·综述·

5-羟色胺与帕金森病非运动症状研究进展

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【摘要】 帕金森病是临床常见的神经系统变性疾病，通常伴有胃肠功能障碍、嗅觉减退、睡眠障碍、抑郁、疼痛和幻觉等非运动症状，严重降低患者生活质量。帕金森病患者存在5-羟色胺能神经元退行性变等非多巴胺能系统弥漫性病理改变，且5-羟色胺在情绪、认知功能、疼痛等多种神经功能调节方面发挥重要作用，与帕金森病非运动症状密切相关。本文综述5-羟色胺与帕金森病非运动症状之间的相关性及其研究进展，以明确帕金森病非运动症状的发病机制，为实现疾病的早期诊断与精准治疗提供理论基础。

【关键词】 帕金森病； 血清素； 综述

Advance on association between 5-hydroxytryptamine and non-motor symptoms in Parkinson´s disease

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【**Abstract**】 Parkinson's disease (PD) is a common neurodegenerative disease in clinical practice. Patients with PD are usually accompanied by non-motor symptoms (NMS) such as gastrointestinal dysfunction, hyposmia, sleep disorders, depression, pain and hallucinations, which seriously reduce the quality of life. Recent studies have found that PD patients were accompanied by diffuse pathological changes in non-dopaminergic system such as progressive degeneration of 5-hydroxytryptamine (5-HT) ergic neurons, and 5-HT plays an important role in the regulation of emotion, cognitive function, pain and other neural functions, and is closely related to non-motor symptoms of PD. This article reviews the correlation between 5-HT and non-motor symptoms of PD and its research progress, in order to further clarify the pathogenesis of non-motor symptoms of PD and provide a theoretical basis for the treatment of PD.

【**Key words**】 Parkinson disease; Serotonin; Review

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帕金森病(PD)是临床常见的神经系统变性疾病,好发于中老年人群[1]。我国帕金森病疾病负担逐年加重,预计截至2025年帕金森病患者可达38.85万例[2]。除静止性震颤、肌强直、运动迟缓等典型运动症状外,随着疾病进展,帕金森病患者还可出现一定程度的非运动症状(NMS)包括胃肠功能障碍、嗅觉减退、睡眠障碍、抑郁、疼痛和幻觉等,进而加重运动症状,降低生活质量。帕金森病的主要病理学特征是黑质-纹状体通路多巴胺能神经元变性坏死;存活的多巴胺能神经元则在其细胞质内形成路易小体[3],主要成分为α-突触核蛋白(α-Syn),α-Syn变性可形成具有毒性作用的不可溶性聚集体,促进帕金森病的发生[4]。近年来有研究发现,除多巴胺能神经元变性坏死外,帕金森病还涉及5-羟色胺(5-HT)能神经元进行性退化等非多巴胺能系统弥漫性病理改变[5],帕金森病患者的脑干中缝核损伤可使血液和脑脊液5-HT水平显著降低[6];此外,5-HT在情绪、认知功能、疼痛等多种神经功能调节方面发挥重要作用,与帕金森病非运动症状存在密切关系。本文拟综述5-HT与帕金森病非运动症状之间的相关性及其研究进展,以期进一步明确帕金森病非运动症状的发病机制,为帕金森病治疗提供理论基础。

一、5-羟色胺生物学特性

5-HT又称血清素,由人体必需氨基酸色氨酸经色氨酸羟化酶和芳香族氨基酸脱羧酶的两次酶促反应合成。人体约95%的5-HT在肠道中由肠嗜铬细胞和肠肌间神经丛合成;其余小部分由位于脑干中缝核的5-HT能神经元合成并储存于突触囊泡中,突触囊泡在突触间隙释放5-HT,并与突触前膜5-羟色胺转运体(SERT)相结合,维持突触间隙5-HT稳定[7]。目前已发现7个5-HT亚家族共14种5-HT受体亚型,脑干中缝核5-HT能神经元传出纤维可投射至黑质、纹状体、苍白球、下丘脑、丘脑和皮质等脑区;还可以透过室管膜和软脑膜直接进入脑脊液,经脑脊液直接作用于其他脑区[6],进而通过兴奋不同受体介导各种生物学作用。

二、5-羟色胺与常见帕金森病非运动症状

1.胃肠功能障碍 胃肠功能障碍是帕金森病患者最早出现的非运动症状,发生率约为65%,主要包括流涎、吞咽障碍、胃排空障碍、便秘、肠易激综合征等[8]。胃肠功能障碍可抑制左旋多巴吸收[9],出现症状波动,导致病情加重[10]。5-HT作为信号转导分子,可将神经信号经肠道传递至内源性或外源性神经元,抑制肠道蠕动、吸收和促进胃肠道炎症反应等[11]。5-HT4受体可以调节胃肠道功能,业已证实5-HT4受体激动剂普卡必利可以用于治疗慢性特发性便秘[12]。有研究发现,帕金森病患者胃肠道5-HT4受体水平显著降低,肠道蠕动减慢[13]。此外,5-HT4受体水平降低还可导致肠道分泌功能减退、吸收功能增强,使肠道内容物体积和液体含量减少,不利于粪便软化和排便,最终导致便秘[14]。普卡必利通过Janus激酶2(JAK2)/信号转导与转录激活因子3(STAT3)非依赖性信号转导通路促进白细胞介素-6(IL-6)释放,减轻肠屏障损伤,缓解帕金森病患者胃肠道症状。5-HT4受体阻断剂GR125487通过JAK2/蛋白激酶A(PKA)/cAMP应答元件结合蛋白(CREB)信号转导通路可促进1-甲基-4-苯基-1,2,3,6-四氢吡啶(MPTP)诱导的黑质纹状体神经元退行性变,并加剧肠道菌群紊乱,进一步减慢肠道蠕动,导致胃肠功能障碍[15]。西酞普兰作为选择性5-羟色胺再摄取抑制剂(SSRI)可以降低食管机械化学敏感性、增强胃肠道蠕动,但目前尚无明确证据表明5-HT与帕金森病患者吞咽困难有关[16]。上述研究证实,5-HT与胃肠道功能密切相关,帕金森病患者5-HT能系统损害可导致胃黏膜保护功能减弱,肠道蠕动减慢,肠道炎症反应增加,水电解质平衡紊乱。目前,帕金森病相关胃肠道症状尚未引起足够重视,有待更多研究进一步明确其发病机制。

2.嗅觉障碍 约90%的帕金森病患者前驱期可出现嗅觉障碍,有可能成为早期诊断帕金森病的生物学标记[17]。脑干中缝核5-HT纤维可投射至嗅球僧帽细胞,参与嗅觉调节。研究发现,帕金森病患者嗅觉系统5-HT水平显著降低,提示5-HT与帕金森病患者嗅觉功能密切相关[18]。曾有动物实验显示,鱼藤酮诱导的帕金森病模型小鼠嗅球酪氨酸羟化酶(TH)阳性神经元减少,5-HT水平降低,导致小鼠嗅觉辨别能力减退[19];在同法构建的帕金森病模型小鼠中也同样发现嗅球5-HT代谢速度明显增快[20]。星形胶质细胞在帕金森病炎症反应、氧化应激、神经营养因子调节等发病过程中发挥重要作用,5-HT可诱导星形胶质细胞基因表达变化,下调*ALDH1L1-GFP*转基因小鼠嗅球γ-氨基丁酸(GABA)合成基因表达,减少GABA释放,增强嗅球神经元兴奋性,减弱嗅觉正常感知和处理能力,最终导致嗅觉障碍[21],但5-HT在帕金森病嗅觉障碍中的病理

生理学机制尚待进一步研究。

3.睡眠障碍 帕金森病患者通常伴有睡眠障碍，如失眠、日间过度思睡（EDS）、快速眼动睡眠期行为障碍（RBD）、梦魇、睡眠呼吸暂停综合征（SAHS）等症状，导致认知功能减退、负面情绪加重，严重影响日常工作与生活[22]。5-HT能系统是参与睡眠调节的重要神经递质系统，帕金森病患者5-HT能系统功能异常可导致睡眠障碍[23]。脑干中缝背核和中缝中核是5-HT能神经元的主要来源，针对帕金森病患者中缝背核和中缝中核的连通性分析发现，中缝背核与边缘系统、枕叶、躯体感觉皮质间以及中缝中核与额颞叶、边缘系统、小脑之间功能连接降低与非运动症状相关，中缝背核和中缝中核部分5-HT投射通路相同，其中，中缝背核与双侧前额皮质和扣带回皮质的5-HT投射通路损伤与日间过度思睡相关；中缝中核与脑桥和脑岛的5-HT投射通路损伤与快速眼动睡眠期行为障碍相关[24]。5-羟色氨酸（5-HTP）是5-HT生成过程中的中间代谢物，已证实5-HTP可安全有效地提高帕金森病患者睡眠稳定性，增加快速眼动睡眠期（REM）睡眠占总睡眠时间的比例，且不加重快速眼动睡眠期行为障碍，有助于改善患者整体睡眠质量[25]。近年有研究发现，5-HT2A受体阻断剂奈洛坦色林对帕金森病痴呆患者的快速眼动睡眠期行为障碍无效，推测其发病机制与5-HT2A受体无关，为后续研究提供参考[26]。研究发现，快速眼动睡眠期行为障碍发病越早，帕金森病非运动症状越严重[27]，因此为帕金森病患者开发针对睡眠障碍的药物尤为重要。

4.抑郁症状 研究显示，40%～50%的帕金森病患者伴有抑郁症状，对生活质量、认知功能、运动功能均可产生负面影响[28]。近年有学者采用放射配体^{11}C-Cimbi-36 PET显像对抑郁症患者的5-HT释放能力进行评价，发现重度抑郁患者的5-HT释放能力减退[29]，且帕金森病患者5-HT能神经传导减少程度与抑郁严重程度呈正相关[30]。帕罗西汀和艾司西酞普兰均为选择性5-羟色胺再摄取抑制剂，二者对帕金森病伴抑郁患者均有较好疗效，可以显著改善抑郁症状[31-32]。帕金森病相关抑郁症状可能与5-HT能系统障碍有关联。Miquel-Rio等[33]构建一种α-突触核蛋白病小鼠模型以模拟帕金森病患者神经精神症状和组织病理改变，结果发现，*α-Syn*基因过表达可诱导小鼠中缝核5-HT能神经元出前脑区轴突病变，脑源性神经营养因子（BDNF）水平降低，5-HT能神经传导障碍，导致抑郁症状。6-羟基多巴胺（6-OHDA）诱导的帕金森病模型大鼠抑郁样行为研究发现，外侧缰核5-HT1B受体/腺苷酸环化酶（AC）/PKA信号转导通路可以调节抑郁样行为，多巴胺减少可降低该通路活性，予以5-HT1B受体阻断剂可诱导抑郁样行为[34]。过氧化物还原酶6（PRDX6）作为一种双功能蛋白，具有谷胱甘肽过氧化物酶（GSH-Px）和钙依赖性磷脂酶活性，可加重帕金森病多巴胺能神经元变性。动物实验显示，PRDX6蛋白过表达小鼠抑郁样行为增加，大脑皮质5-HT水平显著降低，5-HTP诱导的头部抽搐反应受到抑制，芳香族L-氨基酸脱羧酶水平降低，提示PRDX6蛋白通过调节大脑皮质5-HT能神经传导调节抑郁样行为[35]。此外，帕金森病相关抑郁症状还与5-HT能系统通路相关基因多态性相关，钠依赖性血清素转运蛋白基因*SLC6A4*、*TPH2*被证实可以促进帕金森病患者抑郁易感性[36]。

5.疼痛 逾50%的帕金森病患者伴有疼痛，长期疼痛可导致生活质量严重下降，但药物治疗通常效果欠佳[37]。目前，帕金森病疼痛的发病机制尚不完全明确，虽已证实基底节多巴胺可以调节疼痛反应，但是临床实践中拟多巴胺类药物并不能完全抑制疼痛症状[38]。5-HT能神经元是神经信号转导的重要枢纽，不仅可以接收来自不同脑区的信号，还可以将信号转导至感觉神经末梢。动物实验显示，6-OHDA诱导的帕金森病模型大鼠表现出明显的对高温和机械刺激痛觉过敏，且脊髓背角5-HT水平降低[39]，而抑制5-HT3受体功能可降低脊髓背角神经元兴奋性，缓解大鼠痛觉过敏症状[40]。

6.幻觉 幻觉是帕金森病患者的常见非运动症状，约75%的患者可能出现幻视[41]。帕金森病患者药物治疗以多巴胺受体激动剂为主，升高脑组织多巴胺水平的同时，可加重幻觉。匹莫范色林是一种5-HT2A受体反向激动剂，已被美国食品与药品管理局（FDA）批准作为帕金森病伴幻觉的一线治疗药物，可促进脑源性神经营养因子和胶质细胞源性神经营养因子（GDNF）释放[42]。脑源性神经营养因子分为前体脑源性神经营养因子和成熟脑源性神经营养因子，其中后者主要由前者在细胞内或细胞外裂解产生。动物实验显示，皮下注射匹莫范色林的大鼠血浆成熟脑源性神经营养因子水平明显升高，提示成熟脑源性神经营养因子可能是匹莫范色林神经保护作用的潜在机制[43]。此外，匹莫范色林还

可通过胶质细胞源性神经营养因子依赖性方式保护多巴胺能神经元免受1-甲基-4-苯基吡啶离子(MPP^+)毒性作用的干扰[44]。5-HT3受体阻断剂昂丹司琼可用于治疗帕金森病相关幻觉，显著改善帕金森病啮齿动物模型感觉门控缺陷和视觉感知处理功能[45]。

综上所述，帕金森病患者5-HT能神经元退行性变与多种非运动症状密切相关，深入探究二者相关性有助于实现疾病的早期诊断与精准治疗，对提高患者生活质量具有重要意义。

利益冲突 无

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