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无创迷走神经刺激在帕金森病中的研究进展

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摘　要

帕金森病(Parkinson's disease, PD)是一种常见的神经系统疾病，其具有多种运动性和非运动性症状特征。药物治疗是现在治疗PD的主要方法，但常常也带来一些严重的副作用。因此，探究新的治疗方法，为治疗PD添砖加瓦是必要的。迷走神经刺激是一种新兴的神经调控技术，具有抗炎、神经保护的作用，这为PD的治疗提供了新思路。本综述总结了目前国内外迷走神经刺激在PD中的研究，其中重点放在了PD步态障碍的研究上。迷走神经具有改善冻结步态的作用，此外对PD病人的认知功能、吞咽功能、焦虑抑郁、胃肠道功能有潜在的治疗作用。

关键词

帕金森病，迷走神经刺激，冻结步态

Research and Progress of Noninvasive Vagus Nerve Stimulation in Parkinson's Disease

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Abstract

Parkinson's disease is a common neurological disorder with a variety of motor and non-motor symptoms. Drug therapy is the main treatment for Parkinson's disease, but it often comes with some serious side effects. Therefore, it is necessary to explore new therapeutic methods for the treatment of Parkinson's disease. Vagus nerve stimulation is a new neuroregulatory technique with anti-inflammatory and neuroprotective effects, which provides a new idea for the treatment of Parkinson's disease. This review summarizes the current research on vagus nerve stimulation in Parkinson's disease at home and abroad, and focuses on gait disorders in Parkinson's disease. Vagus nerve can improve frozen gait, and has potential therapeutic effect on cognitive function, swallowing function, anxiety and depression, gastrointestinal function in patients with Parkinson's disease.

Keywords

Parkinson's Disease, Vagus Nerve Stimulation, Freezing of Gait

1. 引言

帕金森病(Parkinson's disease, PD)是一种可识别的临床综合征，具有多种原因和临床表现[1]，是一种常见的神经退行性疾病[2]。在 65 岁以上的人群中患病率大约为 1/600 [3]。它是由遗传因素、环境因素和衰老所引起的[4]。其病理特征是黑质(Substantia Nigra, SN)致密部中的多巴胺能神经元逐渐丧失，以及 α-突触核蛋白的大量沉积[5]。PD 常具有运动性和非运动性功能障碍。PD 通常被描述为具有四种主要症状的运动系统疾病：运动迟缓，肌强直(四肢和躯干的僵硬)，姿势不稳(平衡和协调受损)和静止性震颤(手、手臂、腿和面部颤抖) [6]。非运动功能障碍最典型的表现：嗅觉减退、便秘、睡眠障碍和情绪障碍[7]。90%以上的患者存在嗅觉减退，且多发生在运动症状之前。60%~90%的患者伴有睡眠障碍[8]。PD 给患者的日常生活带来很大的困扰。举例来说，步态障碍会增加平衡问题并导致跌倒；肢体语言和面部表情的丧失，可能导致患者焦虑抑郁[9]。

PD 的治疗原则是综合治疗，多学科团队参与和长期的管理。治疗包括药物方法(通常使用左旋多巴制剂，联合或不联合其他药物)和非药物方法(如运动、职业、手术和言语) [10]。对左旋多巴治疗的积极反应是 PD 领域治疗和诊断的金标准[11]，但长期使用通常与运动并发症(消退和运动障碍的总患病率分别为 46.5%，10.3%) [12]的发展相关。对于以运动症状特别严重且药物疗效不佳的 PD 患者，可以选择深部脑刺激(Deep Brain Stimulation, DBS)的手术干预。虽然 DBS 可以改善运动症状是公认的，但术后 DBS 随访研究揭示了认知的不同情况，其中可能包括语言流利度，处理速度，工作记忆和执行功能任务的表现下降[13]。虽然药物干预是 PD 的主要治疗方法，但这种方法具有不必要的副作用[14]。因此，我们需要增强我们的疾病治疗的工具库。

2. 迷走神经的解剖及功能

迷走神经起源于脑干延髓的一系列小根，通过颈静脉孔离开颅骨[15]，后进入颈动脉鞘，沿着颈总动脉或颈内动脉和颈内静脉之间的后沟到达颈部根部，然后进入胸腔和腹部。颈部的传入神经纤维约占其80%，大多数向颈迷走神经提供传入纤维的神经元的细胞体位于上(颈静脉)迷走神经节和较大的下(结节)迷走神经节，它们位于颈静脉孔的正下方[16]。一小群迷走体感传入神经携带来自耳上和耳旁皮肤的感觉信息，迷走神经的耳支是它在体表的唯一传入支[17]。

迷走神经传入神经在孤束中穿过脑干，终末突触主要位于迷走神经延髓背侧复合体的核内[18] [19]。大多数迷走神经传入突触位于延髓的孤束核(Nucleus Tractus Solitarius, NTS)、三叉神经脊束核、延髓内侧网状结构、极后区、迷走神经背侧运动核、疑核[20]。在这些结构中，NTS 接受的迷走神经传入突触数量最多[21]，每条迷走神经在 NTS 上都有双侧突触。迷走神经传入通过 NTS 投射到脑和脊髓的去甲肾上腺素能和 5-羟色胺能神经调节系统[16]。NTS 向蓝斑核(Locus Coeruleus, LC)投射[22]，LC 是大脑皮层中去甲肾上腺素的主要来源[23]。电生理学研究表明，迷走神经刺激首先引起 LC 放电增加，从而导致去甲肾上腺素的释放。其次去甲肾上腺素刺激中缝背核中的 A1-肾上腺素能受体，导致 5-羟色胺(5-hydroxytryptamine, 5-HT)的释放[24] [25]。去甲肾上腺素和 5-羟色胺在许多大脑生理和病理过程中起着关键作用。研究表明，去甲肾上腺素通过减少氧化应激提供神经保护[26]，为神经元提供神经营养支持[27]，抑制谷氨酸释放[28]，限制神经炎性激活的发展[29]，并维持海马神经发生[30]。5-羟色胺被发现可以抑制兴奋性毒性[31]，并调节成人海马神经发生[32]。Kakeru Hosomoto [33]的研究发现，传入迷走神经通路在迷走神经刺激(Vagus Nerve Stimulation, VNS)治疗 PD 中起重要作用。

乙酰胆碱(Acetylcholine, ACH)是一种神经递质和神经调节剂，对认知、感觉及运动功能的调控十分重要[34]。中枢胆碱能网络(涉及内侧前额叶皮质、前扣带回皮质、岛叶皮质、室旁核、杏仁中央核和下丘脑外侧区)通过中脑导水管周围灰质，通过桥脑的臂旁核向延髓核(包括 NTS、疑核和延髓腹外侧核)发送信号。ACH 通过中枢神经系统中的两种受体发挥作用，即嗜电性烟碱 N 受体和嗜代谢性 M 受体[35]。中枢胆碱能系统的主要输出途径是迷走神经和星状神经节[36]。这与 Pavlov 等人的发现一致，即脑室内注射选择性毒蕈碱激动剂可激活外周胆碱能抗炎通路，从而减少内毒素血症中肿瘤坏死因子-α 的产生[37]。胆碱能抗炎通路是炎症反射的产物，炎症反射的传入臂感知组织损伤，并通过传入迷走神经向大脑发送信号。传出臂由传出迷走神经信号组成，通过 ACH 与巨噬细胞上表达的 nAChRα7 结合，减少细胞因子的表达[38]。

3. 迷走神经刺激

迷走神经刺激是一种神经调控技术[39]，包括植入式迷走神经刺激(implantable vagus nerve stimulation, iVNS)及非侵袭性迷走神经刺激(noninvasive vagus nerve stimulation, nVNS)。iVNS 通过缠绕在迷走神经上的导线发送间歇性电流。由于右侧迷走神经与心脏的联系更大，一般刺激左侧迷走神经。但它可能导致感染、迷走神经损伤、气管周围血肿、声带损伤和迷走神经损伤引起的呼吸短促(呼吸困难)。目前市面上有两种类型的 nVNS 设备。一种是经皮耳穴 VNS (transccutaneous auricular VNS, taVNS)用于刺激外耳结构，如耳屏和耳锥，这些结构受迷走神经耳支支配[40]。另一种是经皮颈迷走神经刺激(tcVNS)是通过手持装置进行的，同时间接刺激颈动脉鞘内的迷走神经颈支。iVNS 已被美国食品和药物管理局批准作为抗药癫痫[41]和治疗难治性抑郁症患者的辅助治疗[42]；iVNS 也被欧洲药品管理局批准用于后者。VNS 在预防和改善神经退行性和神经精神疾病症状方面的疗效已经引起了多个临床领域的关注。

4. 迷走神经刺激可缓解 PD 患者步态障碍

步态冻结(Freezing of Gait, FoG)被定义为：企图行走时或前进过程中步伐短暂、突然中止或明显减少[43]。冻结步态影响了大约 26%的轻度 PD 患者和 80%的重度 PD 患者，它是跌倒和依赖的最常见原因之一，并且对左旋多巴反应性不佳[44] [45]。常出现在 PD 后期[46] [47]。造成 FoG 的机制目前尚未明确，大脑功能障碍与自我启动运动的关系，可能是 FoG 相关的一个因素。Bartels 和 Leenders 汇集了来自脑功能成像的最新发现，以强调额叶基底节连接功能障碍可能是造成 FoG 的病理生理学基础[48]。从步态分析的角度，正在进行的步态干扰可能与 FoG 的发生有关。严重的运动不足和运动不稳定构成了一些潜在的运动障碍。步态的节律性、对称性和两侧协调性的异常也可能是诱因，甚至与 FoG 有因果关系[43]。它可能是由 PD 以外的疾病引起的，包括与移动性相互作用的认知领域的功能障碍[49]。PD 患者的认知缺陷和步态障碍可能部分由胆碱能神经传递[50] [51] [52]以及黑质纹状体多巴胺通路的神经变性所致[53]。最近的证据表明，c 型全能变性也可能与步态功能障碍和姿势不稳有关。基底前脑(Meynert 的基底核)和脑干(蒂丘脑核)的 Euronal 胆碱能缺失导致步态障碍[54]。

4.1. 动物实验

最近的研究表明，VNS 可以改善 PD 大鼠模型的运动能力。主要指标表现在 VNS 刺激后显著逆转 PD 大鼠模型在光束行走任务中受损的表现以及增加它的总行程。有研究[11] [55] [56]表明耳迷走神经刺激(auricular vagus nerve stimulation, aVNS)后，在对大鼠模型的黑质进行了 TH 免疫组织化学染色时，发现 aVNS 处理增加了 6-羟色胺(6-hydroxydopamine, 6-OHDA)损毁的 SN 中 TH 阳性细胞的数量，这表明 aVNS 对 6-OHDA 处理的大鼠多巴胺能神经元具有保护作用。此外，他们还发现迷走神经刺激可以显著下调大鼠腹侧中脑炎性细胞因子(肿瘤坏死因子-α 和白介素 1-β)的表达和抑制胶质纤维酸性蛋白阳性细胞总数，这些结果表明，VNS 减轻了损伤大鼠的炎症反应，炎症的减少可能有助于神经元和行为的改善。迷走神经还具有调节 α 阳性神经元内突触核蛋白密度的潜力。迷走神经刺激可以上调脑源性神经营养因子(brain-derived neurotrophic factor, BDNF) [57] [58]。BDNF 是一种神经营养因子，对神经元的存活和维持非常重要，包括多巴胺和去甲肾上腺素细胞群[59] [60]。BDNF 与其受体原肌球蛋白受体激酶 B (TrkB)结合，导致受体细胞内酪氨酸激酶结构域上几个位点的自动磷酸化。然后，磷酸化的 TrkB 受体复合体通过丝裂原激活的蛋白激酶、磷酸肌醇-3-激酶/蛋白激酶 B 和磷脂酶-C-γ 通路激活促生存信号，从而诱导神经保护[61]。BDNF 的增加是 VNS 的一个重要作用机制，它可以减少神经炎症，促进 LC-NE 和黑质纹状体系统中神经元的存活。一项研究[62]在 PD 模型中，通过给予 TrkB 特异性拮抗剂 ANA-12 阻断 BDNF-TrkB，证明了迷走神经对黑质 TH 阳性神经元的黑质纹状体效应、黑质 DA 神经元中 α-突触核蛋白的积聚以及黑质纹状体炎症是依赖于 BDNF 的。然而，ANA-12 仅部分减少了 LC 内的 TH 阳性神经元，并不影响 VNS 后的运动活动，提示 BDNF 不是 VNS 的唯一作用机制。

此外，VNS 的神经保护和抗炎作用与其刺激的参数相关。Ittetsu Kin [63]在研究中发现 0.25 mA，0.5 mA VNS 组中大鼠的 NA 神经元的密度显著增加，纹状体 TH 阳性纤维密度显著保留及离子钙结合衔接分子 1 阳性小胶质细胞的数量显著减少，在纹状体和黑质致密部中均显示出对胶质纤维酸性蛋白阳性细胞的显著抑制。轻度至中度强度的 VNS 更具抗炎和神经保护作用。Ariana Q. Farrand [64]研究发现高频 VNS 对大鼠的运动明显提高，对 LC-NE 损失的衰减最大。这表明更高的刺激频率，对 PD 进展的标志物影响最大。

4.2. 临床研究

目前已经有迷走神经刺激对 PD 冻结步态的初步临床研究。一项研究中[65]，招募了 30 名 PD 患者，给予左颈部单次 120 s nVNS，在干预前后 1 小时采集数据，他们发现实验组的步长变异性减少。Banashree

Monda [66]招募了 19 名 PD 相关步态障碍患者，给予左颈部 nVNS，每次治疗 120 秒，共行 2 次 nVNS 治疗，间隔 15 分钟。治疗前后 15 分钟采集数据，他们发现 nVNS 后二维时空步态参数发生显著变化，包括步数、速度、步长和步幅速度变异性。FoG 患者的视频分析显示，转弯时间、转弯步骤和启动犹豫步骤均有改善。唯一显示显著改善的参数是转弯时采取的步数。他们在另一项 36 名 PD 患者的研究[67]中他们发现，nVNS 除了能够改善患者的步态参数和临床量表评分外，在对血生化分析时，nVNS 还能够降低患者的肿瘤坏死因子-α 水平，升高还原型谷胱甘肽浓度，上调 BDNF。Massimo Marano 的研究[68]首次评估了 aVNS 对 FoG 的影响，他们的结论与之前的研究相似，步幅、摆动幅度、步态速度和步态时间仅在 aVNS 后有显著变化。PD 患者在正常行走时左背外侧前额叶皮层、运动前区、辅助运动区、初级运动皮层和初级躯体感觉皮层的 HbO_2 的相对变化高于对照组[69]。一项前瞻性随机对照研究[69]发现经 taVNS 治疗后 PD 患者正常行走时初级体感皮层血流动力学反应明显降低，这可能与步态障碍的改善有关。Vanessa K. Hinson 的研究[70]对 aVNS 的安全性及耐受性进行了研究，包括监测参与者报告的不良事件、MDS UPDRS 第三部分检查、认知测试和哥伦比亚自杀严重程度评定量表(Columbia-Suicide Severity Rating Scale, C-SSRS)。在刺激前、刺激后 10 分钟和刺激后 50 分钟监测生命体征(心率和血压)。他们发现在研究及随访期间刺激组最常见的轻微不良事件是失眠，假刺激组是头晕，无严重的不良事件。根据 C-SSRS 的监测，没有证据表明出现自杀倾向。在整个研究过程中监测生命体征并保持稳定，血压和心率的变化在刺激组与假刺激组之间无统计学意义。因此，他们认为 aVNS 对于轻度至中度 PD 患者是一种可行、耐受性良好且安全的神经调节方法。

5. 迷走神经刺激在焦虑抑郁中的作用

PD 患者比普通人群更容易出现神经精神症状,其中焦虑、抑郁症特别常见[71]，它对 PD 患者的日常活动能力有很大影响[72] [73]。抑郁症可以早于 PD 的运动症状长达几年[71]，这表明精神症状也是由 PD 本身的病理生理调节的。其潜在机制可能是与抑郁有关的大脑区域的变化，去甲肾上腺素和 5-羟色胺水平以及 BDNF 水平的增加，这可能反过来减少与抑郁障碍相关的神经元丢失[74] [75]。已有研究表明 VNS 在减轻抑郁症状方面有效[76] [77] [78]。同样，也有研究显示 VNS 在改善焦虑方面可能都是有益的[79] [80]。到目前为止，还不清楚这些结果是否能在 PD 患者中实现，但 VNS 已被批准用于难治性抑郁症，有证据表明 VNS 有助于抑郁症的治疗[81]。

6. 迷走神经刺激对胃肠道的作用

多数的 PD 患者都会出现各种胃肠道症状，例如便秘、胃轻瘫、恶心、及腹胀等。其中便秘可能早于 PD 运动症状很多年出现[82]。目前认为 PD 相关的便秘可能是由于肠神经系统(enteric nervous system ENS)神经元的局部变化引起的，例如聚集的 α-突触核蛋白的积累[83] [84]。另一方面，PD 患者的便秘可能与继发于黑质纹状体神经元变性的中枢多巴胺能张力丧失有关，黑质纹状体神经元是 PD 的主要神经病理改变[85] [86] [87]。目前尚不清楚脑－肠轴串扰的这种改变如何发生，迷走神经背侧运动核可能发挥核心作用，其广泛地支配 ENS 丛，涉及 PD 的神经变性过程，并且对多巴胺介导的调节敏感[88] [89] [90]。此外，有两项研究表明[91] [92]，nVNS 对非 PD 人群的胃轻瘫有有益的影响。这两项研究都要求参与者依次对左侧和右侧迷走神经进行 tcVNS，至少持续 3~4 周。这两项研究都报告了参与者的胃瘫主要症状有所改善。

7. 其他

PD 痴呆(Parkinson’s disease dementia, PDD)的发展是 PD 常见的一种并发症，累积发病率接近 80% [93] [94]。PD 患者的轻度认知障碍可能是 PDD 的前驱阶段，可出现高达 40% [95]。虽然迷走神经刺激后

的认知功能增强还没有在 PD/PDD 中被评估，但它在阿尔茨海默病(Alzheimer's Disease, AD)中的应用已经取得了一些成功[96] [97] [98]。一项最初的先导研究[97]招募了 10 名接受植入式 VNS (implantable vagus nerve stimulation, iVNS)治疗的 AD 患者，为期 10 周。在 3 个月的随访中，分别有 7/10 和 9/10 的患者在阿尔茨海默病评定量表和简易智力状态检查的认知子集上获得改善。这些结果大多维持在 6 个月内，7/10 的患者在两个量表上的得分仍然较高。后来，又有 7 名 AD 参与者加入到样本中，并进行了为期 1 年的跟踪调查[98]。植入后 1 年，阿尔茨海默病评定量表(7/17 例)和简易智力状态检查(12/17 例)评分持续改善。该治疗耐受性良好，不良反应极小，在研究期间没有报告生活质量或情绪下降。虽然这项初步工作表明 iVNS 可以改善 AD 的认知功能，但证据基础很少，而且受试者人数少和缺乏对照组的限制。

PD 吞咽障碍是常见的非运动症状，可发生在病程的任何时期，发生率高达 82% [99]，但是其主观评估发生率仅为 35%，隐性吞咽障碍所占比例较高。随着疾病加重，隐性吞咽障碍进展为显性吞咽障碍，严重吞咽障碍增加吸入性肺炎风险，甚至出现窒息死亡，这是 PD 患者预后不良的主要因素之一[100]。目前暂无迷走神经刺激对 PD 患者吞咽功能障碍的研究，但有一项研究显示在脑卒中伴有吞咽功能障碍的患者中，aVNS 治疗 3 周后，aVNS 组患者唾液评分、舌动评分、舌力评分、咳嗽反射评分、软腭评分均显著高于对照组。这表明在常规康复训练的基础上进行 aVNS 治疗更有利于脑卒中吞咽困难患者吞咽功能的改善。基于以前的研究，笔者认为迷走神经刺激配合康复训练在伴有吞咽障碍的 PD 患者中具有极大研究价值。

8. 结论

VNS 具有增强胆碱能传递，减少神经炎症，升高 BNDF 和增强去甲肾上腺素释放，有神经保护作用，具有改善步态和认知功能的潜力，此外其对胃肠道功能、焦虑抑郁、吞咽障碍有潜在的治疗作用。因我们认为，迷走神经是 PD 的一种潜在的非药物干预。

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