其他紊乱, 如昼夜节律改变[41]等。当HPA轴功能异常, HPA轴慢性过度活跃导致出现糖皮质激素抵抗时, 糖皮质激素的抗炎作用以及对HPA轴的负反馈调节作用减弱[42], 从而导致体内炎症无法受到抑制, 促肾上腺皮质激素释放因子(corticotropin releasing factor, CRF)分泌异常增多[43-45]。

应激系统异常对肠道屏障有损害作用。母婴分离大鼠模型是一种常用的抑郁症动物模型, 有研究表明这种大鼠模型存在HPA轴紊乱, 成年后体内CRF反应性, 这导致了肠上皮细胞旁通道通透性升高[46]。在动物回肠模型中发现, CRF可以诱导肥大细胞释放TNF-α和蛋白酶[47]。TNF-α可以通过增加MLCK-MLC途径增加肠道通透性[48]; 肥大细胞释放的类胰蛋白酶可调节结肠细胞紧密连接旁F-肌动蛋白的重组, 导致肠道通透性增加[49]。

肠道通透性升高可以导致HPA轴激活, 对抑郁症的发生有潜在影响。肠道通透性增高引起肠道细菌易位, 肠道细菌的内毒素及肽聚糖可激活HPA轴[50-51]。同时, 肠道细菌易位引起的炎症反应会导致各种炎症因子IL-1β、IL-6和TNF-α升高, 激活HPA轴[52-53]。HPA轴激活后, 糖皮质激素水平升高, 它能激活色氨酸2,3-双加氧酶, 降低色氨酸水平, 从而抑制中枢神经系统血清素的合成[54]。

4　抗抑郁症药物与肠道通透性改善药物

目前, 多种抗抑郁药物已被允许用于脑-肠互动障碍疾病(disorders of gut–brain interaction, DGBI), 如肠易激综合征[55], 在炎症性肠病中也有抗抑郁药物减轻局部炎症及微观损伤、改善疾病活动指数的证据[56-57], 但目前针对抗抑郁药物改善肠道通透性的直接证据仍然缺乏, 但抗抑郁药物在消除炎症免疫反应、改善迷走神经功能、促进应激系统稳定方面的作用或许能够改善肠道通透

性。抗抑郁药物能消除炎症免疫反应,选择性五羟色胺再摄取抑制剂(selective serotonin reuptake inhibitor, SSRI)抗抑郁药降低了全身促炎因子IL-6、TNF-α和 IL-1β的水平[58],炎症因子水平的降低会通过MLCK-MLC等机制改善肠道通透性;抗抑郁药物可以改善迷走神经功能,抑郁小鼠模型迷走神经功能受损导致肠道炎症,服用去甲基丙咪嗪(一种三环类抗抑郁药)后副交感神经功能得以恢复,保护肠道免于炎症[35];抗抑郁药物能够促进应激系统稳定,抗抑郁药物能够降低人体脑脊液中的CRF水平[59-60],恢复糖皮质激素在体内正常的抗炎作用和对CRF释放的负反馈调节[61]。

改善肠道通透性药物益生菌的长期治疗有抗抑郁作用[62],并且在临床试验中也有改善抑郁症状的作用[63]。在抗炎方面,益生菌可以调节黏膜免疫系统和相关炎症因子水平,在肠道起到抗炎作用[64],在肠道的抗炎作用可以减轻炎症对肠道屏障和中枢神经系统的损坏。在改善应激方面,益生菌能降低血浆皮质醇和ACTH水平,恢复HPA轴的稳定[62]。在应激大鼠模型中,益生菌可改善其抑郁样行为[62,65]。

5 小结与展望

肠道通透性在抑郁患者中升高,但在采用不同标志物的研究之间通透性改变结果差异较大。I-FABP、zonulin、LBP和IgM/IgA的相关研究发现抑郁症患者肠道通透性升高,但目前总体来说研究数量过少,且研究样本量也比较小。作为中枢神经系统和胃肠道交流的门户,肠道屏障对抑郁症的进展有着非常重要的意义,我们期待在今后的抑郁症“微生物-肠-脑”轴研究中,看到更多探索肠道屏障完整性的基础和临床研究。

炎症、迷走神经、HPA轴三条通路在抑郁症与肠道通透性改变之间具有重要的联系作用。本文还探讨了抗抑郁药物对肠道通透性及改善肠道通透性药物对抑郁症的作用机制,但抗抑郁药物对肠道通透性改善的直接临床证据目前尚缺乏,有待以后的研究加以探索。

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利益冲突 所有作者均声明不存在利益冲突

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