

结肠移行性复合运动产生和传播机制的研究进展

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江苏省中医院院级课题基金资助项目, No. Y14012

国家自然科学基金资助项目, No. 81273839

作者贡献分布: 本文综述由鞠露与吴晓亮完成; 鞠露与陆高负责文献搜集与资料提取; 鞠露进行资料整理与文章撰写; 吴晓亮与孙建华审核。

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收稿日期: 2015-07-19 修回日期: 2015-08-07

接受日期: 2015-08-17 在线出版日期: 2015-09-18

Colonic migrating motor complex: Generation and propagation mechanism

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Supported by: Project of Jiangsu Provincial Hospital of TCM, No. Y14012; National Natural Science Foundation of China, No. 81273839

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Received: 2015-07-19 Revised: 2015-08-07

Accepted: 2015-08-17 Published online: 2015-09-18

Abstract

The colonic migrating motor complex (CMMC) is a critical neurally mediated, cyclical contractile and electrical event. CMMC is the primary motor

pattern underlying fecal pellet propulsion along the murine colon. Abnormal CMMC has important implications in a number of gastrointestinal disorders, especially slow transit constipation. This review focuses on the mechanisms involved in producing and propagating the CMMC, which is likely dependent on mucosal and neuronal serotonin and pacemaker interstitial cells of Cajal networks and how peristaltic reflexes or occult reflexes affect them, and emphasizes the important role of intrinsic primary afferent neurons, ascending excitatory and descending inhibitory neural pathways. In addition to these, we also introduce some new tools to detect specific neuronal activity so as to offer some exciting insights into the role of 5-hydroxytryptamine in colonic motility.

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Key Words: Colonic migrating motor complex; 5-hydroxytryptamine; Interstitial cells of Cajal; Intrinsic neural reflexes; Neural pathways

Ju L, Sun JH, Lu G, Wu XL. Colonic migrating motor complex: Generation and propagation mechanism. *Shijie Huaren Xiaohua Zazhi* 2015; 23(26): 4221-4226
URL: <http://www.wjgnet.com/1009-3079/23/4221.asp>
DOI: <http://dx.doi.org/10.11569/wcjd.v23.i26.4221>

摘要

结肠移行性复合运动(colonic migrating motor complex, CMMC)是一种神经介导的、周期性的收缩和电活动,是推动小鼠结肠中粪便颗粒前进的主要动力。CMMC异常对胃肠功能紊乱,尤其是慢传输型便秘有重要影响。本文以CMMC产生和传

■背景资料

结肠移行性复合运动(colonic migrating motor complex, CMMC)是一种神经介导的、周期性的收缩和电活动,是推动小鼠结肠中粪便颗粒前进的主要动力,研究发现慢传输型便秘的患者或小鼠模型中, CMMC仍同步发生,但构成CMMC的紧张性抑制活动减少,且慢波活动明显增加。通过探讨5羟色胺(5-hydroxytryptamine, 5-HT)、肠道Cajal间质细胞(interstitial cells of Cajal, ICC)网络、蠕动反射、隐匿反射对CMMC产生和传播的作用机制,为胃肠道功能紊乱疾病提供新的治疗思路,比如目前通过改变5-HT信号通路来治疗因霍乱毒素或胆汁盐导致的腹泻和肠易激综合征等。

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体内或体外肠道CMMC检测技术主要包括胞内外电生理记录、紧张度测量、压力传感器、钙离子成像技术, 实验动物涉及小鼠、豚鼠、猪、犬类, 采用不同拮抗剂或激动剂抑制或兴奋CMMC, 探讨其产生和传播机制, CMMC是神经介导的, 依赖于肠肌间神经网络和ICC网络。目前关于5-HT在肠道动力方面的作用仍存在争议, 这与实验观测技术的限制不无关系, 如何在复杂的神经网络中准确分辨5-HT神经元及其他神经元, 使之可视化并记录其活动是未来研究的重要拓展方向。

播机制为切入点, 集中探讨黏膜5羟色胺(5-hydroxytryptamine, 5-HT)、肠肌间5-HT神经元、肠道Cajal间质细胞(interstitial cells of Cajal, ICC)网络、蠕动反射、隐匿反射对CMMC的影响, 强调内在初级传入神经元(intrinsic primary afferent neurons, IPANs)、上行兴奋性神经通路和下行抑制性神经通路的重要作用, 并介绍特定神经元活动检测新方法以佐证5-HT神经元在肠道动力方面的重要价值。

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关键词: 结肠移行性复合运动; 5羟色胺; 肠道Cajal间质细胞; 固有神经反射; 神经通路

核心提示: 结肠移行性复合运动(colonic migrating motor complex)产生和传播与5羟色胺(5-hydroxytryptamine, 5-HT)、肠道Cajal间质细胞(interstitial cells of Cajal, ICC)网络等密切相关。黏膜5-HT和肌间5-HT神经元均参与内在初级传入神经元(intrinsic primary afferent neurons)活化, 激活上行兴奋性和下行抑制性神经通路, 后激活兴奋性、抑制性运动神经元, ICC同步活化, 相邻平滑肌层同步收缩。

鞠露, 孙建华, 陆高, 吴晓亮. 结肠移行性复合运动产生和传播机制的研究进展. 世界华人消化杂志 2015; 23(26): 4221-4226
URL: <http://www.wjgnet.com/1009-3079/23/4221.asp> DOI: <http://dx.doi.org/10.11569/wjcd.v23.i26.4221>

■ 相关报道

Bayguinov等首次通过钙成像技术观察CMMC过程中不同神经元、ICC、平滑肌的钙瞬变活动, 发现钙瞬变活动与CMMC收缩活动基本一致, 并提出CMMC产生与激活终末Dogiel Type II/AH神经元相关。Akerboom等发现GCaMP5能更敏感地检测体内神经活动, 可广泛应用于一般的细胞成像, 可为准确分辨并记录5-HT神经元活动提供新方法, 明确其在肠道动力中是否发挥重要作用。

小鼠与正常小鼠相比, 粪便排出减少, 在粪便集中部位结肠运动抑制, 空的结肠部位粪便缓慢传输, CMMC仍同步发生, 但构成CMMC的紧张性抑制活动减少, 且慢波活动明显增加^[5]。既往研究发现CMMC的产生和传播与5羟色胺(5-hydroxytryptamine, 5-HT)、肠道Cajal间质细胞(interstitial cells of Cajal, ICC)、固有神经反射等有关, 本文就CMMC的产生和传播机制做一综述。

1 CMMC与5-HT

血清素是肠道最丰富的信号分子, 由色氨酸羟化酶(tryptophan hydroxylase, TPH)合成, 他包含人体约95%的5-HT。肠道中的5-HT超过90%来源于黏膜肠嗜铬细胞(enterochromaffin cells, ECC), 由TPH1合成; 约2%-5%来源于肠肌间下行性5-HT神经元, 由TPH2合成^[6,7]。除5-HT以外, 肠道中还有约14种不同的5-HT受体(5-HT₁-5-HT₇及其亚型), 其中5-HT₃受体是配体门控离子通道, 其他受体则通过不同的信号通路耦联G蛋白, 其中一些受体影响靶细胞的cAMP的水平^[8,9]。目前研究^[10,11]发现通过改变5-HT信号通路可治疗胃肠道疾病, 如因霍乱毒素或胆汁盐导致的腹泻和肠易激综合征(irritable bowel syndrome, IBS), 已研制的药物如5-HT₃受体拮抗剂可有效治疗腹泻型IBS, 而5-HT₄受体激动剂可治疗便秘型IBS。同时也将研制5-HT_{2B}及5-HT₇受体拮抗剂/激动剂以治疗胃肠功能紊乱疾病^[12,13]。

肠腔内压力增高、黏膜刺激促使ECC分泌5-HT, 与5-HT₃受体结合激活终末Dogiel Type II/AH神经元产生CMMC^[14], 或与5-HT₄/5-HT_{1p}受体结合激活黏膜末梢内在初级传入神经元(IPANs-Type 2/AH神经元)引发蠕动反射, 传播CMMC, 推进粪便颗粒移动^[15]。肠肌间5-HT神经元在大肠中相对较少, 但他几乎与所有的一氧化氮合酶(neuronal nitric oxide synthase, nNOS)阳性抑制性运动神经元、中间神经元、IPANs、神经胶质细胞、肌内ICC形成突触连接, 也通过神经递质5-HT释放点与肌间ICC、黏膜下ICC相联系^[16]。他可能发挥着“中央处理器”的作用, 调节各级ENS和ICC网络, 促进肠神经元、ICC等的形成和维护。

在哺乳动物大肠中, 黏膜5-HT和肠肌间5-HT神经元共同调节CMMC^[11]、肌肉的紧张

0 引言

结肠移行性复合运动(colonic migrating motor complex, CMMC)作为许多哺乳动物大肠中的主要运动模式, 他是一种神经介导的、周期性的收缩和电活动^[1], 等效于人类的高振幅传播收缩(high amplitude propagating contractions, HAPCs), 平均每2-4 min出现1次, 持续时间约为40-60 s, 可向口端或肛门端传播^[2]。CMMC在离体的结肠中仍然存在, 可以自发产生或通过黏膜刺激、纵向牵拉诱发^[1], 提示其不受中枢神经系统(central nervous system, CNS)控制, 内源性激素或外周神经冲动并不是其启动或传播的主要因素, 而是由肠神经系统(enteric nervous system, ENS)和结肠壁“小脑”产生^[3]。其目前在大型哺乳动物尤其是人类的生理机制尚不明确, 但在小鼠粪便颗粒的推进中起主要作用^[4]。局部出口梗阻引起慢传输型便秘的

性抑制^[17]、血清素分泌和血流活动^[16,18]。他们均参与IPANs活化,从而激活上行兴奋性神经通路和下行抑制性神经通路,分别激活兴奋性运动神经元和抑制性运动神经元,最终导致平滑肌收缩和起搏细胞活动,产生CMMC^[11,19]。在CMMC传播过程中,有明确的模式开关,即抑制性运动神经元的“关闭”允许兴奋性运动神经元的完全“开放”,释放乙酰胆碱和速激肽,致平滑肌和ICC完全兴奋^[14,20,21]。在CMMC间期中,一些肠肌间5-HT神经元自发激活,直接作用于外周自主神经系统,从而产生平滑肌和ICC的紧张性抑制^[17]。

相较于黏膜5-HT,肠肌间5-HT神经元似乎对肠道运动有更重要的影响。研究发现TPH2敲除小鼠加速胃排空,并显著减慢肠道传输和粪便颗粒从直肠排出,可能因为肠神经元和其他细胞的总体数目减少,而5-HT神经元是肠神经元、ICC、黏膜形成过程中的重要前体细胞。相反,TPH1敲除小鼠不影响整体胃肠道传输时间,表明黏膜5-HT对于肠道基础运动是非必需的^[22,23]。但最新研究^[11]提示黏膜5-HT缺乏对离体TPH1敲除小鼠结肠推进有显著影响,推断可能有其他代偿机制来恢复肠道传输。

2 CMMC与ICC

ICC依据其在肠壁的位置和功能分为多个亚型,包括位于纵向肌表面的浆膜层ICC(subserosal layer ICC, ICC-SS)^[24,25],位于纵向肌和环形肌之间的肌间ICC(myenteric plexus ICC, ICC-MY)^[26-29],以及环绕肌束的隔膜ICC(septa ICC, ICC-SEP)^[30]、肌内ICC(intramuscular ICC, ICC-IM)^[31,32]、深肌层ICC(deep-muscular plexus ICC, ICC-DMP)^[33]和黏膜下ICC(submucosal plexus ICC, ICC-SM)^[34-37]。在胃和小肠中,ICC-MY产生慢波,被称为“肠道起搏器”^[36,38]。钙成像研究表明ICC-MY起搏活动能顺利传播依赖于其与纵向肌、环形肌等形成的致密网络^[39,40]。在大型哺乳动物中,ICC-MY的起搏活动通过ICC-SEP传导至肌束。ICC-SS可能也产生起搏活动,因为自发动作电位的发生接近浆膜层,并使其传播到纵向肌深处^[30]。ICC-IM和ICC-DMP可调节从运动神经元至平滑肌细胞的胆碱能和肠道氮能神经传递^[41]。此外,ICC-IM也可作为牵张感受器,通过非神经机制兴奋平滑肌^[42]。不同于胃和小肠,大肠中的ICCs在

CMMC的产生中发挥着不同的作用。大多数哺乳动物包括人类,大肠中的慢波是由ICC-SM产生(3-7次/min, ICC-MY产生肌间电势震荡(myenteric potential oscillations, MPOs),是一种比慢波更快的电冲动(18-40次/min)^[43]。ICC-SM产生的慢波与ICC-MY产生的MPOs均参与CMMC的形成^[44]。

从电生理活动上看,CMMC由短暂超极化、动作电位快速震荡、缓慢去极化组成^[45]。下行抑制性神经通路激活后,促使抑制性运动神经元释放一氧化氮、嘌呤,从而使平滑肌短暂超极化及抑制性动作电位产生。而上行兴奋性运动神经元激活后,释放乙酰胆碱、速激肽,并减少抑制性运动神经元活性,最终形成动作电位快速震荡、缓慢去极化^[17]。研究通过观察CMMC过程中的钙瞬变活动,发现动作电位引起Ca²⁺大量内流后,ICC-MY产生快速的电势震荡即MPOs,后叠加缓慢的钙离子上升,其与纵向肌、环形肌的缓慢去极化持续时间相似,ICC-MY的Ca²⁺活动图像类似于相邻纵向肌、环形肌中动作电位快速震荡、缓慢去极化图像^[21]。

3 CMMC与固有神经反射

肠道神经反射与肠道内容物(粪便颗粒)密切相关,肠道中的粪便可以引起黏膜刺激、肠道径向扩张及肠道延长。而前两者可触发蠕动反射(peristaltic reflexes),后者可触发隐匿反射(occult reflexes),此两种反射可从根本上影响CMMC。

3.1 蠕动反射 肠腔内球囊扩张可同时激活蠕动反射和CMMC^[11,46]。相较于CMMC,蠕动反射是针对刺激点的上行性兴奋和下行性抑制反应,能更快地在肌间神经丛传播^[47]。蠕动反射通路与CMMC有共通性,一方面,黏膜刺激引起ECC分泌5-HT,与5-HT₃受体结合激活黏膜末梢IPANs;肠道径向扩张兴奋肠肌间机械敏感性中间神经元^[47,48],而且黏膜刺激可降低肠道径向扩张触发蠕动反射的阈值,提示IPANs与机械敏感性中间神经元之间存在着突触连接^[46]。另一方面,CMMC能更容易地向肛门端方向传播,部分原因是因为蠕动反射通路(口端兴奋,肛门端抑制)的调节^[44]。

3.2 隐匿反射 肠道延长可触发隐匿反射,抑制粪便颗粒传输^[49]。研究^[50]发现当豚鼠和小鼠的结肠内充满粪便颗粒,其肠道分别延长约40%

■创新盘点

本文系统探讨黏膜5-HT、肠肌间5-HT神经元、ICC网络、蠕动反射、隐匿反射对CMMC产生和传播的影响,强调内在初级传入神经元(intrinsic primary afferent neurons, IPANs)、上行兴奋性和下行抑制性神经通路的重要作用,并介绍特定神经元活动检测新方法佐证5-HT神经元在肠道动力方面的价值。

应用要点

本文以黏膜5-HT、肠肌间5-HT神经元为起点, 通过上行兴奋性和下行抑制性神经通路分别激活兴奋性和抑制性运动神经元, 释放相关神经递质, 促使ICC活化及平滑肌同步收缩, 产生并传播CMMC。其中5-HT不再单是一种神经递质, 也是一种神经元, 利用新方法检测5-HT神经元活动, 探讨其在肠道动力中的作用仍需进一步的深入研究。

和20%, 且粪便颗粒排出率显著减少。之所以称之隐匿反射, 是因为其不直接作用于肌肉, 而是通过抑制蠕动神经回路中的神经元实现的。不同于蠕动反射, 当口端结肠延长时, 激活机械敏感的nNOS阳性下行性神经元, 使其释放一氧化氮, 抑制许多肠肌间神经元, 其中包括IPANs, 从而减少或阻断CMMC; 当肛门端结肠延长时, 激活机械敏感的胆碱能上行性神经元, 兴奋IPANs和其他神经元推动CMMC产生^[4,49]。目前所知IPANs、黏膜下神经元可被隐匿反射兴奋或抑制, 而隐匿反射对5-HT神经元的影响仍未知。

4 展望

目前研究已通过胞内外电生理记录、紧张度测量、压力传感器、钙离子成像等技术观察CMMC过程中肠肌间神经元、ICC、平滑肌等的活动变化, 关于5-HT在肠道动力方面的作用仍存在争议, 尽管5-HT已证实对消化系病理生理学方面的重要意义, 这与实验观测技术的限制不无关系, 除可运用基因敲除技术观察5-HT外, 如何在复杂的神经网络中准确分辨5-HT神经元及其他神经元, 使之可视化并记录其活动? Nagel等^[51]采用光门控离子通道ChR2观察线虫兴奋细胞及特定神经元活动。Zariwala等^[52]运用基因编码的荧光钙指示剂蛋白GCaMP3观察体内特定神经元活动, 并培育成功能靶向表达GCaMP3的Ai38受体小鼠。Akerboom等^[53]发现GCaMP5能更敏感地检测体内的神经活动, 并可广泛应用于一般的细胞成像。这些新方法可能会提供一些关于5-HT在肠道动力中的重要性的有力佐证。

5 结论

黏膜和神经元型5-HT对CMMC的正常启动、产生、有效传播及粪便颗粒推进是非常必需的。比如在出口梗阻引起的慢传输型便秘中, 由于前列腺素和环氧酶的上调^[5,17,54], 导致下行性抑制和黏膜5-HT的释放受到破坏, 结肠传输不能正常运行。肠肌间存在非常复杂、密集、庞大的神经网络, 具有许多突触连接及交互作用的兴奋性、抑制性神经通路。当黏膜刺激或纵向牵拉结肠时, ECC释放5-HT, 激活肠肌间和黏膜下IPANs, 兴奋神经通路中的多种神经元。尽管肠肌间5-HT神经元数目相对较少, 但其可与多种5-HT受体结合, 或与肠神经

系统、ICC网络形成广泛的突触连接, 在肠道动力方面可能发挥着核心作用, 参与结肠的紧张性抑制和CMMC的产生, 调节肠神经系统。

ICC通常在紧张性抑制状态下, 黏膜刺激后ICC可变为“肠道起搏器”, ICC-SM产生慢波, ICC-MY产生MPOs, 并传播至相邻的纵向肌、环形肌层。有趣的是, ICC的起搏活动并不通过ICC网络相互传播, 而在其他胃肠道区域传播。肠肌间神经网络中的兴奋性运动神经元激活后, ICC同步活化, 同时确保相邻的纵向肌、环形肌层同步收缩。因而CMMC的产生、传播依赖于肠肌间神经网络和ICC网络。

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■名词解释

肠道Cajal间质细胞(ICC): 位于消化管肌层的结缔组织中, 成多突起状, 核椭圆形, 胞质较少, 含较多线粒体。他可产生电信号, 通过缝隙连接传递给平滑肌细胞, 引起肌层的节律性收缩。ICC是一类独立的、特殊类型细胞, 为非神经元、间质起源。他可能是胃肠肌肉的起搏细胞, 可能是抑制性神经传递的介质。其发育异常可能是一些儿童胃肠道疾病如婴儿肥厚性幽门狭窄、先天性巨结肠及其同源病发病的重要因素。

■同行评价

作者对CMMC产生和传播机制进行了综述, 选题合理, 逻辑严谨, 语言流利, 具有一定的可读性.

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编辑: 郭鹏 电编: 闫晋利

