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文献综述 REVIEW

心理因素在溃疡性结肠炎中的作用及机制

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Role of psychological factors in pathogenesis of ulcerative colitis

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Abstract
Ulcerative colitis (UC) is a chronic inflammatory disease of the colon of unknown etiology. Multiple factors induce the occurrence and development of UC. Among these factors, psychological factors play an important role. As psychoneuroimmunology concept is gradually being accepted, it is currently believed that emotion can affect immune function through the nervous system. Recent studies suggest that psychological stress can be involved in alterations in intestinal inflammation by changing brain-gut axis function, exciting vegetative nerve, releasing neurotransmitters and altering bacterial-mucosal interactions. This paper reviews recent advances in understanding the role of psychological factors in the pathogenesis of UC and emphasizes the ways for the development of therapeutic psychological interventions.

Key Words: Psychological factors; Ulcerative colitis; Mechanism

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摘要
溃疡性结肠炎(ulcerative colitis, UC)是一种直肠及结肠慢性炎症性疾病, 目前病因尚未明确, 现认为多种因素参与了UC的发生及发展, 其中心理因素起了重要作用. 随着心理神经免疫学的概念逐渐被接受, 目前认为情绪可通过神经系统来影响人体免疫功能. 有研究表明, 心理应激可能通过改变脑-肠轴功能、兴奋植物神经、促进神经递质释放及改变细菌黏膜交互作用等途径参与肠道炎症的发生发展. 本文综述了近年来心理因素在UC中的作用及机制, 并为心理干预治疗的研究做好铺垫.

关键词: 心理因素; 溃疡性结肠炎; 机制

核心提示: 溃疡性结肠炎(ulcerative colitis, UC)是一种原因未明的结肠慢性炎症性疾病. 众多研究表明心理因素与UC相关, 并通过调节脑-肠轴、植物神经、神经递质的释放、细菌和黏膜交互作用等参与UC的发生及发展.

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0 引言
溃疡性结肠炎(ulcerative colitis, UC)是一种反复发作的慢性非特异性结肠炎性疾病, 病变主要在大肠黏膜及黏膜下层, 以腹泻、腹疼、黏液血便为主要临床特征. 其病程长, 反复发作, 难根治, 长期不愈者有癌变的可能. 该病在西方国家常见, 欧洲和北美的患病率达79-268/10^5, 我国目前缺乏相关的确切资料, 但近年报道的病例明显增多, 已成为我国消化系统常见疾病. 目

■背景资料
目前溃疡性结肠炎(ulcerative colitis, UC)在我国发病率逐年增高, 已成为我国消化系统常见疾病. 该病目前病因及机制尚未明确, 使得UC的预防及治疗比较棘手. 目前认为UC的发病除与感染、遗传、免疫有关外, 可能还与精神因素相关, 研究精神因素在UC中的作用及机制, 可为UC的治疗提供新的治疗靶点.

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精神因素在UC中的作用目前尚有争议, 对其机制的探讨成为近年来研究的热点.

前UC病因及机制尚未明确, 多数学者认为与感染、遗传、免疫相关, 另外近年大量研究表明UC的发病可能还与精神因素有关[1]. 已有研究证实, 心理因素在心脑血管病、内分泌疾病和神经精神疾病的发生中起了重要作用[2-4], 而其在UC中的作用机制目前尚有争议. 因此, 本文对心理因素影响UC的作用机制进行综述, 以期为心理因素作为UC治疗靶点的研究做好铺垫.

1 UC与心理因素相关

精神心理障碍可以引起胃肠道功能紊乱, 除已知的肠易激综合征、功能性消化不良与心理因素密切相关外[5,6], 有研究发现约74%的UC患者的疾病进程与精神心理因素有关[7,8]. 临床观察研究发现UC患者存在多种心理健康问题, 但以不同程度焦虑、抑郁最为常见, 且焦虑、抑郁的发生率高于其他慢性疾病及正常人群[9-11]. 有学者认为焦虑及抑郁与UC的诱发、活动、复发及恶化有关, 同时也可以是UC反复发作后的继发表现[12,13]. 另外很多UC缓解期患者常可同时并存不同程度的肠易激综合征样症状, 这些患者普遍存在焦虑和抑郁等心理异常[14]. Triantafillidis等[15]研究发现, 精神心理因素与UC病情程度有关, 其中焦虑和抑郁情绪是影响治疗恢复的最大障碍. Timmer等[16]和Bryant等[17]发现同时治疗UC疾病本身及并发的心理障碍可以明显改善病情, 提高患者的生活质量. 目前对于心理因素与UC的因果顺序尚无定论, 但心理因素对UC的影响是肯定的.

2 心理因素影响UC的机制

心理因素影响UC的疾病进程, 这在众多研究中得到证实, 但其作用机制尚未明确. 1981年美国心理学家Robert Adert提出心理神经免疫学的概念, 认为心理、神经、免疫系统之间相互关联, 免疫系统和大脑通过交互作用可影响健康. 目前认为情绪可通过神经系统影响人体系统免疫及胃肠黏膜免疫功能. 结合大量文献分析, 精神心理因素可能是通过改变脑-肠轴功能、兴奋植物神经系统、促进多种神经递质释放及增加免疫细胞活性、改变细菌和黏膜交互作用等途径导致UC的发生及发展[18].

2.1 脑-肠轴以及脑-肠互动理论 神经系统对胃肠道的调节包括: 肠神经系统(enteric nervous system, ENS)的局部调控; 中枢神经系统(central nervous system, CNS)整合内外环境变化时传入的各种信息, 经植物神经系统以及神经-内分泌-免疫网络作用于ENS或直接作用于肠效应器; 椎前神经节接受和调控来自ENS和CNS两方面的信息. 这种将胃肠道和CNS在不同层面上联结在一起的神经-内分泌网络称为脑-肠轴, 其间发生的信息交流则称为脑-肠互动[19]. 脑-肠轴通过信息的双向传递将胃肠道功能与中枢的情感认知联系起来. 外部及内部的感受信息可影响胃肠道感觉、运动、分泌和炎症, 胃肠道的信息也能影响行为及情绪[20].

精神因素通过脑-肠轴上神经-内分泌-免疫网络的调节, 影响UC. 焦虑、抑郁等负性情绪可能引起人体中枢神经系统、免疫系统及内分泌系统的生理变化, 在中枢神经系统的直接或间接影响下, 通过自主神经系统及肠神经系统来调节消化系统的运动、分泌功能[21]. 而杏仁核是脑-肠轴的核心结构, 在情绪应激时起最基础的神经调节作用, 最近有研究发现UC患者杏仁核的血氧水平依赖信号明显下降, 提示UC与心理因素有关, 而杏仁核的功能障碍影响UC病情发展[22,23].

2.2 植物神经紊乱 精神因素与消化系的关系密切, 长期持续的心理精神障碍可使植物神经功能紊乱. 精神状态的变化能影响胃肠道黏膜和肝脏等的血流动力学和分泌, 也能引起胃肠道运动功能的变化, 导致肠平滑肌和血管痉挛, 局部组织营养障碍、肠黏膜抵抗力下降, 这是形成炎症、溃疡的基础[24]. 情绪对结肠功能的影响表现为: 失望、抑郁等消沉情绪可使结肠推进性蠕动增强、黏液分泌增加, 非推进性收缩减弱, 出现腹泻; 焦虑、愤怒等对抗性情绪可使结肠收缩增强, 蠕动减弱, 可致肠痉挛、便秘. Barreau等[25]发现负性情绪可兴奋副交感神经, 使肠道的运动和分泌出现失调, 导致肠黏膜脆性增加, 削弱和破坏肠黏膜的防御功能而出现相应的病理生理改变.

2.3 神经递质及相关免疫细胞 现公认与精神心理活动有关的神经递质包括5-羟色胺(5-hydroxytryptamine, 5-HT)、促肾上腺皮质激素释放因子(corticotropinreleasing factor, CRF)、多巴胺(dopamine, DA)、去甲肾上腺素(norepinephrine, NE)等[26-29], 相应的神经递质的合成、分泌、贮藏等均与精神心理因素具有一定的联系[30]. 而免疫细胞中, 肠嗜铬细胞、巨细胞、肥大细胞等参与介导神经系统与UC之间的信号传导, 从而参与UC的发病[31].

5-HT及其受体被认为是与焦虑、抑郁症状关系较为密切的单胺类物质[32]. 焦虑、抑郁状态可使5-HT分泌增加, 且焦虑、抑郁评分与5-HT成正相关[33]. 而5-HT增加, 可使神经细胞突触前膜对5-HT再摄取的增多, 5-HT到达突触后膜与相应受体结合, 临床上即出现焦虑、抑郁症状[33]. 目前针对不同5-HT受体亚型产生的选择性5-HT再摄取抑制剂(delective serotonin reuptake inhibitors, SSRIs)已成为治疗焦虑、抑郁障碍的主要药物[34]. 另外, 5-HT是一种重要的脑肠肽, 广泛存在于中枢神经系统、胃肠道, 与不同受体结合参与调节肠道运动及敏感性、平滑肌收缩、痛觉传导、神经递质的释放, 与UC的肠道功能性症状相关[35]. 同时5-HT也是一种免疫调节因子, 与位于T淋巴细胞、B淋巴细胞、单核细胞、NK细胞等免疫细胞表面上的5-HT受体结合, 诱导产生第二信使, 对免疫系统起调节作用[36]. 在UC免疫反应中T细胞占重要地位, 5-HT可促进T细胞的增殖, 调节T细胞功能, 并分泌白介素(interleukin, IL-6)、IL-12、IL-2、IFN-γ等细胞因子, 而所分泌的细胞因子反过来影响肠神经系统, 可见免疫细胞与肠神经系统的双向调节在UC的发展中起重要作用[37-39]. 故推测精神心理因素是通过影响5-HT的分泌, 来调节中枢、胃肠、免疫系统, 从而参与UC的疾病进展.

CRF是由41个氨基酸组成的多肽, 在中枢神经系统主要由下丘脑室旁核(paraventricular nucleus of hypothalamus, PVN)分泌, 在下丘脑-垂体-肾上腺轴(hypothalamic-pituitary-adrenal axis, HPA)的神经内分泌调节过程中起关键作用[40]. 精神心理应激兴奋大脑皮质, 再通过边缘系统和网状结构兴奋下丘脑释放CRF[41]. 实验发现, 有焦虑、抑郁等心理异常的动物, PVN及中央杏仁核等脑区CRF的mRNA表达增加, 而脑室中注入外源性CRF与其受体结合, 可引起焦虑等心理异常反应[42]. 应激引起的小鼠焦虑样反应主要由CRF1受体介导, 在非应激情况下PVN区的CRF1受体mRNA无表达, 心理应激情况下CRF1受体表达明显升高, CRF是CRF1受体的诱导剂, 心理应激时CRF升高, 从而引起CRF1受体升高[43]. 中枢过表达CRF1受体基因小鼠可表现焦虑样行为, 封闭CRF1受体的小鼠焦虑程度降低[44]. 实验证实, 心理因素影响UC, 是通过CRF的释放使糖皮质激素、儿茶酚胺的等激素释放增加, 并使肥大细胞数量增多及活性增强, 从而抑制免疫功能、增加肠黏膜通透性、削弱肠道屏障作用、增加结肠能动性和敏感性、使肠道菌群失调或移位、增加炎症介质释放, 这一系列反应导致肠道炎症, 促进了UC的发生发展[45,46].

2.4 细菌和黏膜交互作用 近年微生物致病的观点日益受到重视, 目前大量实验及临床分析显示, 肠道菌群参与UC的发病[47,48]. 正常肠道黏膜对肠道正常菌群处于免疫耐受状态[49]. 而焦虑及抑郁等负性情绪通过兴奋副交感神经、增加神经递质分泌、增加免疫细胞活动, 使肠道正常的屏障作用减弱, 肠内菌群失调移位[50,51]. 肠腔内环境改变, 特别是肠内菌群的改变可能作为抗原刺激肠上皮细胞, 改变黏膜的通透性并对黏膜的免疫系统造成影响, 在肠道炎症过程中产生重要作用[52,53].

■相关报道
大量研究资料表明, 心理因素与UC相关, 并通过调节脑-肠轴、植物神经、神经递质的释放、细菌和黏膜等参与UC的发生及发展.

3 结论

UC是一种心身疾病, 实验证实心理因素在UC的发生、发展中起着重要的作用. 进一步研究心理因素在UC中的作用及机制, 为UC提出了新的治疗靶点, 将有利于UC患者控制病情、改善生活质量.

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■创新盘点

本文叙述心理因素在UC中的作用，并进一步着重深入探讨其机制，进而发现心理因素在UC中的研究及应用价值.

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■同行评价

研究心理因素在UC中的作用及机制, 可为UC治疗提出新的靶点, 对于控制UC患者病情、改善生活质量有所帮助.