

肠神经系统对肠上皮屏障的影响及其在炎症性肠病发生发展中的作用

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Effect of enteric nervous system on intestinal epithelial barrier in inflammatory bowel disease

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Abstract

Both enteric nervous system and intestinal epithelial barrier are vital components to ensure gut homeostasis. Recent studies have shown the implications of their close relationship for gut health and disease. By secreting neurotransmitters, the enteric nervous system plays an important role in regulating the epithelial barrier function. Meanwhile, communicating largely through the vagal nerve, the central nervous system could also interact with the intestinal epithelium through the enteric nervous system. Although the etiology and pathogenesis of inflammatory bowel disease remain elusive, increasing evidence has shown that the dysregulation of enteric nervous system affects both epithelial integrity and barrier function, which contributes to the occurrence and development of inflammatory bowel disease. This review will summarize the current knowledge regarding the effect of enteric nervous system on intestinal epithelial barrier and its implication in the development of inflammatory bowel disease.

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Key Words: Enteric nervous system; Intestinal epithelial barrier; Inflammatory bowel disease; Enteric neurotransmitters; Enteric glial cells

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■背景资料

肠上皮屏障(intestinal epithelial barrier, IEB)主要由单层肠上皮细胞及其之间的细胞连接构成, 其功能缺陷主要由表现为IEB通透性增加以及肠上皮修复功能减弱. 肠神经系统(enteric nervous system, ENS)可通过多种途径加强或减弱IEB功能, 进而对炎症性肠病(inflammatory bowel disease, IBD)的发生与发展产生不同的影响.

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■ 研究前沿

探索不同神经递质或神经调节因子对IEB的影响及其在肠道疾病中的启示是本研究领域中的热点及重点。进一步揭示神经递质或神经调节因子的作用靶点及观察神经递质类药物对于IBD患者的治疗效果, 这是今后研究中亟待解决的问题。

摘要

肠神经系统(enteric nervous system, ENS)与肠上皮屏障(intestinal epithelial barrier, IEB)均是参与维持肠道“稳态”的重要组织结构。近年来, 越来越多的证据表明ENS与IEB之间具有密切的联系。肠神经元细胞、神经胶质细胞可通过分泌神经递质、神经调节因子等多种物质持续地、多维度地对肠黏膜上皮屏障的功能与状态产生影响。同时, 中枢神经系统也可通过迷走神经等间接的激活ENS, 进而与肠上皮产生联系。目前炎症性肠病(inflammatory bowel disease, IBD)的病因及发病机制尚不清楚, 但已有较多研究显示ENS对IEB的影响参与IBD的发生与发展。因此, 本文将以文献综述的形式就这一方面的研究进展进行简单阐述。

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关键词: 肠神经系统; 肠上皮屏障; 炎症性肠病; 肠神经递质; 肠神经胶质细胞

核心提要: 肠神经系统与肠上皮屏障均是参与维持肠道“稳态”的重要组织结构。近年来研究显示两者之间的紧密联系参与炎症性肠病(inflammatory bowel disease, IBD)的发生与发展。将目光聚焦于此有望进一步揭示IBD病因, 同时也为疾病治疗提供新的方向。

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0 引言

炎症性肠病(inflammatory bowel disease, IBD)包括溃疡性结肠炎(ulcerative colitis, UC)与克罗恩病(Crohn's disease, CD)。近年来, 随着经济的发展, 我国IBD的发病率不断增加, 已逐渐成为危害人们健康的常见病和难治性疾病。IBD病因复杂, 其确切发病机制仍不清楚, 但已有大量研究^[1]表明肠上皮屏障(intestinal epithelial barrier, IEB)功能缺陷是参与IBD发生发展的重要因素之一。另一方面, 随着研究的深入, 人们也开始逐渐认识到肠神经系统(enteric nervous system, ENS)在IBD发生发展中所起到的重要作用^[2-4]。同时, 越来越多的文献表明, ENS与IEB关系密切: 神经元细胞、神经胶质细胞及其他分泌

的神经调节因子均可对肠黏膜上皮屏障产生影响^[5]。目前甚至有文献提出“神经-胶质细胞-上皮单位”的概念来凸显ENS与IEB的密切联系^[6]。因此, 本文现就ENS对肠黏膜上皮屏障的影响及其在IBD发生发展中作用作一综述。

1 IEB

IEB功能缺陷是IBD发生发展中的重要因素, 同时也是IBD的主要疾病特征^[7,8]。其功能缺陷主要由于多种原因造成的IEB通透性(包括细胞旁通透性及跨细胞通透性)增加以及肠上皮修复功能减弱^[9]。上皮屏障功能缺陷易产生“肠漏症”, 使得大量细菌及食物抗原进入结肠组织, 产生过度的免疫反应, 促进IBD的发生与发展^[1,9]。

IEB主要由单层肠上皮细胞及其之间的细胞连接构成。正常情况下该屏障具有高度的选择通透性: 在允许营养物质通过的同时限制肠腔内的细菌或大分子向黏膜固有层的过度渗入^[10]。构成IEB的细胞间连接主要分为3类, 即黏着连接(adherent junction, AJ)、桥粒及紧密连接(tight junction, TJ)。AJ及桥粒依靠其强力的黏附力为上皮屏障提供了足够的机械强度, 而存在于肠上皮细胞顶端的TJ则通过形成顶端闭锁结构而主要发挥封闭相邻细胞间隙及调节细胞旁通透性的作用^[11]。TJ由多种跨膜蛋白组成, 如封闭蛋白、闭合蛋白、紧密连接蛋白(zonula occludens, ZO)及连接黏附分子等。这些蛋白相互连接, 同时通过ZO蛋白与肌动蛋白骨架系统相连, 进而形成稳定的连接系统^[12]。正常情况下, 细胞连接中的各种结构蛋白总是处于动态的循环与精密的调控之中。但当上述机能出现功能障碍时, 则有可能导致上皮屏障功能障碍及IBD的发生^[10]。来自基因组学的研究也证实了细胞间连接相关蛋白基因多态性与IBD的发生发展密切相关^[13,14]。

另一方面, 肠道上皮细胞的凋亡、增殖与更新也与IEB的功能状态密切相关。肠上皮细胞起源于肠黏膜隐窝基底部中的干细胞, 正常情况下每3-5 d更新1次。如果肠上皮细胞的生理性增殖或凋亡发生改变亦可导致IEB功能受损, 进而促进IBD的发生与发展^[15]。

2 ENS

ENS是外周最大、最复杂的自主神经系统, 包含交感、副交感神经及非肾上腺素非胆碱能

神经,能独立于中枢神经系统(central nervous system, CNS)对胃肠功能进行调控^[5]。同时ENS也包含了迷走神经、脊神经等CNS传入神经,成为“脑-肠轴”中重要的中继站^[5,16],因此CNS亦可通过影响ENS的活动而调节胃肠功能。在微观上,ENS主要由肠神经元细胞及肠神经胶质细胞(enteric glial cell, EGC)组成。肠神经元通过神经轴突相互连接形成网络,并由神经胶质细胞支持着,在肠道内形成了以黏膜下丛及肠肌丛为代表的神经网络^[4]。近年来,通过神经逆行示踪染色等技术显示ENS于肠黏膜层亦广泛分布并相互连接呈网状结构^[17,18],构成所谓的“黏膜丛”。该处的神经元细胞与神经胶质细胞可通过细胞凸起或通过分泌神经递质与肠免疫细胞或肠上皮细胞进行密切的接触,进而参与维持并调控IEB功能^[5,19]。

近年来,人们开始逐渐认识到ENS在参与调节与维持IEB中所起到的重要作用以及这种作用在胃肠道疾病(如IBD)发生发展中的启示^[5]。在肠道炎症中,研究提示ENS可通过多种直接或间接途径影响IEB通透性和/或IEB修复功能,加强或减弱IEB功能,进而对IBD的发生与发展产生不同的影响。

3 ENS对IEB的影响及其在IBD的发生发展中的作用

3.1 肠神经元细胞 肠神经元细胞主要通过分泌神经递质对IEB功能产生影响。ENS可分泌30多种神经递质并且多数肠神经元均具有表达多种神经递质的能力^[20]。研究^[6]显示不同的神经递质对上皮屏障的通透性具有不同的影响,同时部分神经递质还参与调节肠上皮细胞的增殖与创伤修复。目前研究较为集中的神经递质主要为乙酰胆碱(acetylcholine, ACh)与血管活性肠肽(vasoactive intestinal peptide, VIP)。

3.1.1 ACh: ACh是典型能增加肠上皮细胞旁及跨细胞通透性的神经递质。Cameron等^[21]使用河豚毒素阻断肠神经元或使用阿托品阻断胆碱能神经元均可显著降低IEB的通透性,而胆碱能受体激动剂(乌拉胆碱)可显著增加IEB大分子的通透性及肠上皮细胞中核内体的面积(跨细胞通透性检测指标)。同时,乌拉胆碱增强IEB通透性的效应可被阿托品阻断却无法被河豚毒素阻断,意味着胆碱能受体位于肠黏膜上皮细胞或其他相关细胞之上而非ENS之

上。ENS可通过持续性分泌神经递质(如ACh)来调节IEB的通透性。在疾病状况下,Gareau等^[22]的研究显示应激刺激造成的IEB通透性增高可能与结肠组织中胆碱乙酰转移酶(choline acetyltransferase, ChAT)的表达增加有关。ChAT是合成ACh的关键限速酶,应激可能导致肠道胆碱能神经过度激活从而增强IEB的通透性,而胆碱及烟碱受体拮抗剂可阻断上述过程。结肠炎症中也显示出类似的过程,Saijo等^[23]使用胆碱受体拮抗剂(丁基东莨菪碱)抑制ENS活动可抑制葡聚糖硫酸钠诱导结肠炎的肠上皮损伤,进而抑制结肠炎的进展。另外,ACh还可通过影响免疫细胞而对IEB通透性产生影响。Wallon等^[24]的研究显示UC患者IEB通透性增高与胆碱能神经系统激活嗜酸性粒细胞与肥大细胞相关,同样,阿托品可逆转上述过程。

3.1.2 VIP: 在ENS中,VIP是一种重要的促分泌性神经递质。VIP神经元主要分布于黏膜下丛,其神经突起向黏膜及上皮广泛投射^[25,26]。同时,肠上皮细胞亦广泛表达VIP受体-VPAC1^[27]。随着研究的深入,目前已发现VIP是参与调节IEB通透性的主要神经递质之一。Neunlist等^[25]的研究显示电场刺激黏膜下层组织中的神经元可使共培养的结肠上皮通透性下降,同时显著上调TJ相关蛋白(ZO-1蛋白)的表达。而河豚毒素或VIP受体阻滞剂可阻断上述效果。另外,在使用河豚毒素阻断肠神经元的情况下,单独给予结肠上皮VIP却可复现上述电场刺激所产生的现象。在结肠炎症中,Conlin等^[28]的研究显示VIP能明显改善柠檬酸杆菌引起的结肠上皮损伤及上皮通透性的增高,而这一效应与VIP能减少TJ相关蛋白(ZO-1蛋白、闭合蛋白以及封闭蛋白-3)的重分布有关。同样,VIP亦能通过免疫调节作用间接的对IEB产生保护作用^[29]。

另外,VIP还参与调节肠上皮细胞的增殖而影响上皮屏障功能。Toumi等^[30]的研究显示电刺激肠神经元可通过释放VIP来抑制人结肠上皮细胞的增殖。在VIP敲除小鼠中可发现结肠隐窝结构的异常、结肠上皮增殖与迁移的异常以及上皮细胞凋亡增加,同时伴随结肠通透性的改变。与野生型小鼠相比,使用二硝基苯磺酸(dinitrobenzenesulfonate, DNBS)或硫酸葡聚糖(dextran sulfate, DSS)可在VIP敲除小鼠中诱导出更为严重的肠道炎症^[31]。

3.2 EGC 作为ENS重要的组成部分,EGC的数

□ 相关报道
ENS对IEB功能状态的影响主要是由可溶性的神经递质或神经调节因子介导的。同时,这些递质或因子还参与调节肠免疫系统功能。因此,深入了解ENS、肠黏膜上皮屏障与肠免疫系统这三者之间的联系对于揭示IBD的病因有重大意义。

创新盘点

以往有关IBD发病机制的研究多集中在遗传、环境、感染和免疫方面, 而ENS异常在IBD发生发展中的作用却较为忽视. 本文关注于ENS对IEB的影响及其在IBD发病机制中的启示作用, 有助于进一步揭示IBD的病因.

量近4倍于肠神经元. 长久以来, EGC仅被认为对肠道神经元起保护及支持作用. 直到近年来随着选择性EGC剥离动物模型的进展, 我们才开始认识到EGC在维持IEB功能中所起到的重要作用^[32]. Savidge等^[33]采用基因敲除方法选择性地去除小鼠EGC造成了严重的IEB功能障碍, 使上皮通透性的增加、修复能力减弱, 最终导致小鼠肠道炎症、出血及坏死, 出现与人类IBD极为相似的临床和病理改变. 在细胞试验中, EGC表现出与星形胶质细胞在维持血脑屏障中相似的特性, 能降低与之共培养的肠上皮细胞层的细胞间通透性并显著增强ZO-1蛋白及闭合蛋白的表达. 进一步研究表明S-亚硝基谷胱甘肽(S-nitrosoglutathione, GSNO)是介导EGC上述能力的关键物质: 在剥离EGC的小鼠中注射GSNO可预防上皮损伤甚至阻断因剥离EGC而引起的结肠炎. 另外, GSNO可降低CD患者肠上皮组织的通透性但对健康患者无效, 提示EGC源性GSNO功能缺陷可能参与了CD的发生与发展^[33].

随着研究的进展, 研究者们还发现了其他与EGC有关的调节因子. 肠黏膜胶质细胞源性神经营养因子(glial-derived neurotrophic factor, GDNF)主要来源于EGC, 在炎症环境如大鼠结肠炎模型及人类IBD肠段中GDNF的含量明显增高^[34]. 在DSS结肠炎中, GDNF可上调小鼠结肠上皮TJ蛋白ZO-1的表达, 降低上皮的通透性并缓解结肠炎症^[35]. 另外, EGC可通过表达15-脂氧化酶-2而产生高水平的15-羟基二十碳四烯酸(15-hydroxyeico satetraenoic acid, 15-HETE), 后者可抑制AMP活化蛋白激酶(PRKAA1/AMPK)并上调ZO-1蛋白的表达, 进而降低肠上皮的通透性. 人体试验^[36]亦显示CD患者EGC较正常人群产生15-HETE的能力明显下降.

同时, EGC还参与调控肠上皮细胞的增殖与黏膜创伤的修复. EGC的缺失将导致肠黏膜修复能力减弱, 从而使DSS诱导的结肠炎更为严重^[19]. 体外研究^[19]显示EGC可促进黏膜损伤部位肠上皮细胞的扩散与上皮重建. 而上述现象与EGC释放proEGF及激活上皮黏着斑激酶信号通路相关. 对肠上皮细胞, EGC还具有明显的抗增殖效应^[37].

3.3 迷走神经 作为脑-肠轴的重要组成部分, 迷

走神经使得CNS可以参与并调控ENS, 并进一步影响整体胃肠功能^[4,38]. 近年来许多研究者^[39]观察到迷走神经具有“抗炎”的能力. 激活迷走神经可以抑制系统性炎症, 减少炎症因子的释放, 进而缓解肠道炎症, 恢复肠道稳态^[40]. 而这一能力与迷走神经促进ACh的分泌并抑制免疫细胞分泌炎症因子有关^[41]. 值得注意的是, 完整的上皮屏障对缓解肠道炎症、维持肠道稳态亦有重要的作用. 当研究者们将目光转向迷走神经与上皮屏障之间的联系时, 发现迷走神经亦可对IEB的功能产生明显的影响. 直接刺激迷走神经可缓解多种疾病模型(败血症休克、结肠炎、烧伤)所造成的IEB屏障损伤, 并可稳定ZO-1蛋白及闭合蛋白的分布与表达^[42-44]. 反之, 迷走神经切除术可加重DSS及DNBS诱导的结肠炎^[45]. 在烧伤与结肠炎动物模型中, 尼古丁(胆碱及烟碱受体激动剂)可模拟刺激迷走神经所产生的效果^[45,46]. 遗憾的是, 目前刺激迷走神经所产生的IEB保护作用其中的具体机制: 是与上皮细胞的直接相互作用还是通过抗炎效应来间接产生目前还并不清楚. 迷走神经活动释放的主要神经递质为ACh, 但迷走神经向节后肠神经元投射, 而这些肠神经元主要表达VIP^[47]. 使用抗VIP血清也可以阻断一些迷走神经兴奋所产生的效应^[48].

另一方面, EGC表达胆碱能等多种神经递质受体^[49], 可接受来自迷走神经及ENS的信息. 刺激迷走神经(同时也间接兴奋ENS)可激活EGC, 使EGC特异的标记蛋白-胶质纤维酸性蛋白表达增加^[50]. 提示EGC可能参与迷走神经调节上皮屏障功能. 进一步的研究^[50,51]显示激活后的EGC可通过分泌GSNO、NO等因子调节上皮屏障通透性.

4 结论

目前, 越来越多的证据表明ENS与IEB之间具有密切的联系. 肠神经元细胞、神经胶质细胞可通过分泌神经递质、神经调节因子等多种物质持续地、多维度的对肠黏膜上皮屏障产生影响. CNS也可通过迷走神经等间接的激活ENS. IBD的发生机制目前还并不清楚, 但肠黏膜屏障的缺损却在其发生发展中具有关键作用. 将目光聚焦在ENS与IEB之间的联系有望进一步揭示IBD发生发展的原因, 同时也为治

疗IBD提供了新的方向.

5 参考文献

- 1 Abraham C, Cho JH. Inflammatory bowel disease. *N Engl J Med* 2009; 361: 2066-2078 [PMID: 19923578 DOI: 10.1056/NEJMra0804647]
- 2 Di Giovangiulio M, Verheijden S, Bosmans G, Stakenborg N, Boeckxstaens GE, Matteoli G. The Neuromodulation of the Intestinal Immune System and Its Relevance in Inflammatory Bowel Disease. *Front Immunol* 2015; 6: 590 [PMID: 26635804 DOI: 10.3389/fimmu.2015.00590]
- 3 Ochoa-Cortes F, Turco F, Linan-Rico A, Soghomonyan S, Whitaker E, Wehner S, Cuomo R, Christofi FL. Enteric Glial Cells: A New Frontier in Neurogastroenterology and Clinical Target for Inflammatory Bowel Diseases. *Inflamm Bowel Dis* 2016; 22: 433-449 [PMID: 26689598 DOI: 10.1097/mib.0000000000000667]
- 4 Taylor CT, Keely SJ. The autonomic nervous system and inflammatory bowel disease. *Auton Neurosci* 2007; 133: 104-114 [PMID: 17234460 DOI: 10.1016/j.autneu.2006.11.005]
- 5 Snoek SA, Verstege MI, Boeckxstaens GE, van den Wijngaard RM, de Jonge WJ. The enteric nervous system as a regulator of intestinal epithelial barrier function in health and disease. *Expert Rev Gastroenterol Hepatol* 2010; 4: 637-651 [PMID: 20932148 DOI: 10.1586/egh.10.51]
- 6 Neunlist M, Van Landeghem L, Mahé MM, Derkinderen P, des Varannes SB, Rolli-Derkinderen M. The digestive neuronal-glial-epithelial unit: a new actor in gut health and disease. *Nat Rev Gastroenterol Hepatol* 2013; 10: 90-100 [PMID: 23165236 DOI: 10.1038/nrgastro.2012.221]
- 7 Bjarnason I, MacPherson A, Hollander D. Intestinal permeability: an overview. *Gastroenterology* 1995; 108: 1566-1581 [PMID: 7729650 DOI: 10.1016/0016-5085(95)90708-4]
- 8 Antoni L, Nuding S, Wehkamp J, Stange EF. Intestinal barrier in inflammatory bowel disease. *World J Gastroenterol* 2014; 20: 1165-1179 [PMID: 24574793 DOI: 10.3748/wjg.v20.i5.1165]
- 9 Sánchez de Medina F, Romero-Calvo I, Mascaraque C, Martínez-Augustín O. Intestinal inflammation and mucosal barrier function. *Inflamm Bowel Dis* 2014; 20: 2394-2404 [PMID: 25222662 DOI: 10.1097/mib.0000000000000204]
- 10 Groschwitz KR, Hogan SP. Intestinal barrier function: molecular regulation and disease pathogenesis. *J Allergy Clin Immunol* 2009; 124: 3-20; quiz 21-22 [PMID: 19560575 DOI: 10.1016/j.jaci.2009.05.038]
- 11 Turner JR. Intestinal mucosal barrier function in health and disease. *Nat Rev Immunol* 2009; 9: 799-809 [PMID: 19855405 DOI: 10.1038/nri2653]
- 12 Fanning AS, Jameson BJ, Jesaitis LA, Anderson JM. The tight junction protein ZO-1 establishes a link between the transmembrane protein occludin and the actin cytoskeleton. *J Biol Chem* 1998; 273: 29745-29753 [PMID: 9792688 DOI: 10.1074/jbc.273.45.29745]
- 13 Wapenaar MC, Monsuur AJ, van Bodegraven AA, Weersma RK, Bevoa MR, Linskens RK, Howdle P, Holmes G, Mulder CJ, Dijkstra G, van Heel DA, Wijmenga C. Associations with tight junction genes PARD3 and MAGI2 in Dutch patients point to a common barrier defect for coeliac disease and ulcerative colitis. *Gut* 2008; 57: 463-467 [PMID: 17989107 DOI: 10.1136/gut.2007.133132]
- 14 Barrett JC, Lee JC, Lees CW, Prescott NJ, Anderson CA, Phillips A, Wesley E, Parnell K, Zhang H, Drummond H, Nimmo ER, Massey D, Blaszczyk K, Elliott T, Cotterill L, Dallal H, Lobo AJ, Mowat C, Sanderson JD, Jewell DP, Newman WG, Edwards C, Ahmad T, Mansfield JC, Satsangi J, Parkes M, Mathew CG, Donnelly P, Peltonen L, Blackwell JM, Bramer E, Brown MA, Casas JP, Corvin A, Craddock N, Deloukas P, Duncanson A, Jankowski J, Markus HS, Mathew CG, McCarthy MI, Palmer CN, Plomin R, Rautanen A, Sawcer SJ, Samani N, Trembath RC, Viswanathan AC, Wood N, Spencer CC, Barrett JC, Bellenguez C, Davison D, Freeman C, Strange A, Donnelly P, Langford C, Hunt SE, Edkins S, Gwilliam R, Blackburn H, Bumpstead SJ, Dronov S, Gillman M, Gray E, Hammond N, Jayakumar A, McCann OT, Liddle J, Perez ML, Potter SC, Ravindrarajah R, Ricketts M, Waller M, Weston P, Widaa S, Whittaker P, Deloukas P, Peltonen L, Mathew CG, Blackwell JM, Brown MA, Corvin A, McCarthy MI, Spencer CC, Attwood AP, Stephens J, Sambrook J, Ouwehand WH, McArdle WL, Ring SM, Strachan DP. Genome-wide association study of ulcerative colitis identifies three new susceptibility loci, including the HNF4A region. *Nat Genet* 2009; 41: 1330-1334 [PMID: 19915572 DOI: 10.1038/ng.483]
- 15 Okamoto R, Watanabe M. Cellular and molecular mechanisms of the epithelial repair in IBD. *Dig Dis Sci* 2005; 50 Suppl 1: S34-S38 [PMID: 16184419 DOI: 10.1007/s10620-005-2804-5]
- 16 Sharkey KA, Savidge TC. Role of enteric neurotransmission in host defense and protection of the gastrointestinal tract. *Auton Neurosci* 2014; 181: 94-106 [PMID: 24412639 DOI: 10.1016/j.autneu.2013.12.006]
- 17 Timmermans JP, Adriaensen D, Cornelissen W, Scheuermann DW. Structural organization and neuropeptide distribution in the mammalian enteric nervous system, with special attention to those components involved in mucosal reflexes. *Comp Biochem Physiol A Physiol* 1997; 118: 331-340 [PMID: 9366065]
- 18 Song ZM, Brookes SJ, Llewellyn-Smith IJ, Costa M. Ultrastructural studies of the myenteric plexus and smooth muscle in organotypic cultures of the guinea-pig small intestine. *Cell Tissue Res* 1995; 280: 627-637 [PMID: 7606771 DOI: 10.1007/BF00318365]
- 19 Van Landeghem L, Chevalier J, Mahé MM, Wedel T, Urvil P, Derkinderen P, Savidge T, Neunlist M. Enteric glia promote intestinal mucosal healing via activation of focal adhesion kinase and release of proEGF. *Am J Physiol Gastrointest Liver Physiol* 2011; 300: G976-G987 [PMID: 21350188 DOI: 10.1152/ajpgi.00427.2010]
- 20 Furness JB. Types of neurons in the enteric nervous system. *J Auton Nerv Syst* 2000; 81: 87-96 [PMID: 10869706 DOI: 10.1016/S0165-1838(00)00127-2]
- 21 Cameron HL, Perdue MH. Muscarinic

应用要点

更深入的了解ENS对IEB的联系有助于进一步揭示IBD的病因,特别是精神心理因素对病程影响的原因.同时也为治疗提供了新的方向、给予神经递质类药物有助于恢复ENS功能进而改善IEB功能紊乱,缓解结肠炎症,预防疾病复发.

■ 名词解释

肠神经系统 (ENS): 是外周最大、最复杂的自主神经系统, 包含交感、副交感神经及非肾上腺素非胆碱能神经。在微观上, ENS主要由肠神经元细胞及肠神经胶质细胞组成, 细胞相互连接在肠道内形成了以黏膜下丛及肠肌丛为代表的神经网络。

- acetylcholine receptor activation increases transcellular transport of macromolecules across mouse and human intestinal epithelium in vitro. *Neurogastroenterol Motil* 2007; 19: 47-56 [PMID: 17187588 DOI: 10.1111/j.1365-2982.2006.00845.x]
- 22 Gareau MG, Jury J, Perdue MH. Neonatal maternal separation of rat pups results in abnormal cholinergic regulation of epithelial permeability. *Am J Physiol Gastrointest Liver Physiol* 2007; 293: G198-G203 [PMID: 17510196 DOI: 10.1152/ajpgi.00392.2006]
- 23 Saijo H, Tatsumi N, Arihiro S, Kato T, Okabe M, Tajiri H, Hashimoto H. Microangiopathy triggers, and inducible nitric oxide synthase exacerbates dextran sulfate sodium-induced colitis. *Lab Invest* 2015; 95: 728-748 [PMID: 25938626 DOI: 10.1038/labinvest.2015.60]
- 24 Wallon C, Persborn M, Jönsson M, Wang A, Phan V, Lampinen M, Vicario M, Santos J, Sherman PM, Carlson M, Ericson AC, McKay DM, Söderholm JD. Eosinophils express muscarinic receptors and corticotropin-releasing factor to disrupt the mucosal barrier in ulcerative colitis. *Gastroenterology* 2011; 140: 1597-1607 [PMID: 21277851 DOI: 10.1053/j.gastro.2011.01.042]
- 25 Neunlist M, Toumi F, Oreschkova T, Denis M, Leborgne J, Laboisse CL, Galmiche JP, Jarry A. Human ENS regulates the intestinal epithelial barrier permeability and a tight junction-associated protein ZO-1 via VIPergic pathways. *Am J Physiol Gastrointest Liver Physiol* 2003; 285: G1028-G1036 [PMID: 12881224 DOI: 10.1152/ajpgi.00066.2003]
- 26 Cooke HJ. Neurotransmitters in neuronal reflexes regulating intestinal secretion. *Ann N Y Acad Sci* 2000; 915: 77-80 [PMID: 11193603 DOI: 10.1111/j.1749-6632.2000.tb05225.x]
- 27 Banks MR, Farthing MJ, Robberecht P, Burleigh DE. Antisecretory actions of a novel vasoactive intestinal polypeptide (VIP) antagonist in human and rat small intestine. *Br J Pharmacol* 2005; 144: 994-1001 [PMID: 15711593 DOI: 10.1038/sj.bjp.0706128]
- 28 Conlin VS, Wu X, Nguyen C, Dai C, Vallance BA, Buchan AM, Boyer L, Jacobson K. Vasoactive intestinal peptide ameliorates intestinal barrier disruption associated with *Citrobacter rodentium*-induced colitis. *Am J Physiol Gastrointest Liver Physiol* 2009; 297: G735-G750 [PMID: 19661153 DOI: 10.1152/ajpgi.90551.2008]
- 29 Chandrasekharan B, Nezami BG, Srinivasan S. Emerging neuropeptide targets in inflammation: NPY and VIP. *Am J Physiol Gastrointest Liver Physiol* 2013; 304: G949-G957 [PMID: 23538492 DOI: 10.1152/ajpgi.00493.2012]
- 30 Toumi F, Neunlist M, Cassagnau E, Parois S, Laboisse CL, Galmiche JP, Jarry A. Human submucosal neurones regulate intestinal epithelial cell proliferation: evidence from a novel co-culture model. *Neurogastroenterol Motil* 2003; 15: 239-242 [PMID: 12787332 DOI: 10.1046/j.1365-2982.2003.00409.x]
- 31 Wu X, Conlin VS, Morampudi V, Ryz NR, Nasser Y, Bhinder G, Bergstrom KS, Yu HB, Waterhouse CC, Buchan AM, Popescu OE, Gibson WT, Waschek JA, Vallance BA, Jacobson K. Vasoactive intestinal polypeptide promotes intestinal barrier homeostasis and protection against colitis in mice. *PLoS One* 2015; 10: e0125225 [PMID: 25932952 DOI: 10.1371/journal.pone.0125225]
- 32 Neunlist M, Rolli-Derkinderen M, Latorre R, Van Landeghem L, Coron E, Derkinderen P, De Giorgio R. Enteric glial cells: recent developments and future directions. *Gastroenterology* 2014; 147: 1230-1237 [PMID: 25305504 DOI: 10.1053/j.gastro.2014.09.040]
- 33 Savidge TC, Newman P, Pothoulakis C, Ruhl A, Neunlist M, Bourreille A, Hurst R, Sofroniew MV. Enteric glia regulate intestinal barrier function and inflammation via release of S-nitrosoglutathione. *Gastroenterology* 2007; 132: 1344-1358 [PMID: 17408650 DOI: 10.1053/j.gastro.2007.01.051]
- 34 Steinkamp M, Geerling I, Seufferlein T, von Boyen G, Egger B, Grossmann J, Ludwig L, Adler G, Reinshagen M. Glial-derived neurotrophic factor regulates apoptosis in colonic epithelial cells. *Gastroenterology* 2003; 124: 1748-1757 [PMID: 12806607 DOI: 10.1016/S0016-5085(03)00404-9]
- 35 Zhang DK, He FQ, Li TK, Pang XH, Cui DJ, Xie Q, Huang XL, Gan HT. Glial-derived neurotrophic factor regulates intestinal epithelial barrier function and inflammation and is therapeutic for murine colitis. *J Pathol* 2010; 222: 213-222 [PMID: 20632386 DOI: 10.1002/path.2749]
- 36 Pochard C, Coquenlorge S, Jaulin J, Cenac N, Vergnolle N, Meurette G, Freyssinet M, Neunlist M, Rolli-Derkinderen M. Defects in 15-HETE Production and Control of Epithelial Permeability by Human Enteric Glial Cells From Patients With Crohn's Disease. *Gastroenterology* 2016; 150: 168-180 [PMID: 26433161 DOI: 10.1053/j.gastro.2015.09.038]
- 37 Neunlist M, Aubert P, Bonnaud S, Van Landeghem L, Coron E, Wedel T, Naveilhan P, Ruhl A, Lardeux B, Savidge T, Paris F, Galmiche JP. Enteric glia inhibit intestinal epithelial cell proliferation partly through a TGF-beta1-dependent pathway. *Am J Physiol Gastrointest Liver Physiol* 2007; 292: G231-G241 [PMID: 16423922 DOI: 10.1152/ajpgi.00276.2005]
- 38 Bonaz BL, Bernstein CN. Brain-gut interactions in inflammatory bowel disease. *Gastroenterology* 2013; 144: 36-49 [PMID: 23063970 DOI: 10.1053/j.gastro.2012.10.003]
- 39 Van Der Zanden EP, Boeckxstaens GE, de Jonge WJ. The vagus nerve as a modulator of intestinal inflammation. *Neurogastroenterol Motil* 2009; 21: 6-17 [PMID: 19140954 DOI: 10.1111/j.1365-2982.2008.01252.x]
- 40 Borovikova LV, Ivanova S, Zhang M, Yang H, Botchkina GI, Watkins LR, Wang H, Abumrad N, Eaton JW, Tracey KJ. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. *Nature* 2000; 405: 458-462 [PMID: 10839541 DOI: 10.1038/35013070]
- 41 Miceli PC, Jacobson K. Cholinergic pathways modulate experimental dinitrobenzene sulfonic acid colitis in rats. *Auton Neurosci* 2003; 105: 16-24 [PMID: 12742187 DOI: 10.1016/s1566-0702(03)00023-7]
- 42 Luyer MD, Greve JW, Hadfoune M, Jacobs JA, Dejong CH, Buurman WA. Nutritional stimulation of cholecystokinin receptors inhibits

- inflammation via the vagus nerve. *J Exp Med* 2005; 202: 1023-1029 [PMID: 16216887 DOI: 10.1084/jem.20042397]
- 43 Krzyzaniak M, Peterson C, Loomis W, Hageny AM, Wolf P, Reys L, Putnam J, Eliceiri B, Baird A, Bansal Vw, Coimbra R. Postinjury vagal nerve stimulation protects against intestinal epithelial barrier breakdown. *J Trauma* 2011; 70: 1168-1175; discussion 1175-1176 [PMID: 21610431 DOI: 10.1097/TA.0b013e318216f754]
 - 44 Ghia JE, Blennerhassett P, El-Sharkawy RT, Collins SM. The protective effect of the vagus nerve in a murine model of chronic relapsing colitis. *Am J Physiol Gastrointest Liver Physiol* 2007; 293: G711-G718 [PMID: 17673544 DOI: 10.1152/ajpgi.00240.2007]
 - 45 Ghia JE, Blennerhassett P, Kumar-Ondiveeran H, Verdu EF, Collins SM. The vagus nerve: a tonic inhibitory influence associated with inflammatory bowel disease in a murine model. *Gastroenterology* 2006; 131: 1122-1130 [PMID: 17030182 DOI: 10.1053/j.gastro.2006.08.016]
 - 46 Costantini TW, Krzyzaniak M, Cheadle GA, Putnam JG, Hageny AM, Lopez N, Eliceiri BP, Bansal V, Coimbra R. Targeting α -7 nicotinic acetylcholine receptor in the enteric nervous system: a cholinergic agonist prevents gut barrier failure after severe burn injury. *Am J Pathol* 2012; 181: 478-486 [PMID: 22688057 DOI: 10.1016/j.ajpath.2012.04.005]
 - 47 Yuan PQ, Kimura H, Million M, Bellier JP, Wang L, Ohning GV, Taché Y. Central vagal stimulation activates enteric cholinergic neurons in the stomach and VIP neurons in the duodenum in conscious rats. *Peptides* 2005; 26: 653-664 [PMID: 15752581 DOI: 10.1016/j.peptides.2004.11.015]
 - 48 Dahlstrand C, Theodorsson E, Dahlström A, Ahlman H. VIP antisera inhibit the relaxatory motor responses of the feline sphincter of Oddi and gall-bladder induced by VIP or vagal nerve stimulation. *Acta Physiol Scand* 1989; 137: 375-378 [PMID: 2596332 DOI: 10.1111/j.1748-1716.1989.tb08766.x]
 - 49 Cheadle GA, Costantini TW, Bansal V, Eliceiri BP, Coimbra R. Cholinergic signaling in the gut: a novel mechanism of barrier protection through activation of enteric glia cells. *Surg Infect (Larchmt)* 2014; 15: 387-393 [PMID: 24828283 DOI: 10.1089/sur.2013.103]
 - 50 Costantini TW, Bansal V, Krzyzaniak M, Putnam JG, Peterson CY, Loomis WH, Wolf P, Baird A, Eliceiri BP, Coimbra R. Vagal nerve stimulation protects against burn-induced intestinal injury through activation of enteric glia cells. *Am J Physiol Gastrointest Liver Physiol* 2010; 299: G1308-G1318 [PMID: 20705905 DOI: 10.1152/ajpgi.00156.2010]
 - 51 MacEachern SJ, Patel BA, McKay DM, Sharkey KA. Nitric oxide regulation of colonic epithelial ion transport: a novel role for enteric glia in the myenteric plexus. *J Physiol* 2011; 589: 3333-3348 [PMID: 21558161 DOI: 10.1113/jphysiol.2011.207902]

□ 同行评价
本文综述全面, 条理清楚, 科学结论较明确, 提出将目光聚焦在ENS与上皮屏障之间的联系有望进一步揭示IBD发生发展的原因, 同时也为治疗IBD提供了新的方向。

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