·专题综述·

吸烟与帕金森病嗅觉障碍

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【摘要】 帕金森病是临床常见的神经变性病，根据临床症状可以分为运动症状和非运动症状，嗅觉障碍作为帕金森病最常见的非运动症状越来越受到重视。既往研究显示，尼古丁可能降低帕金森病发病风险，而有吸烟史的帕金森病患者嗅觉障碍轻微，因此吸烟可能通过嗅觉系统对帕金森病产生保护作用。吸烟对帕金森病患者嗅觉功能的影响可能有助于我们更全面地了解帕金森病发病过程。

【关键词】 吸烟； 帕金森病； 嗅觉障碍； 综述

Relationship between smoking and olfactory dysfunction in Parkinson´s disease

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【**Abstract**】Parkinson´s disease (PD) is a common neurodegenerative disease. It is characterized by a combination of motor symptoms and non-motor symptoms (NMS) based on clinical symptoms. More and more attention has been drawn to olfactory dysfunction as an early NMS in PD. It is believed that nicotine in cigarettes may lower the risk of getting PD and people with smoking history may have lower risk of olfactory dysfunction. So smoking may have protective effect on PD. The effect of smoking on olfactory function in PD patients may lead us to have a better understanding of the pathogenesis of PD.

【**Key words**】 Smoking; Parkinson disease; Olfaction disorders; Review

This study was supported by the National High Technology Research and Development Program of China (863 Program, No. 2012AA02A514).

帕金森病(PD)是一种渐进性神经变性病，主要病理改变为基底神经节黑质多巴胺能神经元缺失。帕金森病临床症状分为运动症状和非运动症状(NMS)，前者表现为静止性震颤，肌强直，少动和姿势步态异常；后者包括嗅觉减退，自主神经功能紊乱，睡眠障碍，认知功能障碍等[1]。在上述非运动症状中，嗅觉减退可以出现在帕金森病临床前期，有研究显示，在发展为帕金森病的前4年即可出现显著的嗅觉减退[2]，故嗅觉障碍可能是帕金森病临床早期诊断的标记。此为早期预测帕金森病的可能性提供依据。Braak研究团队曾经提出帕金森病病理发展过程最先由鼻黏膜和胃肠系统开始，即神经毒素可能通过上述两个系统由外环境直接进入内环境，引起嗅觉障碍和以便秘为主的胃肠功能障碍[3-4]。因此，研究帕金森病非运动症状发生、发展机制有助于了解基因与环境如何共同作用引起帕金森病的过程[5]，这也是目前越来越多的研究关注环境因素相关帕金森病非运动症状的原因。与帕金森病相关的环境和生活习惯因素众多，有多项研究显示，吸烟可以降低帕金森病发病风险[6-7]，但目前对帕金森病嗅觉障碍与吸烟保护作用之间的关系研究甚少。

一、嗅觉障碍与帕金森病

帕金森病嗅觉障碍于20世纪70年代由Ansari和Johnson[8]通过对22例帕金森病患者进行研究后首次提出，此后Doty等[9]采用美国宾夕法尼亚大学嗅觉识别测验(UPSIT)进一步证实约75%的帕金森病患者存在嗅觉察觉力损害，而90%的帕金森病患者存在嗅觉识别力损害。并且，帕金森病患者的这种嗅觉障碍与疾病进展和严重程度无关联性，也不

doi:10.3969/j.issn.1672-6731.2017.02.004

基金项目：国家高技术研究发展计划(863计划)项目(项目编号：2012AA02A514)

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随抗帕金森病药物的使用而改善[10]。多数研究通过对帕金森病亚型(静止性震颤为主型,肌强直为主型及其他型)分析显示,帕金森病各亚型之间嗅觉障碍并无显著差异[11-12]。Hawkes等[3]和Duda[13]发现,α-突触核蛋白(α-Syn)相关病理改变最早出现于嗅球处,由此提出假说即帕金森病嗅觉障碍是这种病理过程逐渐向脑内进展的过程[3]。当然,有研究显示,这种嗅觉减退可能是由于嗅球处出现病理性损伤,嗅球内神经元减少,嗅球旁多巴胺能神经元代偿性增多导致多巴胺能神经递质增多,而这种神经递质阻碍嗅觉神经冲动传递,从而引起嗅觉减退[13-14]。尽管嗅觉障碍的发生机制尚未阐明,目前研究普遍认为,嗅觉减退是发生在帕金森病运动症状前的非运动症状,且国际运动障碍学会(MDS)从2015年开始将嗅觉减退纳入帕金森病支持诊断标准,突出嗅觉减退对帕金森病诊断的重要性[15]。

二、吸烟与帕金森病

据统计,有超过60项流行病学调查研究均提示吸烟可以降低帕金森病发病风险[16-17]。其中一项纳入300×10^3例受试者的流行病学调查研究显示,在具有相同吸烟强度的人群中,烟龄与帕金森病发病风险呈负相关,且烟龄越久、帕金森病发病风险降低越明显,但在相同烟龄人群中,日吸烟量与帕金森病发病风险无关联性[18]。不可否认,吸烟给人体带来很多负面影响,增加心脑血管病和肺部恶性肿瘤等的发病风险,但是由于上述诸多流行病学研究提示吸烟可能具有神经保护作用,这为随后的相关机制研究提供研究背景。现有研究主要认为尼古丁可能是神经保护和降低帕金森病发病风险的重要因素[19]。Morens等[20]曾试图解释尼古丁对帕金森病的保护机制,即尼古丁可以刺激多巴胺能神经递质释放,通过一氧化碳阻止自由基损伤黑质神经元,同时抑制单胺氧化酶B(MAO-B)或通过竞争性抑制神经毒素以保护神经元。在动物模型中也可以观察到尼古丁减缓黑质纹状体的损害进展[21],但在针对帕金森病患者的临床实验中,尼古丁皮贴或口香糖均无法缓解帕金森病症状,因此尼古丁也许并不能单独发挥神经保护作用[21-23]。纵向研究显示,吸烟的帕金森病患者与非吸烟的帕金森病患者在运动症状进展与病死率方面无显著差异[24-27],提示对于明确诊断的帕金森病患者,吸烟并不能起保护作用,但是有研究显示,吸烟人群帕金森病发病年龄高于非吸烟人群[28]。因此认为,尼古丁对帕金森病患者的影响可能在发病前即已存在,并且是缓慢影响过程,这也可能是明确诊断为帕金森病的患者再次使用尼古丁制剂治疗效果不明显的原因[29]。

三、吸烟对帕金森病患者嗅觉的影响

尽管针对帕金森病患者嗅觉障碍的相关研究已进行近40年,但关于吸烟对帕金森病患者嗅觉影响的研究却较少。帕金森病患者UPSIT评分较低。但近期一项研究显示,有吸烟史的帕金森病患者UPSIT评分优于非吸烟的帕金森病患者,而在正常对照组中却未观察到类似现象,研究者猜测吸烟可能对帕金森病患者的嗅觉功能具有保护作用[29]。另一项研究也发现吸烟人群中帕金森病患者与正常对照者UPSIT评分无显著差异,而帕金森病患者中吸烟人群UPSIT评分显著优于非吸烟和既往吸烟者[30]。这一结果并不受吸烟习惯如是否戒烟、戒烟时间长短、吸烟量和帕金森病药物治疗的影响。大多数研究显示,吸烟可引起正常人群嗅觉障碍[31-32],Moccia等[33]的横断面研究显示,正常人群中吸烟者UPSIT评分显著低于非吸烟者,但是这一现象并未出现在帕金森病患者中,因此他们认为,帕金森病患者嗅觉障碍可能受帕金森病与吸烟的共同影响。另有针对毒气引起嗅觉障碍的研究显示,非吸烟者出现嗅觉障碍的风险相对增加,尽管其发生机制尚不清楚,但吸烟可能对嗅觉功能存在某种保护作用[34-35]。基于Braak等[36]对帕金森病病理进展过程的解释,吸烟降低帕金森病发病风险可能是由于吸烟损害嗅黏膜,导致外环境毒素较少通过嗅觉系统进入中枢。有研究显示,尼古丁成分可影响胆碱能系统,而胆碱能系统能够辅助嗅觉的气味察觉功能[37-39]。其他研究则提出尼古丁可以增加嗅球处血流量从而减少自由基对嗅球的损害[40]。Rothermel等[41]认为,尼古丁可以上调或直接刺激基底前脑突触前尼古丁受体,而此区域与嗅觉有关,推测尼古丁可以使受损嗅皮质功能增强。在阿尔茨海默病(AD)动物模型研究中发现,尼古丁可以减少嗅束淀粉样变性[42]。将胆碱能受体阻断剂注入小鼠嗅球,嗅觉辨别功能增强,而阻断嗅球处尼古丁受体时,嗅觉功能减退[10]。但Bryant等[43]认为,尼古丁并未直接通过尼古丁-胆碱能受体作用于嗅觉系统,而是通过cAMP介导的嗅觉感受器通路激活嗅觉神经元。因此,对于尼古丁如何影响嗅觉功能的作用机制尚待进一步研究。流行病学研究显示,戒烟困难的人群相对于戒烟容易的人群,帕金森病发病风险

降低约31%[44]。研究者认为这种吸烟行为的改变可能是并列于其他非运动症状如嗅觉减退、便秘、睡眠障碍等[45]的另一种帕金森病临床前期非运动症状。但是吸烟行为中仍有许多不确定因素，如吸烟强度不能仅考虑数包或数只香烟而忽略每种香烟的尼古丁含量，开始吸烟年龄、烟龄、戒烟年龄和戒断时间，研究对象是否携带帕金森病风险基因，吸烟人群所占研究队列中的比例等因素，均有可能影响研究结果。因此，尚不能确定吸烟对帕金森病的嗅觉功能具有保护作用。

四、结语

上述研究阐述吸烟与帕金森病嗅觉障碍的关系。嗅觉障碍作为帕金森病较为明确的临床前期症状，受多种外环境因素的影响，而吸烟作为流行病学研究发现的可能降低帕金森病发病风险的因素之一，很可能通过嗅觉系统降低帕金森病发病风险。因此在帕金森病患者中，吸烟与嗅觉系统的相互作用也越来越受到关注。通过吸烟与嗅觉和帕金森病的相关研究，可以更全面地了解帕金森病发病过程，嗅觉障碍发生机制以及如何利用香烟中的成分对帕金森病临床前期进行保护性干预。

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（收稿日期：2016-10-30）

Behavioral Neurobiology of Huntington´s Disease and Parkinson´s Disease published

Behavioral Neurobiology of Huntington´s Disease and Parkinson´s Disease (ISBN: 978-3-662-46343-7, eBook ISBN: 978-3-662-46344-4) was published by Springer - Verlag Berlin Heidelberg in May 2015. The editors of this book are Hoa Huu Phuc Nguyen (Institute of Medical Genetics and Applied Genomics, University of Tuebingen) and M. Angela Cenci (Department of Experimental Medical Science, Lund University).

Motor dysfunction and cognitive impairment are major symptoms in both Huntington´s disease (HD) and Parkinson´s disease (PD). A breakthrough in HD research was the identification of the gene that causes this devastating monogenetic illness. Similarly, several genes were found to cause familial forms of PD. With their identification, a plethora of genetic animal models has been generated and has revolutionized the understanding of the pathobiology and pathophysiology of these disorders. The models allow us to study the earliest manifestations of the diseases behaviorally and neuropathologically and help us understand how they progress over time. Additionally, neurotoxic animal models are still of high interest to the PD field, as they are being used to study e.g. mitochondrial dysfunction in PD. This book focuses on animal models of both diseases and how they have helped and will continue to help understand the behavioral neurobiology in these disorders.

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