

Research progresses of PET molecular imaging for Parkinson disease complicated with levodopa-induced dyskinesia

LI Shuang^{1,2}, SONG Tianbin^{1,3}, YANG Chang^{1,3}, WANG Jingjuan^{1,3}, ZHANG Chun^{1,3}, LU Jie^{1,3*}

(1. Department of Radiology and Nuclear Medicine, Xuanwu Hospital, Capital Medical University, Beijing 100053, China; 2. Department of Nuclear Medicine, Xiangyang No. 1 Peoples Hospital Affiliated to Hubei University of Medicine, Xiangyang 441000, China; 3. Beijing Key Laboratory of Magnetic Resonance Imaging Brain and Brain Informatics, Beijing 100053, China)

[Abstract] Levodopa is the standard therapy for Parkinson disease (PD), however, with the progression of the disease and long-term treatment, levodopa-induced dyskinesia (LID) can occur, greatly reducing the quality of patients' life. PET brain molecular imaging can detect the uptake and distribution of imaging agents at the molecular level *in vivo*, thereby reflecting the brain function and metabolism of patients with PD complicated with LID, which is helpful for early clinical diagnosis and treatment. The research progresses of PET molecular imaging for PD complicated with LID were reviewed in this article.

[Keywords] Parkinson disease; brain; levodopa; positron-emission tomography

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PET 分子成像用于帕金森病伴左旋多巴诱导异动症研究进展

李 霜^{1,2}, 宋天彬^{1,3}, 杨 畅^{1,3}, 王静娟^{1,3}, 张 春^{1,3}, 卢 洁^{1,3*}

(1. 首都医科大学宣武医院放射与核医学科, 北京 100053; 2. 湖北医药学院附属襄阳市第一人民医院核医学科, 湖北 襄阳 441000; 3. 磁共振成像脑信息学北京市重点实验室, 北京 100053)

[摘要] 左旋多巴是治疗帕金森病(PD)的标准方法;但随疾病进展和长期治疗,可产生左旋多巴诱导的异动症(LID),极大降低患者生活质量。PET 脑分子成像可活体检测显像剂在分子水平的摄取分布情况,从而反映 PD 伴 LID 患者脑功能及代谢,有助于临床早诊断及早治疗。本文就 PET 分子成像用于 PD 伴 LID 的研究进展进行综述。

[关键词] 帕金森病; 脑; 左旋多巴; 正电子发射断层显像

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帕金森病(Parkinson disease, PD)是黑质致密部(substantia nigra pars compacta, SNpc)中多巴胺能神经元进行性丧失导致的与年龄相关的神经退行性疾病

病^[1-3]。左旋多巴是治疗 PD 最有效的对症药物^[4],能从根本上恢复纹状体突触多巴胺水平,对运动功能至关重要;然而,长期使用可导致异常不自主运动

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[第一作者] 李霜(1989—),女,湖北襄阳人,在读博士,主治医师。研究方向:帕金森综合征的多模态影像学诊断。E-mail: 28463445@qq.com

[通信作者] 卢洁,首都医科大学宣武医院放射科与核医学科,100053;磁共振成像脑信息学北京市重点实验室,100053。

E-mail: imaginglu@hotmail.com

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(abnormal involuntary movement, AIM), 即左旋多巴诱导异动症 (levodopa-induced dyskinesia, LID)^[5-6], 主要表现包括舞蹈症、肌张力障碍、颤搐、肌阵挛等运动障碍。约 30% PD 患者于左旋多巴治疗 3 年后可出现 LID, 而整个治疗过程中约 80% 可出现 LID^[7]; 其发生率与发病年龄、病程、疾病严重程度和左旋多巴治疗时间有关^[8-10]。分子成像技术可在分子水平上识别脑功能活动的微小变化; PET 脑成像结合靶向分子探针可活体检测显像剂在分子水平的摄取分布情况, 从而可视化反映脑功能及代谢改变, 可用于早期诊断 PD 伴 LID、评估疾病严重程度及监测进展。本文就 PET 分子成像用于 PD 伴 LID 的研究进展进行综述。

1 PD 伴 LID 机制

PD 伴 LID 机制与基底神经节网络功能改变有关, 主要为长期应用左旋多巴导致多巴胺神经元调节直接通路和间接通路失衡^[11-12]。直接和间接通路是基底神经节中的 2 条重要通路; 释放到突触间隙的多巴胺可通过 D1 受体激活内侧苍白球 (globus pallidus internal, GPi) 和黑质网状部 (substantia nigra pars reticulata, SNPr) 的直接通路, 并通过 D2 受体抑制外侧苍白球 (globus pallidus external, GPe) 的间接通路。PD 患者 SNpc 神经元退行性变导致纹状体多巴胺稳态被破坏, 使投射到 GPe 的间接通路活性增加, 直接通路活性降低, 从而导致输出核 (GPi/SNPr) 过度激活, 丘脑-皮质神经元过度抑制, 造成运动功能减退; 而长期外源性补充左旋多巴可促进直接通路过度激活, 导致对输出核 (GPi/SNPr) 的抑制增加, 从而造成丘脑皮层神经元异常激活, 使不自主运动增加^[13-14] (图 1)。

2 PET 分子成像

2.1 ¹⁸F-FDG PET 成像 ¹⁸F-FDG 是目前应用最广泛的脑显像剂, 可于细胞水平准确检测脑葡萄糖代谢水平, 反映神经元活性^[15-17]。有研究^[18]建立单侧纹状体病变 PD 大鼠模型, ¹⁸F-FDG PET 示 non-LID 组运动区 (小脑、脑干和中脑运动区) 代谢亢进, 皮质区代谢减退; 与之相比, LID 组患侧小脑、中缝核和脑干区域葡萄糖代谢显著增高, 纹状体和前额叶皮层代谢明显减低, 其纹状体代谢减低可能与内源性多巴胺对抑制性 D2 受体的亲和力高于激活性 D1 受体有关。

PD 患者、特别是 PD 伴 LID 患者接受左旋多巴治疗时, 可见脑血流量增加, 壳核等关键皮层下区域的大脑代谢率降低。文献^[19]对 10 例 PD 患者 (其中 5 例伴 LID) 行 ¹⁸F-FDG PET 和灌注相 MR 扫描, 结果显示, 以壳核高灌注/低代谢指标诊断 LID 的敏感度为 80%、特异度为 80%, 即其可作为诊断 LID 的潜在生物标志物。

2.2 ¹⁸F-二羟苯丙氨酸 (dihydroxyphenylalanine, DOPA) PET 成像 ¹⁸F-DOPA PET 成像可评估黑质纹状体氨基酸脱羧酶于催化反应下生成多巴胺的能力^[20-21]。PD 伴 LID 患者出现运动症状之前, 壳核中部分多巴胺能末梢已死亡。文献^[22]对 31 例 PD 患者行 ¹⁸F-DOPA PET 脑成像, 并采用定量分析技术测量 ¹⁸F-DOPA 有效分布体积比 (effective distribution volume ratio, EDVR); 结果显示, 平均 6.8 年随访期间, 35.48% (11/31) 患者出现 LID; 与未出现 LID 者相比, LID 患者基线壳核 EDVR 显著减低; 且 Kaplan-Meier 生存曲线显示, 相比基线壳核 EDVR 较高的 PD 患者, EDVR 较低者生存率更低。有研究^[23]分析 9 例 PD 伴 LID 患者 ¹⁸F-DOPA PET 脑成像数据, 结果显示

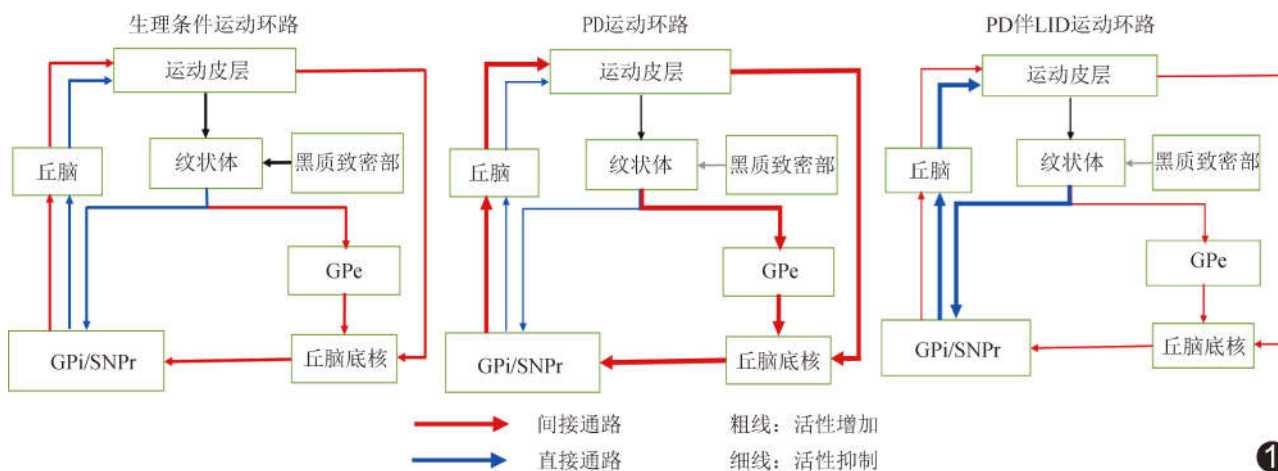


图 1 直接 (蓝色) 和间接 (红色) 基底神经节运动通路作用示意图

LID 程度和病程均与 Hoehn-Yahr (H-Y) 分期、统一 PD 评分量表 (unified PD rating scale, UPDRS) 评分呈正相关, 与壳核部¹⁸F-DOPA 摄取呈负相关; 且苍白球内侧¹⁸F-DOPA 摄取随 LID 进展逐渐降低, 表明苍白球内侧多巴胺储存和功能丧失与 LID 进展有关^[24]。

2.3 多巴胺转运体 (dopamine transporter, DAT) 分子显像 常用 DAT PET 靶向显像剂主要包括¹¹C-哌甲酯 (¹¹C-methylphenidate, ¹¹C-MP)、¹¹C-2β-甲氧甲酰-3β-(4-氟苯基)托烷 [¹¹C-labeled 2β-carbomethoxy-3β-(4-fluorophenyl) tropane, ¹¹C-CFT] 和¹⁸F-N-3-氟代丙基-2-β-羧甲氧基-3β-(4-碘苯基)降托烷 [¹⁸F-N-3-fluoropropyl-2-beta-carboxymethoxy-3-beta-(4-iodophenyl)nortropane, ¹⁸F-FP-CIT], 其中临床应用最广的是¹⁸F-FP-CIT^[25-26]。文献^[27]对 421 例首次接受左旋多巴治疗的 PD 患者行¹⁸F-FP-CIT PET 脑成像, 2 年随访结果显示 65 例出现 LID; 其中, 早发型 LID 后壳核 DAT 活性显著低于晚发型, 且其 DAT 活性减低与出现 LID 较早显著相关。有研究^[28]分析 634 例 PD 患者¹⁸F-FP-CIT PET 脑成像数据, 采用定量分析技术测量每个纹状体亚区多巴胺转运蛋白含量, 并计算多巴胺丢失程度与后壳核多巴胺比值 [即亚区比值 (inter-subregional ratio, ISR)]; 结果显示 ISR 较高与 LID 发生较早相关, 且中-重度突触前多巴胺能末端丢失可诱导多巴胺不受控制地释放。亦有研究^[29]分析 127 例 PD 患者¹⁸F-FP-CIT PET 脑成像数据发现, 平均 3.4 年的随访期间, 其中 35 例发生 LID; 与无 LID 患者相比, LID 患者壳核多巴胺转运蛋白活性更低, 且前壳核、后壳核和整个壳核 DAT 摄取是 LID 的影响因素。

2.4 II 型囊泡单胺转运体 (vesicular monoamine transporter type 2, VMAT2) 分子显像 VMAT2 是负责将单胺从胞质内转运至突触囊泡的蛋白质^[30-31], 其显像剂主要为¹¹C-二氢丁苯那嗪 (dihydrotrabenazine, DTBZ) 及衍生物¹⁸F-FP-DTBZ^[32-33]。文献^[34]纳入接受¹⁸F-FDG 和¹⁸F-FP-DTBZ (¹⁸F-AV133) PET 脑成像的 135 例 PD 患者, 其中致残性 LID 22 例、非致残性 LID 113 例; 结果显示, 致残性组病程更长、H-Y 分期更高、临床症状更严重、睡眠行为障碍发作更频繁、左旋多巴服用剂量更高, 而组间黑质纹状体区域多巴胺、皮质和皮质下区域¹⁸F-FDG 代谢均无显著差异。

2.5 突触后膜分子显像 突触后膜功能显像剂是多巴胺能神经元受体, 目前常用亲和性较低的¹¹C-raclopride 及亲和性较高的¹⁸F-fallypride; 前者可反映释放至突触间隙的多巴胺数量, 后者可评价除纹

状体外其他脑区的 D2 受体分布和功能^[35-37]。

有研究^[38]纳入 12 例 PD 不伴 LID 患者、24 例 PD 伴 LID 患者及 12 名健康对照者, 结果显示, 与 PD 不伴 LID 患者相比, PD 伴 LID 患者尾状核和壳核¹¹C-raclopride 摄取显著降低, 其中尾状核降低 13%、壳核降低 17%; PD 患者纹状体多巴胺 D2 受体结合长期下调可能为慢性多巴胺能治疗诱导或独立于治疗发生, 此为突触后多巴胺能系统对黑质纹状体神经元进行性退变的结构性适应结果。

¹¹C-raclopride PET 脑成像是检查 D2/D3 受体密度的金标准, 但其无法区分 D2 与 D3 受体, 且主要反映 D2 受体水平^[39-40]。¹¹C-(+)-PHNO 是新型 D3 受体放射性显像剂, 对 D3 受体的选择性高于 D2 受体 20 倍以上^[41-42]。研究^[43]纳入 12 例 PD 不伴 LID 患者、12 例 PD 伴 LID 患者及 18 名健康对照者, 结果显示, 与健康对照组相比, PD 伴 LID 患者 D3 受体丰富区域 (苍白球、腹侧纹状体及黑质纹状体)¹¹C-(+)-PHNO 摄取增高了 27%, 而 PD 不伴 LID 患者增高了 15%, 且 PD 伴 LID 患者增高程度显著高于不伴 LID 者。

2.6 血清素能神经系统分子成像 血清素能末端可表达芳香族 L-氨基酸脱羧酶 (aromatic L-amino acid decarboxylase, AADC), 将外源性左旋多巴转化为多巴胺。PET 显像剂¹¹C-DASB 是评估体内血清素能末端的可靠工具。¹¹C-DASB 研究^[44]显示, 血清素能转运蛋白 (serotonergic transporter, SERT) 与 DAT 比值随 PD 进展、出现 LID 而逐渐增加。此外, 5-羟色胺能^[45]、去甲肾上腺素能^[46]、胆碱能^[47]、腺苷能^[48]等 PET 显像剂均可用于评估 PD 伴 LID。

3 小结及展望

PET 分子成像可检测显像剂在分子水平上的摄取分布情况, 可视化反映 PD 伴 LID 患者脑功能及代谢, 有助于临床实现早诊断及早治疗。然而, 由于 PD 伴 LID 机制的复杂性, 未来还需进行不同显像剂的多模态 PET 分子成像研究, 分析 LID 潜在发病机制, 提高 PET 脑成像用于其早期诊断和评估疗效等方面的价值。

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