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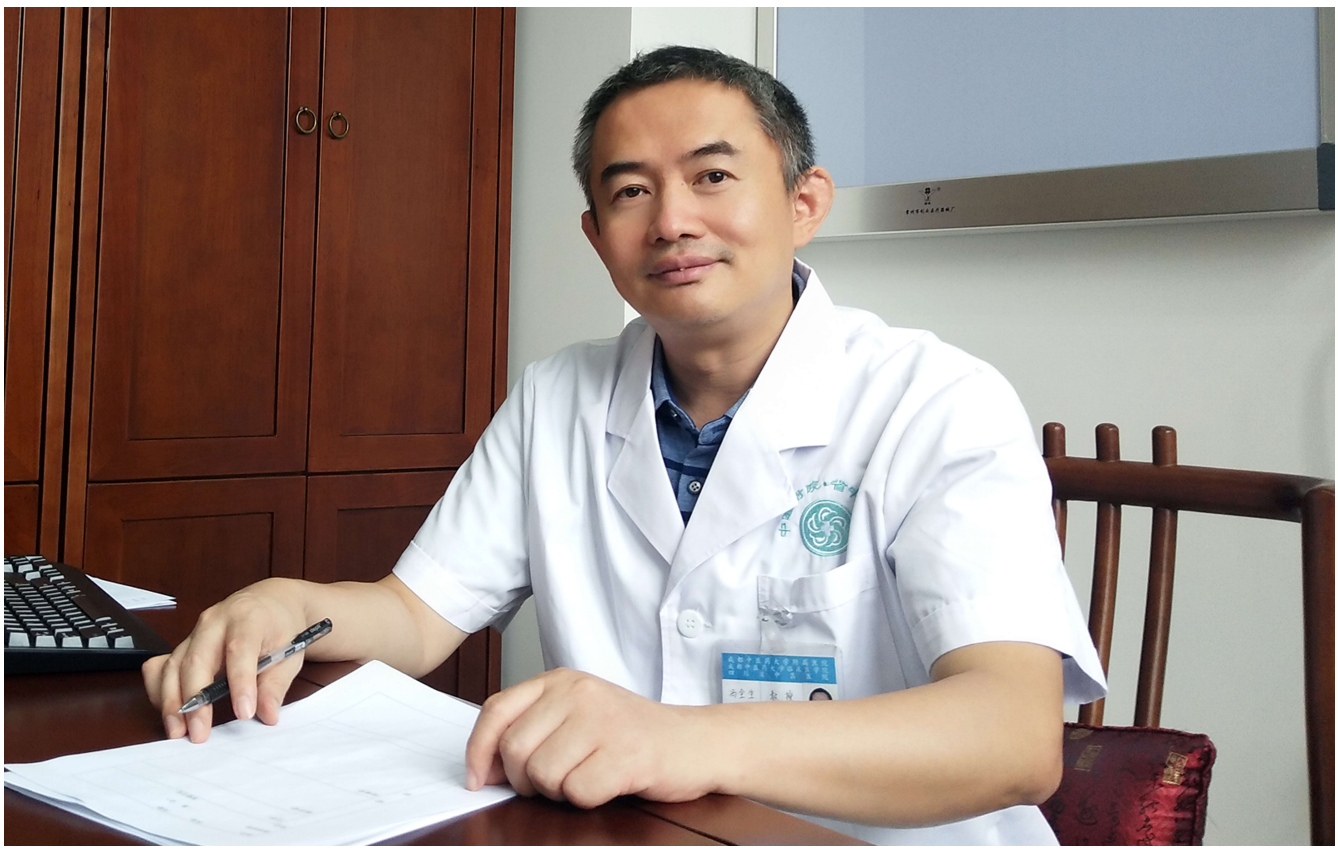

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传真: 010-85381893

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文献综述 REVIEW

5-羟色胺及其受体与肠易激综合征肠道动力异常的关系研究进展

王殷姝, 王恩康, 孟杨杨, 毕紫娟, 袁建业

王殷姝, 王恩康, 孟杨杨, 毕紫娟, 袁建业, 上海中医药大学附属龙华医院脾胃病研究所 上海市 200032

王殷姝, 在读研究生, 从事中医药防治脾胃病的临床与基础研究.

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通讯作者: 袁建业, 研究员, 200032, 上海市徐汇区宛平南路725号, 上海中医药大学附属龙华医院脾胃病研究所. yuanjianye@hotmail.com
电话: 021-64385700

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Advances in understanding relationship between 5-hydroxytryptamine and its receptors and intestinal dysmotility in irritable bowel syndrome

Yin-Shu Wang, En-Kang Wang, Yang-Yang Meng, Zi-Juan Bi, Jian-Ye Yuan

Yin-Shu Wang, En-Kang Wang, Yang-Yang Meng, Zi-Juan Bi, Jian-Ye Yuan, Institute of Spleen and Stomach Diseases, Longhua Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai 200032, China

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Corresponding author: Jian-Ye Yuan, Researcher, Institute of Spleen and Stomach Diseases, Longhua Hospital, Shanghai University of Traditional Chinese Medicine, 725 wanping south road, xuhui district, Shanghai 200032, China. yuanjianye@hotmail.com

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Abstract

Irritable bowel syndrome (IBS) is a common clinical functional gastrointestinal disease, which seriously affects the quality of life of patients. The pathogenesis of this disorder is unclear and may be related to the changes of visceral sensitivity, gastrointestinal motility, and the function of the brain-gut axis. 5-hydroxytryptamine (5-HT) is an important neurotransmitter, which exhibits a variety of biological effects including gastrointestinal secretion and motility regulation by binding to its receptors. The changes in the synthesis and release of 5-HT and in the expression and function of corresponding receptors are all involved in the pathophysiological process of IBS. In this paper, we will review the role of 5-HT and its receptors in intestinal dysmotility in IBS.

Key Words: 5-hydroxytryptamine; 5-hydroxytryptamine receptor; Irritable bowel syndrome; Intestinal dysmotility

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摘要

肠易激综合征(irritable bowel syndrome, IBS)是临床上常见的一种严重影响患者生活质量的功能性胃肠疾病. 本病的发病机制并不清楚, 目前认为可能与内脏敏感性, 胃肠动力, 脑-肠轴功能等的改变有关. 5-羟色胺(5-hydroxytryptamine, 5-HT)是一种参与脑-肠轴改变的重要的神经递质, 通过与其受体结合, 发挥调控胃肠分泌, 肠蠕动等多种生物学作用. 5-HT的合成, 释放及其相应受体的变化均参与了IBS的病理生理过程. 本文就5-HT及其受体参与IBS肠道动力异常的相关研究进展进行综述.

关键词: 5-羟色胺; 5-羟色胺受体; 肠易激综合征; 肠道动力异常

核心提要: 5-羟色胺(5-hydroxytryptamine, 5-HT)及其受体参与了肠易激综合征(irritable bowel syndrome, IBS)肠道动力异常的发生发展, 本文对5-HT及其受体与IBS肠道动力异常的关系及以5-HT受体为靶标的治疗IBS的药物相关研究进展进行了综述.

王殷姝, 王恩康, 孟杨杨, 毕紫娟, 袁建业. 5-羟色胺及其受体与肠易激综合征肠道动力异常的关系研究进展. 世界华人消化杂志 2019; 27(15): 954-960
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0 引言

肠易激综合征(irritable bowel syndrome, IBS)是一种以腹痛或腹部不适伴排便习惯改变为主要临床症状的功能性肠病, 缺乏公认的形态学和生化学异常依据. 其临床表现复杂, 呈多样性, 持续性, 不仅降低了患者的生活质量, 也给社会经济发展带来了严重负担. 根据Rome IV诊断标准, 可将其分为四型, 腹泻型IBS(IBS with predominant diarrhea, IBS-D), 便秘型IBS(IBS with predominant constipation, IBS-C), 混合型IBS(IBS with mixed bowel habits, IBS-M)和未定型IBS(IBS unclassified, IBS-U). IBS的发病机制尚不完全清楚, 可能与肠道动力紊乱, 内脏感觉过敏, 脑-肠轴功能失调, 肠道菌群紊乱等因素有关, 但以肠道动力异常和内脏敏感性异常为主要特征[1].

5-羟色胺(5-hydroxytryptamine, 5-HT)广泛存在于中枢神经系统和外周神经系统, 它首次在肠嗜铬细胞(enterochromaffin, EC)中发现, 随后有科学家发现它存在于血清中, 可作为血管紧张素, 所以又叫做血清素. 在外周, 90%的5-HT由EC分泌, 也可由肥大细胞分泌, 是参与胃肠道运动和感知功能调节的重要信号分子. 5-HT通过与不同受体亚型的相互作用调节消化系统的感觉, 运动和分泌功能. 5-HT受体超家族主要有7种亚型: 5-HT_{1-7}. 在这些受体中, 5-HT_1, 5-HT_2, 5-HT_3, 5-HT_4和5-HT_7受体在胃肠道均有表达, 并参与胃肠动力的调控[2]. 其中对5-HT_3和5-HT_4受体参与胃肠道病理生理的研究最为广泛, 而对5-HT_7, 5-HT_1, 5-HT_2受体的研究也在逐渐增多. 以5-HT受体为作用靶标的一些药物已被证明能有效调节胃肠道运动功能, 而其中作用于5-HT_3, 5-HT_4受体的一些药物已被运用于临床. 越来越多的证据显示5-HT及其受体在IBS的发生发展过程中发挥重要作用, 本文就近年来5-HT及其受体参与IBS肠动力异常的相关研究进展进行综述.

1 5-HT在IBS肠道动力异常中的作用

5-HT信号通路参与调节胃肠运动. 在感受到肠腔内物理与化学刺激后, EC释放5-HT, 5-HT刺激内在初级传入神经元, 使其在肌间神经丛中与上下行中间神经元形成突触, 从而调节局部的兴奋与抑制[1]. 另外, 5-HT也可以直接作用于肠神经元及肌细胞等效应器发挥作用. 在一项对犬在体的研究中发现, 5-HT能通过增加神经效应接头处乙酰胆碱(acetylcholine, ACh)的释放刺激结肠的位相收缩; 在离体实验中也同样发现结肠收缩是由胆碱能神经元上的5-HT受体所介导, 而回肠的收缩则是由平滑肌上的5-HT受体介导的[3]. 临床研究显示, IBS-C患者血浆及肠黏膜中5-HT含量降低[4], 而IBS-D患者血浆及结肠黏膜中5-HT的含量均明显增高[5], 血浆中升高的5-HT浓度与直肠运动加快密切相关[6]. 5-HT通过与不同受体相结合启动下游的信号通路来调控胃肠运动. 在IBS中, 5-HT能与胆碱能神经上的5-HT_3受体和5-HT_4受体结合促进兴奋性神经递质ACh的释放从而诱导平滑肌收缩, 也能与硝基能神经元上的5-HT_{1A}, 5-HT_4, 5-HT_{1D}受体结合促进抑制性分子NO的释放介导平滑肌的舒张[7].

2 5-HT_3受体与IBS肠动力异常

2.1 5-HT_3受体的表达与作用 5-HT_3受体是5-HT受体家族中唯一的配体门控离子通道大家族成员. 目前已经发现了5种5-H_{T3}受体亚型: 5-HT_{3A}, 5-HT_{3B}, 5-HT_{3C}, 5-HT_{3D}和5-HT_{3E}. 5-HT_3受体广泛分布在中枢和外周神经系统中[8]. 在胃肠道, 5-HT_3受体主要在肠黏膜下和肌层神经丛的神经元细胞膜上, 也存在于环行和纵行肌的肌纤维上. 另外, 肠Cajal间质细胞(interstitial cells of Cajal, ICC)以及某些肠内分泌细胞也会表达5-HT_3受体. 5-HT_3受体

介导的5-HT效应可以通过神经元通路以及非神经元通路的激活来实现[9]. 5-HT作用于副交感神经节的5-HT_3受体, 促使平滑肌收缩, 并通过刺激神经末梢ACh的释放增加肠道分泌[10]. 有研究显示在IBS-D患者结肠黏膜组织中, 5-HT_3受体表达明显增加[6], 拮抗5-HT_3受体能抑制5-HT诱导的结肠收缩作用[3].

2.2 以5-HT_3受体为靶标的治疗IBS的药物研究 5-HT_3受体拮抗剂是临床上治疗非IBS-C的有效药物. 它们效力强, 吸收迅速, 并且容易穿透血脑屏障. 已经证明5-HT_3受体拮抗剂可以通过作用于中枢和/或外周的5-HT_3受体, 减少肠道的分泌和运动. 在动物实验中, 5-HT_3受体拮抗剂能抑制非选择性阳离子通道的激活, 并在体外以剂量依赖性的方式阻断5-HT_3受体介导的肠黏膜下神经元的去极化.

目前, 临床上用于治疗IBS的5-HT_3受体拮抗剂包括雷莫司琼, 昂丹司琼, 西兰司琼和阿洛司琼, 它们可以整体改善包括腹痛, 排便习惯和大便性状异常在内的IBS症状. 其主要作用机制是抑制小肠的传输和分泌, 增加直肠的顺应性. 在对IBS模型大鼠的研究中发现, 雷莫司琼可以减少排便, 改善腹泻, 同时提高疼痛阈值, 但是临床研究提示, 雷莫司琼在改善IBS-D患者腹泻的同时还会引发便秘[11]. 有研究表明昂丹司琼和阿洛司琼都可以减少小鼠结肠推进性运动复合波(colonic migrating motor complex, CMMC)的幅度, 减弱对粪球的推进力[12]. 它们的作用存在性别和部位差异, 阿洛司琼对雌性小鼠小肠的作用阈值明显低于其对雄性小鼠小肠的作用阈值, 而昂丹司琼对雄性小鼠结肠的作用阈值低于其对雌性小鼠结肠的作用阈值[13]. 雷莫司琼被认为是目前医疗市场上治疗IBS-D综合效应最佳的5-HT_3受体拮抗剂, 因为它在两性患者中都具有出色的疗效, 且耐受性良好[14]. 鉴于目前治疗药物的局限性, 新的5-HT_3受体拮抗剂正在不断被研发出来, 例如阿戈美拉汀, 就是这样一种能够较好地改善IBS-D患者胃肠动力和内脏敏感性异常的, 新的5-HT_3受体拮抗剂[15]. 此外, 5-HT_3受体部分激动剂因其引发便秘的概率较小, 也被用于治疗IBS-D[16]. Coleman等[17]人的研究表明5-HT_3受体激动剂 MKC-733可延缓液体胃排空, 松弛近端胃平滑肌, 刺激空腹时胃十二指肠移行性复合运动, 加速小肠的转运.

3 5-HT_4受体与IBS肠动力异常

3.1 5-HT_4受体的分布与作用 5-HT_4受体属于鸟苷酸结合蛋白(G蛋白)偶联受体, 具有7个跨膜区. 在胃肠道, 5-HT_4受体表达在肠道神经元, 平滑肌细胞以及上皮细胞上[18]. 在大鼠肠道和脑组织中可检测出的5-HT_4受体亚型有5-HT_{4a}, 5-HT_{4b}, 5-HT_{4e}和5-HT_{4f}. 其中, 5-HT_{4a}和5-HT_{4b}在大肠的各个区域以及肠神经丛中皆有显著表达[19]. 5-HT_4受体在调控肠道运动中起重要作用. 当它们被激活时, 会增强肠蠕动反射. 有研究证明, 胃肠道5-HT_4受体的激活可促使降钙素基因相关肽(calcitonin gene related peptide, CGRP), P物质(substance P, SP)和ACh等神经递质释放, 进而影响胃肠道动力及内脏感知. 位于肠神经元上的5-HT_4受体能够能产生兴奋性的效应, 具有促动力的作用[20]. 位于人类结肠环行平滑肌上的5-HT_4受体介导了平滑肌的舒张[21,22]. 位于肠上皮细胞上的5-HT_4受体则介导了包括增强推进运动, 降低内脏高敏感性在内的多种病理生理反应[23]. 有研究显示IBS-C患者中, 5-HT_4受体的表达量下调[24]. 动物实验也发现5-HT_4受体基因敲除小鼠表现出结肠动力减弱[25].

3.2 以5-HT_4受体为靶标的治疗IBS的药物研究 以5-HT_4受体为作用靶标的药物已被广泛研究. 激动5-HT_4受体具有促进肠道运动和抗伤害性的作用[26], 故5-HT_4受体激动剂在临床上多用于治疗功能性消化不良与IBS-C[27]. 5-HT_4受体的促动力作用与增强的兴奋性神经传递有关. 目前已被开发应用的5-HT_4受体激动剂包括部分激动剂替加色罗和高选择性激动剂普鲁卡必利, 以及新型非选择性5-HT_4受体激动剂伦扎必利. 其中普鲁卡必利和替加色罗具有部分激动5-HT_4受体的效应, 伦扎必利除了作用于5-HT_4受体, 还作用于5-HT_3受体. 普鲁卡必利能增强胆碱能收缩, 促进肠肌层胆碱能神经传递[28]. 伦扎必利和替加色罗可增加烟碱诱发的兴奋性突触后电流幅值[19]. 在临床试验中, 替加色罗能够加速受试者的肠道运输, 促进胃适应性, 对治疗IBS-C有良好的长期疗效和耐受性, 但是其最常见的不良反应是腹泻[29]. 普鲁卡必利与5-HT_4以外的其它5-HT受体亲和力较低, 而且与心脏的K^+通道的亲和力低, 故引起心率失常的副作用较小[30].

大部分传统的5-HT_4受体激动剂的作用机制是通过刺激5-HT_4受体介导的ACh释放增强结肠的推进运动. 新近研发出来的一种新型5-HT_4受体激动剂YKP10811, 同样具有抗伤害和促进结肠运动的作用, 但其作用机制与传统的5-HT_4受体激动剂不同, 它能刺激EC释放5-HT, 从而促进结肠蠕动反射, 而且它的心血管副作用较小[31]; 另一种正在研发的5-HT_4受体激动剂DA-6886是一种苯甲酰胺衍生物生物, 它可以明显缓解IBS-C小鼠的胃肠传输延迟状态, 治疗效果与替加色罗相似[32]; 还有一项新的药物研究表明, 5-HT_4受体部分激动剂DSP-6952, 可缓解IBS内脏高敏感性, 改善实验动物的胃肠功能障碍, 且对于心血管的副作用小[33]; Camilleri等[34]

人的研究显示肠腔注射5-HT$_4$受体激动剂ATI-7505能加快肠道推进性运动, 而5-HT$_4$受体拮抗剂能阻断这一效应. 在临床研究中, ATI-7505能促进受试者的全结肠运动, 且可促进降结肠排空和胃排空. 由Theravance及Alfa Wasserman公司开发的新型高选择性5-HT$_4$受体激动剂TD-5108(Velusetrag, 维司曲格), 能促进结肠传输, 目前正在处在2期临床试验阶段[35]. TD-5108对5-HT$_4$受体的亲和力是其它5-HT受体亚型的500倍以上[36], 对于促进狗平滑肌的收缩效应要优于替加色罗, 且其与另一个新型5-HT$_4$受体高选择性激动剂TD-8954的心血管风险都较低[37].

5-HT$_4$受体拮抗剂具有抑制结肠收缩的效应. Ono等[38]的研究表明5-HT$_4$受体拮抗剂SB-204070能降低大鼠远端纵行平滑肌收缩的频率. SB-207266-A能增加IBS-D患者小肠推进时间[39], SB-207266可以减少小鼠由内源性5-HT刺激引起的排便量增多[40].

4 5-HT$_7$受体与IBS肠动力异常

4.1 5-HT$_7$受体的分布与作用 近年研究显示5-HT$_7$受体与胃肠运动, 感觉等功能密切相关. 5-HT$_7$受体在中枢和外周都有表达, 在中枢可表达在前脑, 间脑以及小脑[41], 在外周可表达在血管平滑肌以及胃肠道[42]. 在胃肠道中, 5-HT$_7$受体主要表达在平滑肌, 肠神经元以及固有淋巴组织中[43]. Bard等[44]人首次研究了人类5-HT$_7$受体的组织分布, 并发现在人类结肠, 回肠, 脑组织中都有丰富的表达, 而在肝, 肾和脾脏中表达相对较少. Tonini等[45]观察了豚鼠回肠中5-HT$_7$受体的表达, 发现其可大量表达在肠肌间神经元以及少量黏膜下神经元和平滑肌细胞中. 5-HT$_7$受体对平滑肌松弛和内脏感觉具有的重要调控作用, 参与了IBS胃肠运动障碍, 腹部疼痛和内脏感觉异常的发病机制. 已有研究表明, 5-HT$_7$受体不仅介导人类环行平滑肌的松弛[46], 还通过促进下行运动神经元NO的释放介导5-HT对豚鼠回肠蠕动的抑制作用[47]. 在IBS-D患者结肠黏膜组织中, 5-HT$_7$受体mRNA的表达与正常人相比无明显差异[6]; 而在IBS-C模型大鼠中, 5-HT$_7$受体在回肠和结肠中的表达明显增高[48]; 在IBS-D模型小鼠结肠组织中, 5-HT$_7$受体蛋白表达量却明显下降[49].

4.2 以5-HT$_7$受体为靶标的治疗IBS的药物研究 5-HT$_7$受体拮抗剂可能会缓解功能性胃肠病运动及感觉异常, 因此, 5-HT$_7$受体可能是解除腹痛的一个药物靶标. 已有研究显示, 5-HT$_7$受体拮抗剂mesulergine能够抑制由5-HT诱导的人类结肠环行肌的舒张效应[46]; 5-HT$_7$受体拮抗剂SB-269970能抑制豚鼠回肠环行肌的松弛[45]; 5-HT$_7$受体阻断剂SB-258719能阻断结肠CMMC[43]; 将5-HT$_7$受体拮抗剂SB-269970微量注射到大鼠海马腹侧, 可显著减少应激引起的排便量增多[50].

5 5-HT其它受体与IBS肠动力异常

5.1 5-HT$_1$受体与IBS肠动力异常 5-HT$_1$受体也有诸多亚型, 其中对胃肠道功能有影响的是5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1D}$与5-HT$_{1P}$等受体. Delesalle等[51]发现在马的空肠环行和纵行平滑肌中有5-HT$_{1A}$受体的表达. 5-HT$_{1A}$受体具有介导肥大细胞脱颗粒, 释放组胺等介质的作用[52]. Tamaoki等[53]人的研究表明5-HT$_{1A}$受体激动剂TZB-30878能够改善应激诱发的IBS-D模型大鼠排便量增多. Asagarasu等[54]人的研究提示5-HT$_{1A}$受体激动剂TZB-30878在缓解IBS-D大鼠腹泻症状的同时还可以改善其焦虑样行为.

5.2 5-HT$_2$受体与IBS肠动力异常 近些年来, 5-HT$_2$受体的两个亚型受体5-HT$_{2A}$与5-HT$_{2B}$与胃肠运动和感知的关系引起了医学界的高度重视. 5-HT$_{2B}$受体在人类肠道平滑肌上有表达. Borman等[55]人研究了5-HT$_{2B}$受体在控制人类结肠运动中的作用, 首次证实了人类结肠中有5-HT$_{2B}$受体表达, 且发现5-HT$_{2B}$ mRNA在包括结肠在内的整个人类胃肠道中都有高表达, 这种受体能介导5-HT在结肠的兴奋性效应. 在IBS模型大鼠结肠中, 5-HT$_{2B}$ mRNA的表达量上调[56]. Wouters等[57]的研究指出5-HT$_{2B}$受体可在一定程度上调控ICC增殖, 促进胃肠传输功能. 另有研究显示5-HT$_{2B}$受体拮抗剂能改善IBS-D模型大鼠的内脏高敏感性, 但对正常的结肠收缩没有影响[56,58], 说明5-HT$_{2B}$受体拮抗剂起到治疗作用而无副作用. 5-HT$_{2A}$在人类外周血单核细胞上有表达, Bertoni等[59]研究发现5-HT$_{2A}$受体拮抗剂ketanserin能够逆转缺血再灌注损伤引起的小鼠胃肠传输延迟, 而5-HT$_{2A}$受体激活剂1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane(DOI)则可以引起胃肠传输延迟(表1).

6 结论

IBS发病机制复杂, 涉及神经, 内分泌, 免疫等多个方面. 饮食, 遗传, 环境等因素都参与其中. 深入探讨IBS的发病机制对研发相应的治疗药物具有重要意义. 5-HT作为肠道内分泌系统最重要的神经递质之一, 其含量的改变及其受体的相关变化都参与了IBS的发病. 随着研究的不断深入, 5-HT及其受体在IBS病理生理中的复杂作用正在不断得到解析, 而与5-HT及其受体相关的一些制剂也已被证明在治疗IBS中确有一定疗效. 但是目前以5-HT受体为靶标的药物存在一定的治疗局限性和副作用, 一些新的药物正在不断被研发出来, 相信随着对

表 1 5-羟色胺及其受体在胃肠道中的组织分布, 功能调节及相应的药物研究

	胃肠道中的分布	功能	药物研究
5-HT	肠嗜铬细胞, 肥大细胞, 肠神经系统神经元	介导胃肠蠕动和分泌反射	/
5-HT_{1A}受体	平滑肌[51]	介导肥大细胞脱颗粒, 释放组胺[52]	激动剂: TZB-30878[53,54]
5-HT_{2A}受体	外周血单核细胞	抑制促炎细胞因子α释放, 引起胃肠传输延迟[59]	激动剂: DOI[59]; 拮抗剂: ketanserin[59]
5-HT_{2B}受体	平滑肌	促进胃肠传输, 促进内脏敏感性[56, 57]	拮抗剂: Compound 15[56,58], RS-127445[56, 58]
5-HT_{3}受体	神经元细胞膜, 肌纤维, 肠间质Cajal细胞, 肠内分泌细胞	促进平滑肌收缩, 增加分泌[10]	拮抗剂: 雷莫司琼[11,14], 昂丹司琼[12], 阿洛司琼[12], 西兰司琼[61], 阿戈美拉汀[15]; 激动剂: MKC-733[17]
5-HT_{4}受体	肠道神经元, 平滑肌细胞, 上皮细胞[18]	调控肠道运动[20-23], 降低内脏敏感性[23]	激动剂: 替加色罗[19,29], 伦扎必利[19], 普鲁卡必利[28,30], YKP10811[31], DA-6886[32], DSP-6952[33], ATI-7505[34], TD-5108[35-37], TD-8954[37]; 拮抗剂: SB-204070[38], SB-207266-A[39], SB-207266[40]
5-HT_{7}受体	平滑肌, 肠神经元, 固有淋巴组织[43]	松弛平滑肌, 抑制蠕动[46, 47]	拮抗剂: SB-258719[43], SB-269970[45], mesulergine[46]

5-HT: 5-羟色胺.

5-HT, 5-HT各受体亚型更加透彻地研究, 一定会有助于我们进一步认识包括肠动力异常在内的IBS的具体发病机制, 并为治疗IBS提供更多的手段.

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