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结肠炎结肠动力紊乱机制的研究

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【摘要】 肠道动力紊乱是结肠炎常见的临床表现,发病率在我国乃至世界范围内日趋升高,严重影响患者的生活质量及社会功能,给患者及社会带来沉重的医疗负担,其发病机制涉及多种因素,如神经、炎症介质、平滑肌、离子通道等方面。本文就结肠炎结肠动力紊乱机制的研究作一概述。

【关键词】 结肠动力紊乱;神经;平滑肌;离子通道;炎症介质

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Research on the mechanism of colonic motility disorder in colitis

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【Abstract】 Intestinal motility disorder is a common clinical manifestation of colitis, the incidence rate is increasing in China and the world, seriously affecting patients' quality of life and social functions, and bringing a heavy medical burden to patients and society. The factors such as nerves, inflammatory mediators, smooth muscles, ion channels, etc, but the mechanism has not been fully elucidated. This article provided an overview of the research in the mechanism of colonic motility in colitis.

【Key words】 Colonic dysfunction; Nerves; Smooth muscle; Ion channels; Inflammatory mediator

结肠炎(colitis)是指各种原因引起的、异常免疫介导的结肠炎症性病变[1-5],主要疾病类型有溃疡性结肠炎(ulcerative colitis,UC)、克罗恩病(Crohn's disease,CD)等。主要临床表现为腹泻、腹痛、黏液便及脓血便、里急后重、大便秘结等。其中肠道动力紊乱是结肠炎较为突出的表现,主要表现为胃肠道及结肠的总传输时间延长、远端结肠的粪便推进速率降低、肠道蠕动频率降低,甚至蠕动消失的情况[6]。本文将通过神经、平滑肌、离子通道、炎症介质等对结肠炎结肠动力紊乱进行阐述。

1 与神经系统方面相关机制

肠神经系统(enteric nervous system,ENS)是由胃肠道壁内神经成分组成,具有高度的自主性,起着感知、启动和调控胃肠运动、胃肠激素分泌和血液供应功能的独立整合系统,能独立调节胃肠运动,在切断肠管所有外来神经的情况下,肠壁神经丛仍能保持其功能,胃肠道的收缩及舒张运动仍能规律地发生[7]。肠神经系统包含胃肠道的黏膜下神经丛(submucosal plexus,SP)和肌间神经丛(myenteric plexus,MP)的神经节细胞、中间连结纤维及从神经丛发出供应胃肠道平滑肌、腺体和血管的神经纤维。

BAYLISS 等[8]认为,在肠道上游的神经元选择性地与兴奋性运动神经元形成突触,通过释放乙酰胆碱和速激肽引起平滑肌的收缩。在肠道下游的神经元通过释放一氧化氮(NO)和嘌呤引起平滑肌松弛。正常情况下,上游收缩和下游松弛导致压力梯度,将管腔内容物向肠道远端推动[9]。

AH 神经元为肠内固有反射回路传入端的神经元,其具有长时间的后超极化(after hyperpolarization,AHP)[9-10]。2、4、6-三硝基苯磺酸(2, 4, 6-trinitrobenzene-sulfonic acid,TNBS)诱发的结肠炎通过 COX-2 依赖机制[9],引起的超极化激活阳离子电流增加从而导致 AH 神经元选择性过度兴奋,使内源性运动反射神经的传入神经在炎症的结肠中被破坏,这可能导致炎性相关性肠病的运动障碍[10]。MANNING 等[11]在豚鼠结肠炎模型中发现,前列腺素 E2(prostaglandin E2,PGE2)可通过调节远端结肠肌肠神经元的活性来促进结肠炎的运动障碍,慢性应用 PGE2 更能反映炎症状态,使神经元去极化,并显著增加 AH 神经元的兴奋性。抑制长时间后超极化电位和减少肌肠嗜酸细胞的动作电位调节,作用于反射弧的传入神经,将使这些神经元对腔内刺激作出更强烈的反应,进而改变运动模式,导致运动障碍。

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S 神经元包括中间神经元和运动神经元以及可能具有对机械刺激敏感的感觉神经元。在 TNBS 诱发的结肠炎中 S 神经元对所触发的电活动较 AH 神经元弱,但在黏膜下和肌间神经丛中,神经元间突触电位的强度显著增加[9]。黏膜下神经丛中,突触促进似乎涉及胆碱能神经介导的突触电位,嘌呤能和 5-羟色胺能相结合共同介导突触电位[12];肌间神经丛中的突触促进作用涉及突触前 inPKA 活性的增加,增加 PKA 的活性和增加存在神经终末的突触小泡的 RRP,增加 Ca^{2+} 流入神经末梢[9],从而引起突触前膜释放神经递质,但不会改变突触传递的药理学或突触接触密度。

在结肠炎中,炎症区域的 AH 神经元及 S 神经元异常过度兴奋并且突触活动增强,从而导致炎症区域的兴奋性及下行的舒张信号重叠,当蠕动波到达炎症区域时,因无法识别自发神经元和下行舒张信号的混合信号,进而引起蠕动被破坏[9]。

2 与平滑肌方面相关机制

结肠炎结肠动力紊乱涉及多环节、多方面的机制,目前尚未完全阐明,但平滑肌的活动均为最终作用靶点。如 H_2S 可参与消化道动力紊乱的调节[13-15],GALLEGO等[16]在研究 H_2S 对小鼠空肠和结肠的肠段肌条收缩的影响中发现,H_2S 对结肠平滑肌收缩的抑制作用是不受河豚毒素(TTX)、辣椒素、吡哆醛-磷酸-6-偶氮苯基 2,4′-二磺酸盐和 N-硝基-L-精氨酸等阻断剂的影响,并且在 TRPV1 敲除小鼠中,抑制作用依然存在,说明 NaHS 可直接作用于平滑肌细胞从而调节肠道动力。近期研究确定了 H_2S 对 RhoA 的硫化导致 RhoA 和 Rho 激酶的活性下降从而抑制平滑肌收缩[17]。SMITH 等[18]研究表明,在结肠炎患者中的肠黏膜和血清中 NO 含量超正常人含量的几倍以上,释放的 NO 通过抑制固有初级传入神经元、起搏器 - 肌间起搏器间质细胞、Cajal 间质细胞从而介导结肠平滑肌松弛。在结肠炎中发现结肠平滑肌细胞中 G 蛋白信号传导 4(RGS4)表达调节剂的上调,通过降低结肠平滑肌中内源性 RGS4 的表达可增加结肠平滑肌的收缩活性[19]。

3 与离子通道方面相关机制

近年来,许多报道认为结肠炎结肠动力紊乱与离子通道相关性极为紧密[20-21],如电压依赖性钾电流(voltage dependent potassium current,IKV)、大电导钙依赖钾电流(large conductance Ca^{2+}-activated K^+ current,IBKca)、L-型钙通道(L-type calcium,L-Ca)及 ATP 敏感性钾通道(ATP-sensitive potassium channels,KATP)[22-23]。在结肠炎模型中发现平滑肌收缩活性降低与 L-Ca 兴奋性降低有关,平滑肌细胞中的 L-Ca 的电流较正常情况下降约 70%[24-25],且 L-Ca α 亚基蛋白表达也明显减少[23]。KATP 通道的激活导致膜电位的超极化增加并导致胃肠道平滑肌的松弛。结肠炎炎症可显著增加 KATP 的活性,而 KATP 兴奋剂又可加重硫酸葡聚糖钠(dextran-sulphate sodiu,DSS)诱导的小鼠结肠平滑肌炎症[26]。炎症期间结肠运动能力的降低可能与 Kir 6.1 和 SUR2B 基因表达的转录调节变化有关[27]。有关研究[13,28-31]报道,H_2S 对肠道动力的调节通过 KV、BKca、KATP 所介导,即 KV、BKca、KATP 电流及亚基表达变化可能参与结肠炎动力减退的发生。

可见,在结肠炎模型中,当离子通道重塑包括亚基蛋白和(或)离子通道电流发生改变时可影响结肠动力。

4 与炎症介质相关机制

目前研究表明,肠易激综合征(irritable bowel syndrome, IBS)和其他功能性胃肠道疾病均涉及炎症介导成分[32-33]。大鼠和小鼠的结肠炎模型中炎症介质如 TNF、粒细胞巨噬细胞集落刺激因子(GM-CSF)、IL-1β、IL-6、IL-10 和 IL-17 在大肠中的表达显著增加[34-36]。有报道显示,这些炎症介质抑制胃肠动力,如 TNF、IL-1α 可浓度依赖性抑制大鼠胃底肌条的收缩[37],粒细胞集落刺激因子、IL-6 可抑制大鼠空肠肌条的收缩[38]。近期研究[39]发现,结肠肌组织中巨噬细胞和/或肥大细胞数量的增加可能与结肠炎后胃肠功能障碍的病理生理学有关。

5 其他方面相关机制

Cajal 间质细胞(interstitial cells of Cajal,ICC)主要分布在胃肠道自主神经末梢与平滑肌细胞之间,是胃肠道起搏细胞,在胃肠动力调节方面发挥着重要的作用[40],现已将针对 ICC 治疗视为胃肠动力障碍的治疗靶标。ICC 根据在胃肠道分布位置及性质不同可分 4 类[41],如肠肌间神经丛 ICC(myenteric ICC,ICC-MY)、深肌层丛 ICC(deep muscular plexus ICC,ICC-DMP)、黏膜下 ICC(sub-mucosal ICC,ICC-SM)、肌内 ICC(intramuscular ICC,ICC-IM)。正常情况下,胃肠运动功能源于胃肠蠕动,而胃肠蠕动依赖于规律的慢波节律(slow wave,SW)。研究发现,特异性将 ICC-MY 基因敲除使 ICC-MY 基因缺如,小鼠胃肠道平滑肌记录不到慢波电位出现[42],可见,ICC 是胃肠道慢波节律的起搏者。APOZNANSKI 等[43]发现,ICC-MY 产生的起搏电流可通过 ICC-IM、ICC-DMP 与平滑肌细胞之间的缝隙连接传导到平滑肌上,从而引起平滑肌兴奋产生慢波节律,产生的慢波沿肠壁向下传布,引起动作电位和肠环肌收缩。同时,慢波的持续时间和振幅在很大程度上决定了收缩力和胃肠活动[44]。近期研究发现,通过抑制肠道炎症级联反应,减少 ICC 自噬,调节 ICC/平滑肌细胞网络通路,从而调节小鼠硫酸葡聚糖

钠诱导的结肠炎肠道蠕动[45]。

肠嗜铬细胞(enterochromaffin cell,EC cell)在结肠中主要分布在结肠黏膜中,富含分泌颗粒,主要产物为5-羟色胺[46-47],其被认为蠕动反射的关键介质[18],主要通过激活内源(5-HT1P、5-HT3 和 5-HT4 受体)和外源(5-HT3 受体)初级传入神经元,当 5-HT 受体被药理学阻断时可减少推进运动或消除蠕动反射的活性[48-49]。LINDEN 等[50]研究表明,结肠炎通过改变的5-HT 可用性可能导致炎性肠病的动力障碍,可能与5-HT受体的脱敏相关。

6 结语与展望

结肠炎所致结肠动力紊乱的机制尚未完全明确,可能存在多种发病机制,随着研究热度的逐渐升高,近年来这一研究领域的进展提示结肠炎结肠动力紊乱可能与炎症介质、神经、平滑肌、离子通道等方面相关,且相互关联性较大。相信随着研究方法及研究技术的发展,结肠炎结肠动力紊乱机制的认识将会得到更加深入的了解,为结肠炎患者提供更加先进、个体化治疗方案,从而提高患者生活质量。

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