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述评 EDITORIAL

胆碱能抗炎通路与胃肠病的研究进展

任玉萍, 熊 艳, 刘小彭, 白爱平

背景资料
胆碱能抗炎通路可以通过刺激迷走神经释放乙酰胆碱(acetylcholine, ACh)与相应受体结合, 抑制炎症反应. 目前, 炎症和炎症相关性疾病是当今医学的挑战, 患者花费较高且预后效果较差, 利用胆碱能抗炎通路治疗此类疾病可能为患者开辟一条新的途径.

任玉萍, 熊艳, 白爱平, 南昌大学第一附属医院消化内科 江西省南昌市 330006
刘小彭, 中山大学第三附属医院泌尿外科 广东省广州市 510630
白爱平, 副教授, 主要从事消化系免疫与炎症方面研究.
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作者贡献分布: 本文由任玉萍、熊艳及刘小彭完成; 白爱平审校.
通讯作者: 白爱平, 副教授, 330006, 江西省南昌市永外正街17号, 南昌大学第一附属医院消化内科. baiap@163.com
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Cholinergic anti-inflammatory pathway and gastrointestinal diseases

Yu-Ping Ren, Yan Xiong, Xiao-Peng Liu, Ai-Ping Bai

Yu-Ping Ren, Yan Xiong, Ai-Ping Bai, Department of Gastroenterology, the First Affiliated Hospital of Nanchang University, Nanchang 330006, Jiangxi Province, China
Xiao-Peng Liu, Department of Urology, the Third Affiliated Hospital of Sun Yat-sen University, Guangzhou 510630, Guangdong Province, China
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Correspondence to: Ai-Ping Bai, Associate Professor, Department of Gastroenterology, the First Affiliated Hospital, Nanchang University, 17 Yongwaizheng Street, Nanchang 330006, Jiangxi Province, China. baiap@163.com
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Abstract
Upon stimulation, vagus nerves release acetylcholine in local tissues, which can regulate immune cell function and inflammatory responses, operationally through alpha 7 nicotinic acetylcholine receptor. This process is termed cholinergic anti-inflammatory pathway (CAP). It has been shown that CAP exhibits physical functions, and also contributes to the progression of a variety of gastrointestinal diseases, such as inflammatory bowel disease, esophagitis, allergic intestine inflammation, peptic ulcer, colitis, and hepatitis. This review discusses the physical function of CAP, as well as its pivotal role in the development of gastrointestinal diseases.

Key Words: Cholinergic anti-inflammatory pathway; Vagus nerve; Acetylcholine; Gastrointestinal diseases

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摘要
胆碱能抗炎通路(cholinergic anti-inflammatory pathway, CAP)是一种神经-免疫调节通路, 即在免疫信号刺激下, 传出迷走神经释放乙酰胆碱, 通过与α7烟碱型乙酰胆碱受体结合, 调节免疫细胞功能并抑制机体炎症反应. 研究证实胆碱能抗炎通路具有强大的生理功能, 并且与许多胃肠道疾病如炎症性肠病、食管炎、过敏性肠炎、消化性溃疡、结肠炎、肝炎等的进展密切相关, 本文着重介绍胆碱能抗炎通路的生理功能及其对胃肠病的干预价值.

同行评议者
姜相君, 主任医师, 青岛市市立医院消化科

关键词: 胆碱能抗炎通路; 迷走神经; 乙酰胆碱; 胃肠病

核心提示: 胆碱能抗炎通路是一种神经-免疫调节通路, 即在免疫信号刺激下, 传出迷走神经可以释放乙酰胆碱, 通过与α7烟碱型乙酰胆碱受体结合, 调节免疫细胞功能、抑制机体炎症反应.

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0 引言

正常情况下, 胃肠道通过神经体液调节及自身器官功能的正常运行来行使其摄取、转运、消化、吸收和排泄等重大生理功能. 一旦这种稳态被破坏, 胃肠道就会出现一系列疾病[1]. 过去的研究较多关注体液因素对胃肠病的影响, 近年来神经系统的免疫调节逐渐成为研究热点. 其中迷走神经及其递质乙酰胆碱(acetylcholine, ACh)所构成的胆碱能抗炎通路在改善胃肠道疾病方面具有重要作用[2,3], 受到医学界广泛重视. 故本文对胆碱能抗炎通路的神经生理机制及其在胃肠病中的治疗作用作一综述.

1 胆碱能抗炎通路

2000年, Borovikova等[4]提出“胆碱能抗炎通路”的概念, 为解开神经抗炎提供了新的思路. 其机制为大脑识别传入迷走神经传来的信号, 刺激迷走神经末梢释放ACh , 与巨噬细胞和其他细胞上表达的α7烟碱型ACh受体(α7 nicotinic acetylcholine receptors, α7nAChR)结合, 作用于下游JAK2/STAT3、MAPK/NF-κB等信号通路, 抑制肿瘤坏死因子(tumor necrosis factor, TNF)、白介素-1(interleukin-1, IL-1)、IL-6等炎症细胞因子, 从而发挥抗炎作用[5,6].

1.1 迷走神经 迷走神经属于自主神经系统, 其节前纤维为胆碱能神经纤维, 节后纤维大部分为胆碱能神经纤维, 过去对迷走神经的认识局限于保护机体、休整恢复、促进消化和积蓄能量[7,8], 近几年研究[9]发现刺激迷走神经可以通过传递胆碱能信号降低炎症细胞因子水平, 抑制全身性或局部的炎症反应.

1.1.1 传入迷走神经与信号转导: 传入迷走神经在免疫信息向神经信号的转换和传递中起重要作用. 神经学解剖发现选择性切断传入迷走神经时, 大脑中被肠道炎症激活的c-fos的表达减弱[10], 研究[11]也发现小鼠管腔内的空肠弯曲杆菌和伤寒沙门氏菌对孤束核神经元的激活必须依赖完好无损的传入迷走神经. 目前认为应激产生的炎症细胞因子浓度升高, 充当信号因子, 通过刺激传入迷走神经可以形成神经冲动, 完成免疫信号向脑的传递.

1.1.2 传出迷走神经与抗炎: 传出迷走神经可以通过调节炎症细胞因子实现抗炎作用[12,13], 但传出迷走神经与肠道免疫系统之间的关系仍然存在争议, 近来的研究[14,15]通过标记传出迷走神经发现传出迷走神经与脾脏内的巨噬细胞无直接联系, 而是通过胆碱能神经或肠神经间接调控肠道内的巨噬细胞, 认为传出迷走神经调控巨噬细胞是独立于脾脏的, 而Vida等[16]的研究则认为在致命性的炎症反应中, 传出迷走神经可以与脾神经连接, 刺激脾内去甲肾上腺素的释放, 抑制巨噬细胞内炎症细胞因子的产生, 即迷走神经和交感神经通过α7nAChR进行连接共同完成机体的抗炎.

1.2 ACh ACh是胆碱的乙酰脂, 是体内重要的神经递质, 可以通过与ACh受体(acetylcholine receptors, AChR)结合抑制TNF、IL-1、IL-6等炎性细胞因子释放发挥抗炎作用[17]. TNF是一种多功能的炎症细胞因子, 主要由巨噬细胞和单核细胞产生, 是导致组织损伤的关键启动因子. Lv等[18]的研究发现含ACh转移酶的RAW264.7细胞中ACh的分泌增加, 而TNF的含量显著降低, 指出ACh可以降低RAW264.7细胞中TNF水平. IL是细胞损伤或感染时介导急性时相反应的一类多肽, 具有广泛的免疫学活性, 在炎症反应中起重要作用. 研究[3]发现抑制ACh分解, 可以降低5%醋酸诱导的实验性结肠炎中IL-1β的水平, 防止组织损伤. 以上表明ACh可以通过适当调节炎症介质的表达, 减轻炎症反应.

1.3 AChR 根据药理学特性, AChR可以分为两类: M受体和N受体[19], ACh与两类受体结合可以产生不同的生物学效应, 其中ACh的抗炎作用主要通过与N型受体结合介导.

α7nAChR作为N型AChR的亚型之一, 在胆碱能抗炎通路发挥重要作用[20,21]. 我们的研

研发前沿
胆碱能抗炎通路不仅在胰腺炎、炎症性肠病(inflammatory bowel disease, IBD)等疾病中发挥重要作用. 近来的研究发现胆碱能抗炎通路在其他胃肠道疾病也发挥重要作用, 能否通过刺激迷走神经或研发类胆碱药物为胃肠病患者提供新的治疗方法是目前研究的重中之重.

相关报道
Zhang的研究中首次提出激活M4受体可以通过抑制JAK2/STAT3信号通路发挥抗炎作用, 提示大家胆碱能抗炎通路不应局限于目前已知的途径, 其他抗炎机制仍需要不断探索.

创新盘点

本文从胆碱能抗炎通路的作用机制及与疾病的关系方面对胆碱能抗炎通路的免疫调节作用进行了说明, 分析了近年来国内外对胆碱能抗炎通路免疫调节作用的研究进展, 探讨了胆碱能抗炎通路今后的研究发展方向及临床用途, 加深了对胆碱能抗炎通路的认识.

究[22]发现α7nAChR激动剂八角枫碱(alamarine, AN)能够明显抑制三硝基苯磺酸诱导的实验性结肠炎的炎症反应, Zhang等[23]在研究中也指出α7nAChR激动剂LXM-10可以显著改善弗氏完全佐剂诱导的大鼠关节炎症状, 给予α7nAChR拮抗剂甲基牛扁碱后其在急慢性关节炎中的抗炎作用减弱. 以上研究表明α7nAChR在调控炎症反应中起着不可替代的作用, 是抑制炎症反应的重要目标, 对α7nAChR的进一步研究可能为临床治疗免疫相关性疾病提供新的靶点[24]. Zhang等[23]的研究中也首次提出激活M4受体可以通过抑制JAK2/STAT3信号通路发挥抗炎作用, 指出胆碱能抗炎通路不止局限于目前已知的途径, 其他抗炎机制仍需要不断探索.

2 胆碱能抗炎通路与胃肠道疾病

2.1 胆碱能抗炎通路与炎症性肠病 炎症性肠病(inflammatory bowel disease, IBD)专指病因不明的炎症性肠病, 包括溃疡性结肠炎(ulcerative colitis, UC)和克罗恩病(Crohn's disease, CD), 其病因和发病机制尚未完全明确, 已知免疫系统异常反应在IBD的发病中起重要作用[25,26], 而目前关于IBD与神经免疫调节关系的研究较少, 下面以尼古丁(α7nAChR激动剂)为例探讨胆碱能抗炎通路在IBD中的作用.

尼古丁可以改善UC, 加重CD. 早在2005年就有学者[27]提出尼古丁可以降低活动性结肠炎的急性神经肌肉症状, 随后的研究[28]发现尼古丁有镇痛作用, 可以缓解肠道痛苦和不适, 在降低IL-1、IL-8水平、减轻肠道炎症反应中发挥重要作用[29,30], 而对IBD患者的问卷反馈则发现尼古丁增加了CD的发病风险[31], 近年的研究发现长期使用塞马莫德(与尼古丁同为α7nAChR激动剂)却可以起到改善中重度CD的效果[32], 提示比较尼古丁与塞马莫德在胆碱能抗炎机制中的区别, 可能为CD患者的治疗找到有效方法.

胆碱能抗炎通路的其他组成部分对IBD的调节也有重要价值. Sun等[6]发现刺激迷走神经可以降低TNBS诱导的实验性结肠炎小鼠的疾病活动指数(disease activity index, DAI)、结肠黏膜损伤指数(colonic mucosa damage index, CMDI), 改善结肠黏膜损伤, 研究发现抑制ACh的分解也可以减少α7nAChR介导的炎症细胞因子的释放, 改善DSS诱导的实验性结肠炎[33]. 以上实验表明迷走神经、ACh、AChR等构成的胆碱能抗炎通路可以参与IBD的调节.

2.2 胆碱能抗炎通路与胃肠道其他疾病 有文献显示胆碱能抗炎通路不仅与炎症性肠病有关, 也参与胃肠道的其他疾病.

氧化应激可以导致慢性炎症. Ruan等[34]在实验中发现给予石杉碱甲联合*D*-半乳糖处理的大鼠与单一注射*D*-半乳糖的大鼠相比, 明显降低了肝脏功能障碍及氧化应激损伤. 得出石杉碱甲可以通过抑制ACh酯酶, 增加ACh含量, 显著减少*D*-半乳糖诱导的肝脏活性氧(reactive oxygen species, ROS)生成及氧化损伤, 抑制炎症反应, 对肝脏起到潜在的保护作用.

胰腺炎是一种常见的急腹症, 同时也是存在病死率的一种疾病, 为探究新的治疗方法, 许多学者研究了胆碱能抗炎通路与胰腺炎之间的关系, 通过刺激迷走神经或给予α7nAChR激动剂发现可以显著降低胰腺炎小鼠的TNF、IL-1、IL-6等炎症细胞因子水平, 明显改善胰腺炎症状及胰腺功能, 进一步证实激活胆碱能抗炎通路在一定程度上可以用于胰腺炎的治疗[35,36].

张静等[37]在实验中发现电刺激迷走神经可以在一定程度上减轻由盐酸-胃蛋白酶刺激引起的大鼠食管损伤, 抑制炎症细胞因子TNF、IL-6等, 而在双侧颈部迷走神经切断后, 大鼠食管损伤程度加重, 炎症细胞因子水平显著升高, 得出胆碱能抗炎通路在大鼠急性食管炎的调控过程中起保护作用.

胃溃疡是一种多发病、常见病, 大量研究认为胃部的组织失去保护或者屏障与胃溃疡的进展密切相关, Fujisawa等[38]在实验中用消炎痛诱导小鼠急性胃溃疡, 发现给予莫沙比利后可以改善消炎痛诱导的小鼠胃黏膜损害, 而选择性的抑制α7nAChR后则会减弱其作用, 表明莫沙比利保护胃黏膜、改善急性胃溃疡的作用可能来自于胆碱能抗炎通路的激活.

此外, 胆碱能抗炎通路在改善术后肠梗阻[39]、肠缺血后再灌注损伤[40]、过敏性腹泻[41]中也发挥重要作用, 对今后临床中免疫相关性胃肠道疾病的治疗具有指导意义.

3 胆碱能抗炎通路在胃肠道外的应用

胆碱能抗炎通路除可能用于以上疾病的治疗外, 其通过调节免疫反应, 可以作用于其他免疫相关性疾病. 近来研究发现胆碱能抗炎通路

不仅在帕金森病(Parkinson's disease, PD)[42]、阿尔茨海默病(Alzheimer's disease, AD)[43]等神经疾病的治疗中有一定临床价值, 也可以减弱受体器官移植后产生的排斥反应, 对今后开展器官移植具有深远意义[44]. 此外, 胆碱能抗炎通路还与改善心肌缺血后血管功能障碍[45]、过敏性哮喘[46]、慢性膀胱炎[47]、类风湿性关节炎[48]、脑缺血再灌注损伤[49]、休克[50]、肥胖[51]、败血症[52]等诸多疾病的进展密切相关.

4 结论

炎症和炎症相关性疾病是当今医学的重大挑战, 目前研究认为胆碱能抗炎通路在炎症相关的胃肠病的器官保护及对抗过度炎症和免疫反应方面具有一定临床意义, 刺激迷走神经或研究开发安全有效的拟胆碱药物可能为胃肠病患者提供一条新的治疗手段或干预措施, 我们有理由相信胆碱能抗炎通路是未来干预胃肠病的重要发展方向.

应用要点

本文提出胆碱能抗炎通路的免疫调节作用在大量疾病治疗中的可能用途, 但目前尚无确切的临床应用资料, 在将胆碱能通路的免疫作用应用于临床前, 仍需要进一步深入的研究.

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名词解释

胆碱能抗炎通路: 大脑识别传入迷走神经传来的信号, 刺激迷走神经末梢释放ACh, 与巨噬细胞和其他细胞上表达的α7烟碱型ACh受体结合, 作用于下游JAK2/STAT3、MAPK/NF-κB等信号通路, 抑制肿瘤坏死因子、白介素-1、白介素-6等炎症细胞因子, 从而发挥抗炎作用.

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编辑: 郭鹏 电编: 闫晋利

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文章选题具有一定的创新性, 逻辑严谨, 语言流利, 具有一定的可读性.