·专题综述·

帕金森病疼痛机制研究进展

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【摘要】 帕金森病是中老年人群常见的神经变性病，临床表现主要包括运动症状和非运动症状，疼痛是常见的非运动症状，因影响患者生活质量而倍受关注。然而目前关于帕金森病疼痛的发病机制仍不明确，尚待进一步研究。本文拟就可能的帕金森病疼痛发病机制进行阐述。

【关键词】 帕金森病；　疼痛；　综述

Advances in mechanism research of pain in Parkinson´s disease

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【**Abstract**】 Parkinson´s disease (PD), a neurodegenerative disease, is very common in middle aged and older people. There are two kinds of symptoms: motor symptoms and non-motor symptoms (NMS). Pain, a commonly reported NMS of PD, can significantly affect the quality of life, thus causing more attention. However, mechanisms of pain in PD is not clear, and need to be further researched.

【**Key words**】 Parkinson disease;　Pain;　Review
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帕金森病（PD）是常见于中老年人群的神经变性病，临床主要表现为静止性震颤、运动迟缓、肌强直和姿势步态异常等运动症状，以及感觉异常、睡眠障碍、认知功能障碍、神经精神症状、自主神经症状等非运动症状（NMS）[1]，其中，疼痛是最常见的感觉异常。据文献报道，有40%～60%的帕金森病患者曾经历急性或慢性疼痛[2]，尤其是长期慢性疼痛给患者带来严重的身心困扰。Ford[3]将帕金森病疼痛分为5种类型，按照患病率由高至低依次为肌肉骨骼样疼痛、肌张力障碍样疼痛、神经根性或神经性疼痛、中枢性疼痛、静坐不能相关疼痛。相关危险因素包括女性、高龄、病程、疾病严重程度、运动并发症和抑郁症状等，其中，随着运动症状的加重，疼痛发生率和严重程度亦升高[4]。目前关于帕金森病疼痛的发病机制尚不明确，中枢神经系统和周围神经系统均可能参与其中，本文拟就其可能的发病机制进行概述。

一、中枢神经系统机制

1. 黑质纹状体系统　早在1982年即有研究显示，黑质纹状体与次级感觉区、岛叶、扣带回、前额叶皮质和丘脑板内核群等疼痛相关皮质区域均存在纤维联系[5]，表明黑质纹状体系统参与疼痛的调控，主要表现为黑质纹状体对疼痛强度的主观感知和对疼痛的情绪反应[6-7]。Anagnostakis等[8]的动物实验显示，大鼠黑质纹状体内注入吗啡具有镇痛作用，且这种镇痛作用可以被纳洛酮逆转，证实黑质纹状体参与疼痛的调控。多巴胺亦参与疼痛的调控，主要于脊髓、丘脑、基底节、扣带回和岛叶等结构进行调控[9]。亦有研究显示，中脑黑质致密部、腹侧被盖区（VTA）和下丘脑等多巴胺聚集区域与疼痛相关通路如中脑皮质通路、中脑边缘系统、黑质纹状体通路和结节漏斗系统均存在广泛联系[10-13]。帕金森病典型病理改变是中脑黑质致密部多巴胺能神经元变性缺失，导致纹状体多巴胺水平降低，因此，多巴胺水平降低可能参与帕金森病疼痛的发病机制。Brefel-Courbon等[14]于“关”期对帕金森病疼痛患者行PET显像，结果显示，疼痛相关区域如右

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侧岛叶、右侧前额叶和左侧前扣带回活动明显增强；予左旋多巴后于“开”期再行PET显像，疼痛相关区域不再处于过度活动状态，表明左旋多巴可以改善帕金森病患者疼痛症状，进一步证实多巴胺参与帕金森病疼痛的调控。Shu等[15]对大鼠纹状体神经元进行研究，发现纹状体内含有脑啡肽、强啡肽和P物质，均与疼痛调控相关，表明黑质纹状体系统中除多巴胺外，上述物质均参与疼痛的调控，然而是否参与帕金森病疼痛的调控，尚待进一步研究。

2. 脑干　疼痛信号首先经内源性痛觉控制系统调控，再从脊髓传入高级疼痛中枢[16]。内源性痛觉控制系统主要由中脑导水管周围灰质、延髓头端腹内侧核（RVM）和部分脑桥背外侧网状结构组成，其轴突经脊髓背外侧束传导伤害性刺激信号而调控疼痛。病理学研究显示，帕金森病患者下行通路中的中脑导水管周围灰质、中缝大核（NRM）、巨细胞网状核等在疾病早期即已变性[17]，表明帕金森病患者内源性痛觉控制系统早期即已损害，其中，中缝大核属延髓头端腹内侧核，是5-羟色胺（5-HT）能神经元，发出的5-羟色胺下行纤维投射至后角，参与疼痛的调控[18]。帕金森病患者予抗抑郁药5-羟色胺和去甲肾上腺素再摄取抑制剂（SNRI）度洛西汀，可以改善疼痛，提示5-羟色胺主要发挥抑制疼痛作用[19]。Tong等[20]的研究显示，帕金森病患者外周血5-羟色胺水平低于正常人群。动物实验显示，5-羟色胺具有镇痛作用，例如，Wei等[21]采用RNA干扰（RNAi）技术处理帕金森病模型大鼠，使延髓头端腹内侧核尤其是中缝大核5-羟色胺水平降低，可以显著改善甲醛溶液诱导的疼痛行为，表明延髓头端腹内侧核5-羟色胺能系统在脊髓后角加重疼痛。因此，帕金森病疼痛是否与延髓头端腹内侧核5-羟色胺能神经元损害有关，尚待进一步研究。蓝斑位于第四脑室底部和脑桥前背部，是合成去甲肾上腺素的主要部位，亦参与疼痛的调控。一方面，蓝斑可以激活脊髓后角神经元突触的肾上腺素受体，继而激活磷酯酶C（PLC）以增加细胞内钙浓度，提高脊髓神经元兴奋性，从而加重疼痛[22]；另一方面，蓝斑可以发出投射纤维至丘脑，进而参与疼痛调控[23]。帕金森病早期蓝斑即出现路易小体变性[24]，提示蓝斑变性可能影响帕金森病患者对疼痛信号的转导和处理。

3. 脊髓　脊髓对疼痛的调控主要位于脊髓后角，来自初级感觉传入纤维末梢，脊髓下行纤维与脊髓后角局部中间神经元共同组成复杂的神经网络；而且，脊髓后角含有丰富的生物活性物质，不仅接受和传递伤害性传入信息，而且对伤害性信息进行加工和处理[25]。病理学研究显示，帕金森病患者不仅存在黑质纹状体系统神经元变性，而且在疾病早期即已发生脊髓后角病理改变[26]。因此，脊髓后角病变可能影响帕金森病患者对疼痛信号的处理，从而导致疼痛。脊髓后角传递疼痛过程中，兴奋性氨基酸（主要是谷氨酸）发挥重要作用，谷氨酸能神经元在脊髓后角激活N-甲基-D-天冬氨酸（NMDA）受体，使突触后膜NMDA受体功能增强，导致神经元敏化[27]。NMDA受体激活进一步引起γ-氨基丁酸（GABA）受体磷酸化，导致GABA受体介导的兴奋性抑制作用减弱[28]，从而引起疼痛。研究显示，帕金森病患者血清谷氨酸水平明显高于正常对照者[29]，表明帕金森病患者对疼痛的敏感程度高于正常人群。此外，谷氨酸作为脑组织主要兴奋性氨基酸，其神经毒性亦参与帕金森病的发生[30]。伤害性退缩反射（NWR）属脊髓反射，伤害性刺激作用于皮肤感受器，经传入纤维传递至脊髓胶状质，经突触与脊髓固有神经元系统的众多中间神经元连接，从而产生疼痛屈肌反射。因此，中缝大核可用于检测脊髓对疼痛的调控[31-32]。Perrotta等[33]发现，与正常对照者相比，帕金森病患者中缝大核疼痛阈值降低，表明帕金森病患者在脊髓平面出现异常的疼痛调控。

4. 神经胶质细胞　既往研究多选择神经元阐述疼痛机制[6-8,13]，而忽略中枢神经系统分布最广泛、数目最多的神经胶质细胞。目前研究显示，神经胶质细胞（主要是星形胶质细胞和小胶质细胞）可以释放细胞因子、炎性介质和神经活性物质，包括疼痛相关活性物质如谷氨酸、ATP等小分子物质，从而参与疼痛信号的转导和调控[34]。胶质纤维酸性蛋白（GFAP）是细胞骨骼蛋白，是星形胶质细胞标志物。各种物理或代谢刺激以及神经损害均可使星形胶质细胞激活并增生，成为反应性星形胶质细胞，升高胶质纤维酸性蛋白水平[35]。离子钙结合蛋白1（Iba1）是小胶质细胞表达的特异性钙结合蛋白，小胶质细胞激活后离子钙结合蛋白1表达上调[36]，因此，可以通过胶质纤维酸性蛋白和离子钙结合蛋白1表达变化判断星形胶质细胞和小胶质细胞活性。研究显示，帕金森病进展过程中不仅有神经元变性，还有星形胶质细胞和小胶质细胞激活[37-39]。

Park等[39]采用1-甲基-4-苯基-1,2,3,6-四氢吡啶(MPTP)诱导损伤建立急性帕金森病疼痛小鼠模型,检测中枢神经系统胶质纤维酸性蛋白和离子钙结合蛋白1表达变化,结果显示,与正常对照组相比,帕金森病疼痛组小鼠丘脑底核(STN)胶质纤维酸性蛋白以及丘脑底核、尾状核和苍白球离子钙结合蛋白1表达上调,提示上述区域神经胶质细胞激活,推测上述区域神经胶质细胞可能参与帕金森病疼痛的调控。丘脑底核脑深部电刺激术(DBS)不仅可以缓解帕金森病运动症状,还可以减轻疼痛症状[40]。晚近研究显示,脑深部电刺激术的作用机制与神经胶质细胞功能密切相关[41]。

二、周围神经系统机制

生理状态下,外周疼痛刺激经外周感受器产生疼痛信号,通过传入纤维传至脊髓;病理状态下,脊髓背角神经节和周围神经系统敏化,使原本无法引起疼痛的低强度刺激即产生疼痛,称为外周敏化。一方面,周围神经系统损害可以引起组胺、缓激肽(BK)、细胞因子、肿瘤坏死因子-α(TNF-α)和白细胞介素(IL)等释放,产生异常自发电位;另一方面,疼痛信号传入C纤维(无髓鞘纤维),引起C纤维与神经元之间突触产生长时程增强(LTP),导致脊髓后角神经元持续激活[42-43]。

帕金森病患者外周感受器和传入纤维均可能参与疼痛的调控。Nolano等[44]对帕金森病患者进行皮肤组织活检术,发现表皮感受器存在退行性变和外周去神经化,亦存在抵抗退行性变而产生的神经芽生现象和血管床。然而,该项研究中帕金森病患者疼痛阈值升高,与既往研究结果相反,例如,Zambito Marsala等[45]和Mylius等[46]发现,与正常对照者相比,帕金森病疼痛患者对电刺激的疼痛耐受性和疼痛阈值降低;Brefel-Courbon等[47]也认为,帕金森病患者冷痛觉阈值降低。上述研究结果相反的原因,可能与各项研究疼痛评价方法或样本量不同有关。因此,外周敏化是否参与帕金森病疼痛的调控尚待进一步研究。亦有研究显示,帕金森病患者外周感受器存在退行性变[48],外周无髓鞘纤维密度减少[49],表明周围感觉神经病变可能参与帕金森病疼痛的发生。

综上所述,帕金森病疼痛的发病机制并非孤立、无联系,而是密切相关的。疼痛极大地影响患者生活质量,因此,研究疼痛发生、发展与维持机制,可以针对性地缓解和有效控制疼痛。然而,目前关于帕金森病疼痛的具体机制尚不明确,进一步探讨其确切发病机制并开展针对性治疗研究,有助于帕金森病患者摆脱疼痛的困扰。

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