DOI: 10.11844/cjcb.2024.12.0012
中国细胞生物学学报 Chinese Journal of Cell Biology 2024, 46(12): 2117–2126 CSTR: 32200.14.cjcb.2024.12.0012

纹状体$A_{2A}R$在运动防治帕金森病中的作用研究进展

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摘要 腺苷2A受体(adenosine 2A receptor, $A_{2A}R$)特异性表达于纹状体间接通路神经元, 在纹状体依赖的程序性行为调控中起着重要的“整合”作用。帕金森病(Parkinson’s disease, PD)病理下间接通路的过度激活与纹状体$A_{2A}R$过表达有关。而$A_{2A}R$特异性拮抗剂在改善PD患者运动障碍的同时, 具有独特的认知促进功能和神经保护作用。各种类型的运动疗法在改善PD相关行为功能障碍方面的积极作用越来越受到关注, 其在神经保护、抗炎、抗氧化应激、调节中枢神经系统中神经递质表达及促进神经可塑性等方面表现出积极效应, 并可显著影响纹状体$A_{2A}R$表达水平。该文从$A_{2A}R$入手, 对$A_{2A}R$在PD神经退行性变及PD运动防治中的可能作用进行阐述, 为PD新型靶向药物的研发及神经生物学机制的研究提供理论依据, 并为无创舒适物理性疗法的改进和推广提供参考。

关键词 腺苷2A受体; 帕金森病; 运动防治

Progress on the Role of Striatal $A_{2A}R$ in the Prevention and Treatment of Parkinson’s Disease by Exercise

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Abstract $A_{2A}R$ (adenosine 2A receptor) is specifically expressed in neurons of the striatal indirect pathway and plays an important “integrated” role in the regulation of striatal-dependent programmed behavior. Excessive activation of the indirect pathway under PD (Parkinson’s disease) pathology is associated with $A_{2A}R$ overexpression in the striatum. However, $A_{2A}R$-specific antagonists have unique cognitive-promoting functions and neuroprotective effects while improving dyskinesia in PD patients. Various types of exercise therapy have received increasing attention for their positive effects in improving PD-related behavioral dysfunction, which show positive effects in neuroprotection, anti-inflammation, anti-oxidative stress, regulating neurotransmitter expression in the central nervous system and promoting neuroplasticity, and can significantly affect striatal $A_{2A}R$ expression levels. Starting with $A_{2A}R$, this paper elaborates the possible role of $A_{2A}R$ in the prevention and treatment of PD neurodegeneration and PD movement, providing a theoretical basis for the development of new targeted drugs for PD and the study of neurobiological mechanisms, and providing a reference for the improvement and promotion of non-invasive physical therapy.

Keywords adenosine 2A receptor; Parkinson’s disease; exercise therapy

收稿日期: 2024-08-18 接受日期: 2024-10-30
国家自然科学基金(批准号: 32360217)、湖南省教育厅科学研究项目(批准号: 23A0413)、湖南省普通本科高校教学改革研究项目(批准号: 202401000933)和湖南省大学生创新训练计划(批准号: S202410531079)资助的课题
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Received: August 18, 2024 Accepted: October 30, 2024
This work was supported by the National Natural Science Foundation of China (Grant No.32360217), the Scientific Research Project of Hunan Provincial Department of Education (Grant No.23A0413), the Hunan Province Undergraduate Teaching Reform Research Project (Grant No.202401000933), and the Hunan College Students’ Innovative Training Program (Grant No.S202410531079)
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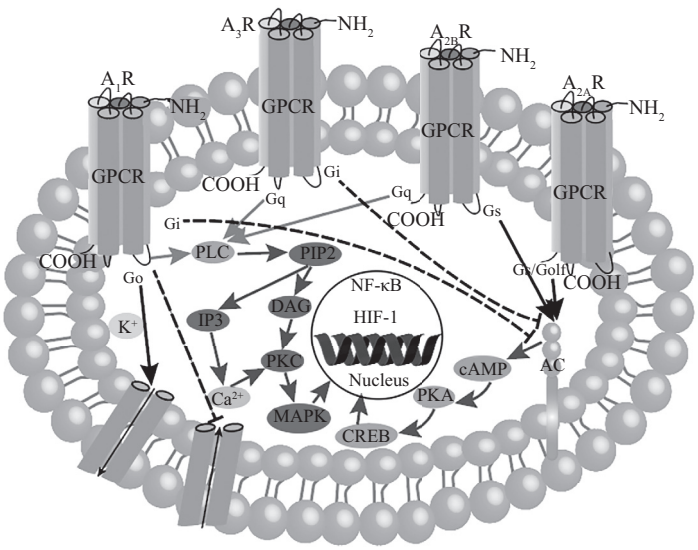
基底神经节(basal ganglia, BG)是皮层下参与运动调控的主要中枢脑区，而作为BG的核心，纹状体整合来自皮层和丘脑的谷氨酸能输入以及丘脑的多巴胺能输入，并与BG的输出结构相连参与协调随意运动，以及运动学习和决策[1]。这些功能主要依赖于纹状体中占绝对主导地位的一类名为“中等多棘神经元(medium spiny neurons, MSNs)”的伽马氨基丁酸(γ-aminobutyric acid, GABA)能神经元。基于脑区之间的联系和化学表型，可将纹状体MSNs分为2个亚群：直接通路上的MSNs(direct-pathway medium spiny neurons, dMSNs)和间接通路上的MSNs(indirect-pathway medium spiny neurons, iMSNs)。dMSNs发出轴突直接投射到BG的输出核团，即苍白球内侧部/黑质网状部复合体(SNr/Gpi)，主要表达与Gαs/Gαolf蛋白偶联的多巴胺1型受体(dopamine 1 type receptor, D_1R)及P物质和强啡肽；相比之下，iMSNs先投射到苍白球外侧部，主要表达与Gαi/Gαo蛋白偶联的多巴胺2型受体(D_2R)和脑啡肽[2]。研究发现：机体运动时，纹状体释放多巴胺(dopamine, DA)作用于D_1-MSNs上Gs偶联的D_1R，增加胞内cAMP浓度，起到激活蛋白激酶A(protein kinase A, PKA)的作用；此外，DA还作用于D_2-MSNs上Gi/o偶联的D_2R，进而抑制PKA。除DA外，腺苷等其他神经调质也可能参与运动调控，MA等[3]研究发现，Gs偶联腺苷$A_{2A}R$特异性表达于D_2-MSNs。$A_{2A}R$可通过相互拮抗的方式调控D_2R和谷氨酸*N*-甲基-*D*-天门冬氨酸受体(*N*-methyl-*D*-aspartate receptor, NMDAR)，且以相互协同的方式调控5型代谢性谷氨酸受体(metabotropic glutamate receptors 5, mGluR5)和1型大麻素受体(cannabinoid 1 receptor, CB1R)，继而在纹状体依赖性行为调控中起着重要的“整合”作用[4-5]。PD状态下，黑质致密部的DA能神经元进行性退变，导致纹状体DA浓度降低，使D_1-MSNs的活动能力降低和D_2-MSNs的活动能力明显增高(即直接通路和间接通路功能失衡)，净作用就是增强SNr/GPi的电活动，进而抑制接受大脑底部基底核投射的靶核团，从而抑制运动的发生，是导致PD相关行为功能障碍的主要原因[6]。因此，调控纹状体腺苷过度释放或抑制腺苷功能效应的发挥，能够达到抑制腺苷传导进而实现降低间接通路活性的目标。而这可以通过调控纹状体中$A_{2A}R$的表达水平来实现。研究表明，$A_{2A}R$特异性拮抗剂在改善PD患者运动障碍的同时，具有独特的认知促进功能和神经保护作用[7]。各种类型的运动疗法在改善PD相关行为功能障碍方面的积极作用越来越受到关注，其在神经保护、抗炎、抗氧化应激、调节中枢神经系统中神经递质表达及促进神经可塑性等方面表现出积极效应，并可显著影响纹状体$A_{2A}R$表达水平[8-9]。本文从$A_{2A}R$入手，对$A_{2A}R$在PD神经退行性病变及PD运动防治中的可能作用进行阐述，为PD新型靶向药物研发及神经生物学机制的研究提供理论依据，并为无创舒适物理性疗法的改进和推广提供参考。

1 $A_{2A}R$

腺苷作为一种内源性嘌呤核苷，存在于所有哺乳动物组织中，其作为中枢神经系统(central nervous system, CNS)中一种非经典的神经调节剂在运动、认知、记忆等控制中发挥重要的作用，不仅控制神经元兴奋性、突触可塑性和神经元变性，还调节星形胶质细胞和小胶质细胞的活性[10]。腺苷在纹状体细胞内主要由单磷酸腺苷(adenosinemonophosphate, AMP)的分解而产生，而在细胞外，腺苷的来源主要是细胞内腺苷的释放以及磷酸二酯酶对环单磷酸腺苷(cyclic adenosine monophate, cAMP)的代谢作用[11]。此外，星形胶质细胞能够通过其膜上的平衡腺苷转运蛋白(equilibrative nucleoside transporter, ENT)直接释放腺苷到细胞外，或者神经末梢通过囊泡的方式释放三磷酸腺苷(adenosinetriphosphate, ATP)到细胞外环境中通过特定的机制转化为腺苷[12]。研究表明，当神经元被激活时，胞外腺苷水平的上升主要依赖于ENT[13]。与经典神经递质相比，胞外腺苷积累缓慢并且需要L-型钙离子通道。腺苷信号传递及其代谢参与多种生理(睡眠–觉醒调控等)及病理(PD、AD和疼痛等)过程[14]。而腺苷发挥生物学效应是通过与其4种不同的受体结合来实现的。腺苷受体主要包括A_1、A_{2A}、A_{2B}及A_3受体(A_1R、$A_{2A}R$、$A_{2B}R$和A_3R)[10]。以上4种受体均属于G蛋白偶联受体(G protein-coupled receptor, GPCR)，其中A_1R和A_3R与Gαi/Gαo蛋白偶联；$A_{2A}R$和$A_{2B}R$与Gαs/Gαolf蛋白偶联[15](图1)。

$A_{2A}R$是腺苷受体家族的一员，主要分布在富含DA的大脑区域[16]。在CNS中，$A_{2A}R$几乎在所有区域(如纹状体、苍白球外侧部和丘脑等核团)都有表达，其在纹状体背侧和腹侧高度富集，纹状体中$A_{2A}R$与D_2R相互拮抗、与NMDA受体以及mGluR5具有协同作用。因此，$A_{2A}R$能够通过整合来自谷氨酸能和



$A_{2A}R$: 腺苷2A受体; A_1R: 腺苷1受体; A_3R: 腺苷3受体; $A_{2B}R$: 腺苷2B受体; NH_2: 氨基; GPCR: G蛋白偶联受体; COOH: 羧基; cAMP: 环单磷酸腺苷; PKA: 蛋白激酶A; CREB: cAMP反应元件结合蛋白; MAPK: 丝裂原活化蛋白激酶; PKC: 蛋白激酶C; DAG: 二酰基甘油; PIP2: 4,5-二磷酸磷脂酰肌醇; NF-κB: 核因子κB; HIF-1: 缺氧诱导因子-1。

$A_{2A}R$: adenosine 2A receptor; A_1R: adenosine 1 receptor; A_3R: adenosine 3 receptor; $A_{2B}R$: adenosine 2B receptor; NH_2: amino; GPCR: G protein-coupled receptor; COOH: carboxyl; cAMP: cyclic adenosine monophosphate; PKA: protein kinase A; CREB: cAMP-response element binding protein; MAPK: mitogen activated protein kinase; PKC: protein kinase C; DAG: diacylglycerol; PIP2: 4,5-diphosphate phosphatidyl inositol; NF-κB: nuclear factor kappa B; HIF-1: hypoxia-inducible factor-1.

图1 不同腺苷受体在激活后的作用机制(根据参考文献[18]修改)

Fig.1 Mechanism of action of different adenosine receptors upon activation (modified from the reference [18])

DA能神经元的信号转导, 进而调控纹状体神经元形态结构与功能的可塑性[17]。在细胞水平上, $A_{2A}R$位于神经元突触前和突触后区室、星形胶质细胞、小胶质细胞、少突胶质细胞和毛细血管内皮细胞[10]。$A_{2A}R$被激活时, 其与大脑中Golf蛋白或外周组织中Gs蛋白偶联, 促进腺苷酸环化酶(adenylyl cyclase, AC)降解, 上调cAMP水平, 激活PKA磷酸化, 促进Ca^{2+}内流而导致胞内钙超载; 而抑制$A_{2A}R$激活有相反的调节作用[18], $A_{2A}R$通过cAMP-PKA磷酸化转录因子cAMP反应元件结合蛋白(cAMP-response element binding protein, CREB), 激活核因子-κB(nuclear factor kappa B, NF-κB), 调控基因表达[19](图1)。此外, $A_{2A}R$还可以激活丝裂原活化蛋白激酶(mitogen activated protein kinase, MAPK), 促进胶原蛋白的产生, 并抑制中性粒细胞的过氧化。与A_1R不同, 腺苷通过激活$A_{2A}R$促进兴奋性递质释放。在血管方面, $A_{2A}R$也介导血管舒张, 并具有抑制血小板聚集的作用, 而$A_{2B}R$具有较弱的舒血管作用[20]。

2 $A_{2A}R$与PD的发生发展

近年来, $A_{2A}R$被认为是PD发病和(或)运动功能障碍的关键调节因子之一。FERRE等[21]研究发现, PD患者纹状体中DA浓度降低, 腺苷系统功能失调, $A_{2A}R$蛋白表达水平显著上调, DA和腺苷水平的改变以及各自受体表达水平的改变影响$A_{2A}R/D_2R$异聚体功能, 从而影响PD的病理过程。CHEN等[22]使用光遗传学方法与奖赏事件同步瞬时性激活背外侧纹状体(dorsolateral striatum, DLS)区$A_{2A}R$抑制了小鼠的习惯性行为, 反之, 在DLS区条件性敲除$A_{2A}R$促进了小鼠的习惯性行为。而与此类似的神经退行性疾病脑出血也表现为A_1R表达水平下调, $A_{2A}R$表达水平上调[23]。啮齿动物研究证实, 膜内$A_{2A}R$与D_2R相互拮抗参与运动行为调节, 表现在$A_{2A}R$的激活抑制了D_2R介导的信号转导, 而$A_{2A}R$拮抗剂增强了D_2R的信号转导[24]。尽管$A_{2A}R$的急性抑制促进了运动, 但$A_{2A}R$去抑制后表达水平上调, 导致动物运动水平降低和习惯性行为受损[25]。RIVAS-SANTISTEBAN等[26]研究表明, 在神经毒素6-OHDA损伤诱导的PD模型大鼠的纹状体D_2-MSNs上与D_2R相互作用的$A_{2A}R$的表达水平显著上调。在人类PD患者死后大脑中, 也观察到$A_{2A}R$表达水平显著上调[27-28]。另一项动物模型研究也证实了ATP释放和$A_{2A}R$激活是PD运动症状发生发展的关键途径[29]。此外, 在海马内注射α-syn原纤维可诱导海马神经元和胶质细胞$A_{2A}R$表达水平的上调[30]。VILLAR-MENENDEZ等[31]通过

正电子发射计算机断层扫描研究发现，在伴有运动障碍的PD患者和早期PD的壳核中也存在$A_{2A}R$表达水平的上调。最近的研究也表明，通过光遗传学激活海马中$A_{2A}R$或特异性过表达腺苷$A_{2A}R$足以导致年轻小鼠的记忆功能障碍[32]。而在PD患者大脑纹状体星形胶质细胞、小胶质细胞和少突胶质细胞中同样也观察到$A_{2A}R$的水平显著上调[33]。在PD状态下或DA去神经支配时，$A_{2A}R$和内源性腺苷结合增加，使纹状体D_2-MSNs活性增强，PD患者和PD模型动物的运动功能障碍更严重[34]。

综上所述，纹状体$A_{2A}R$在D_2-MSNs上异常富集与PD的发病机制有关。在PD中腺苷系统功能失调、纹状体$A_{2A}R$上调导致D_2-MSNs过度兴奋，加剧PD患者或PD动物模型运动功能障碍。

3 $A_{2A}R$与PD防治

$A_{2A}R$选择性富集于纹状体，直接调控纹状体D_2-MSNs突触可塑性。流行病理学调查结果显示，PD发病率与$A_{2A}R$拮抗剂(咖啡因)摄取量呈负相关[35]。同理，在突变体α-syn诱导的PD动物模型中，咖啡因通过激活自噬活性保护动物免受突变体α-syn的损伤[36]。FDA III期药物临床试验证实，$A_{2A}R$特异性拮抗剂(KW6002)改善PD患者运动障碍的同时，具有独特的认知促进功能和神经保护作用[21]，可用于治疗“关闭期”的PD成人患者[37]。CARMO等[27]研究表明，阻断$A_{2A}R$可防止鱼藤酮诱导的PD模型大鼠纹状体中DA表达水平下降和腺苷系统功能失调，改善PD模型大鼠运动功能障碍。此外，腺苷$A_{2A}R$在纹状体D_2-MSNs上高度表达，拮抗D_2R的功能。$A_{2A}R$也位于纹状体Glu能神经元末梢，参与调控Glu释放和皮层纹状体突触传递[18]。HODGSON等[38]通过动物模型研究证实，在MPTP诱导的PD模型动物中，$A_{2A}R$拮抗剂改善了动物的运动功能障碍，降低了AC的活性，下调了cAMP的表达水平，降低了PKA的活性和磷酸化能力，减少了DA能神经元丢失[7]，还抑制了NMDAR介导的Ca^{2+}内流，从而阻断了喹吡罗的作用[39]。$A_{2A}R$阻断减少了SynT-Synphilin-1神经瘤胶质细胞中的α-syn聚集，减少了*α-syn*转基因PD模型的突触丢失并改善了认知功能缺陷[40-41]。总之，$A_{2A}R$拮抗剂通过减少DA耗竭、活性氧产生、α-syn聚集等来减轻多种PD模型中的运动损伤。而对培养的纹状体神经元进行钙成像也发现，$A_{2A}R$敲除显著降低了NMDARs介导的Ca^{2+}内流。脑片电生理记录证实，纹状体MSNs中的NMDARs功能受到抑制，导致α-氨基-3-羟基-5-甲基-4-异恶唑丙酸受体/NMDAR成分电流比率增加[42]。ZHAO等[43]通过动物模型实验证实，靶向$A_{2A}R$的治疗策略可对PD模型大鼠的认知功能障碍表现出改善作用，如执行能力、工作记忆和程序性学习缺陷的改善。体外研究表明，冬虫夏草素调节$A_{2A}R$表达水平改善MPTP诱导的PD模型小鼠的认知功能的同时，还可显著减少MPTP对PD小鼠运动、探索、空间学习和记忆能力的损害[44]。BEGGIATO等[45]使用双探针微透析表明，$A_{2A}R$拮抗剂(ZM241385)和mGluR5拮抗剂(MPEP)组合治疗PD有助于增强纹状体D_2-MSNs上D_2R介导的抑制性信号的转导。此外，$A_{2A}R$可以刺激纹状体神经元中乙酰胆碱的释放，胆碱能神经纤维末梢还可以通过突触前膜中毒蕈碱(M)受体的负反馈来调节乙酰胆碱的释放，M受体拮抗剂可以降低$A_{2A}R$激动剂的作用[46]。因此，靶向腺苷$A_{2A}R$的联合给药干预可能是治疗PD的有效措施。在PD中，*$A_{2A}R$*基因的失活也会减少神经毒素(如6-OHDA)诱导的DA能神经元以及α-syn诱导的DA能神经元的丢失[47-48]。TRITSCH等[49]也研究证实，肌苷作为PD疾病修饰剂，在PD模型小鼠中具有改善神经炎症和氧化应激的能力，以及抑制细胞外信号调节激酶(extracellular regulated protein kinase, ERK)磷酸化和下调$A_{2A}R$表达的能力。

综上所述，$A_{2A}R$拮抗剂或药物治疗不仅能通过减少PD患者或动物模型的DA耗竭、DA能神经元丢失、α-syn聚集等来减轻多种PD模型中的运动损伤，还可改善其认知能力。因此，$A_{2A}R$可作为改善PD运动缺陷的对症治疗的潜在靶点。目前，有关通过调节腺苷$A_{2A}R$改善PD症状的研究多数局限于动物模型，靶向$A_{2A}R$抑制剂的人类研究是未来重要的突破方向。

4 运动与$A_{2A}R$

纹状体是CSN中调节精细运动的重要核团，健康机体(人和动物)在运动后会下调$A_{2A}R$来调节纹状体D_2-MSNs和其他神经元活性以及相关行为功能。EL-GHAIESH等[50]研究表明，机体运动时，纹状体释

放的神经递质DA作用于D_1-MSNs上Gs蛋白偶联的D_1R和D_2-MSNs上Gi/o蛋白偶联的D_2R, 从而参与对运动的调节。除DA外, 腺苷等其他神经调质通过与自身受体结合也参与运动调控。放射性原位杂交检测表明, 6周跑轮训练(前3周每日跑轮训练距离稳步增加, 后3周平均跑步距离为4.49 km/天, 整个实验期间的平均跑步距离为3.66 km/天)和急性应激下调了大鼠纹状体A_1R mRNA和$A_{2A}R$ mRNA表达水平, 并伴有D_1-MSNs上强啡肽神经元中cFos的表达增强, D_2-MSNs上脑啡肽神经元中cFos表达水平降低[51]。近年来, BAUER等[52]也通过免疫组织化学研究证实, 8周跑轮训练(前3周每天跑轮训练距离稳步增加, 后3周平均跑步距离为7.73 km/天, 整个实验的平均跑步距离为7.25 km/天)下调了小鼠纹状体A_1R mRNA和$A_{2A}R$ mRNA表达水平, 上调了D_2R mRNA表达水平, 并伴有平衡核苷转运蛋白1表达的下调。刘军等[53]研究证实, 大鼠在逐渐运动至力竭时, 纹状体D_2-MSNs过度兴奋释放的Glu和GABA增多, 且Glu/GABA值降低, 而$A_{2A}R$拮抗剂(SCH58261)和D_2R激动剂(喹毗罗)可逆转这种情况, 表现在大鼠自主运动期(疲劳初期)时间延长, 大鼠运动力竭时间显著增加, 纹状体及苍白球的局部电位振幅逐渐增大, 频率逐渐减少。

除了健康机体外, 有关运动对$A_{2A}R$蛋白表达水平的影响, 在不同病理状态下也有研究报道。MA等[3]研究证实, 小鼠运动时DLS内腺苷水平显著升高, 随运动时间延长而积累, 且GRINlens的双光子钙成像也显示小鼠自愿跑台运动(速度大于0.8 cm/s, 时间>60 min/天, 最少5天)激活D_1-MSNs与D_2-MSNs, 而给予小鼠$A_{2A}R$拮抗剂Istradefylline或SCH58261时, 发现D_2-MSNs钙信号显著减弱, D_1-MSNs钙信号轻微增强, PD小鼠运动功能障碍得到改善。据报道, 运动下调脑组织中$A_{2A}R$的表达水平和上调纹状体中DA的水平, 此过程中D_2-MSNs通路上的D_2R及D_2-MSNs产生的脑啡肽和内源性大麻素等物质与$A_{2A}R$相拮抗, 下调$A_{2A}R$的活性, 从而改善PD动物模型的运动功能障碍[54]。LEEM等[55]研究证实, 4周跑步机训练(60 min/次, 1次/天)降低了小鼠$A_{2A}R$表达水平, 而重复应激则有相反的调节作用。COSTA等[56]研究表明, 中等强度跑步机运动(对成年和中年大鼠进行为期8周, 每周1天、3天或7天的跑台训练干预)可显著下调焦虑模型大鼠海马$A_{2A}R$表达水平, 尤其是7天/周的运动量在减轻大鼠焦虑行为方面效果最显著(表现为大鼠在高架十字迷宫内张开所花费时间减少, 张开双臂的次数增多, 闭合双臂次数减少; 中年大鼠饲养时间较成年大鼠短)。

综上所述, 不同运动方案对$A_{2A}R$表达水平的影响具有一定的差异。但长期慢性运动对PD(人和动物)中$A_{2A}R$表达水平的影响是一致的, 未来还需要就最适宜运动方式或不同的联合运动方式(如有氧+平衡运动)进行进一步的研究。当前, 运动对$A_{2A}R$调节已有文献报道, 但多数仅局限于对动物行为学的分析以及靶向蛋白成分的检测, 还需采用载体多通道技术、立体多通道技术、光纤光度技术等去证实运动对$A_{2A}R$的靶向调节, 进而验证运动下调纹状体$A_{2A}R$表达水平来调控D_2-MSNs活性是PD有前景的治疗措施。

5 运动与PD

运动是身体活动的一种表现形式, 它可改善PD患者的运动功能障碍, 如运动迟缓、姿势步态障碍和平衡障碍[57]。有关运动防治PD的流行病理学研究最早于1992年发现大学期间进行律性体育锻炼的人群成年后PD的患病率明显降低, 且毕业后仍坚持中至大强度运动的人群PD患病风险进一步降低[58]。近年来, 临床研究证实, 不同运动干预方案在PD康复中既有效又可行, 可显著改善PD患者的步态、平衡、协调等行为功能障碍[59]。AZEVEDO等[60]基于一项Meta分析发现, 体力活动对PD患者有益, 特别是在速度、体能和生活质量等方面。

5.1 有氧运动与PD

在各种不同的运动形式中, 有氧运动(aerobic exercise, AE)被认为是一种能够有效促进人们整个生命周期健康的选择。有氧行走可改善PD患者的运动功能、有氧适能、疲劳、情绪和生活质量[61]。MAX等[62]研究表明, 中等强度(40%~60% HRmax, RPE评分: 11~15)快走(150 min/次, 2次/周, 6周内从60 min/周逐步过渡到150 min/周)可缓解PD患者的症状, 改善认知功能、步态表现、行走能力和动态平衡。DAWSON等[63]研究表明, 运动强度为60%~80% HRmax的拳击训练(45 min/次, 1次/周)可使PD患者UPDRS运动评分显著降低, 并且定期运动有助于缓解PD患者的步态障碍。KHUZEMA等[64]研究表明, 太极拳训练(30~60 min/次, 2~10次/周, 2周后增加到60 min)可改善PD患者平衡、灵活性、运动迟缓及肌僵直和情绪障碍。而长期太极拳训练(60 min/次,

2次/周, 12个月)改善PD患者的运动功能更为显著, 尤其是步态和平衡。此外, 长期太极拳训练还可增强大脑网络功能, 减少炎症, 改善氨基酸代谢、能量代谢和神经递质代谢, 并使DA能神经元退行性病变的程度降低[65]。14项随机对照试验表明, 与对照组比, 舞蹈训练组改善PD患者运动症状的同时, 还对患者功能活动和认知有积极作用[66]。CAO等[67]研究表明, 五禽戏(30~60 min/次, 每次20~30 min, 2~3次/周, 2周后增加到60 min)可改善PD患者步态冻结、平衡能力、认知及情绪障碍。综上, AE是一种非常流行的功能恢复疗法, 它对PD患者的运动、生活质量、认知和情绪等均有积极效应。然而, 仍需要进行大规模的长期随访随机对照试验来证实目前的研究结果, 并且还需要进一步评估各种AE训练的最低运动量要求。

5.2 抗阻运动与PD

抗阻训练(resistance training, RT)是一种重复锻炼的运动训练形式, 每次重复之间有足够的休息时间来恢复, 随着肌肉产生力量能力的增加, 增加额外的阻力, 直到疲劳为止[68]。DANI等[69]研究表明, 32周的水上运动(60 min/次, 2次/周)可改善PD患者的运动习惯行为, 增加SOD活性, 调节PD个体抗氧化酶活性。12周渐进式阻力训练(progressive resistance training, PRT)能改善中度PD患者睡眠质量和肌肉力量[70]。在另一项研究中, 12周的PRT也显示PD患者心血管自主神经功能障碍有所改善[71]。负重跑步机训练(负重50%~100%, 10~30 min/次, 速度1~7 km/h)对PD患者活动范围、本体感觉、生活质量均有改善作用[72]。有报道称, PRT对轻至中度PD患者的肌力、运动功能和耐力均有积极影响[73]。VIEIRA等[74]研究表明, PRT(60~90 min/次, 1次/天, 2~3天/周, 持续12周至24个月)可显著改善PD患者生活质量, 提高步行速度, 增加肌肉耐力, 缓解运动迟缓。HIRSCH等[75]研究证实, 高强度离心阻力训练不仅对PD患者是安全有效的, 而且患者肌肉体积、肌肉力量、功能状态和步行速度等均可得到显著改善。近年来, 平衡训练+PRT组合练习逐渐在PD临床康复治疗中得到普及, 可降低PD患者跌倒和姿势不稳定的风险[76]。

综上, PRT在改善PD患者运动症状、睡眠功能障碍和生活质量, 特别是肌力方面具有益处, 可将其归为PD公共健康促进计划的组成部分。但不同周期或负荷大小的PRT在改善PD患者肌肉力量、功能状态和生活质量等方面均有差异, 这需要进一步探索。

5.3 平衡运动与PD

平衡训练是一种挑战人体在不稳定的平台上运动和/或人体的支撑面减小时控制身体重心的能力的运动[77]。ESCULIER等[78]研究发现, 功率自行车训练(30~60 min/次, 1~2次/天, 5天/周, 3~10周)对PD患者运动、平衡功能障碍有显著改善作用。持续24周的太极拳(60 min/次, 2次/周)干预, 不仅使PD患者的平衡障碍显著改善, 还能够使患者的日常生活能力显著提高, 跌倒次数显著降低[79]。ARCOLIN等[80]研究表明, 持续3周功率自行车训练可使PD患者的跌倒发生率显著降低, 日常生活独立性显著提高。一项随机对照试验表明, 正念瑜伽练习(90 min/次, 2周/次, 4周)显著改善了PD患者的活动能力、焦虑、抑郁和生活质量, 表现在功能平衡性和整体运动症状显著改善, 而焦虑和抑郁症状显著减少[81]。结构化舞蹈课程训练(45 min/次, 2次/周, 持续12周)对于PD患者来说是安全、可行和有效的, 可改善PD患者抑郁症状、疲劳、认知功能障碍等症状[82]。研究表明, 为期6周(150 min/次, 2~3次/周, 6周内从60 min/周逐步过渡到150 min/周)的快走和平衡计划可缓解轻至中度PD患者运动症状, 表现为日常生活活动能力、冻结步态、平衡功能和步行能力显著改善[83]。

综上所述, 流行病学数据表明, 运动可降低PD的患病风险和减缓PD的进程。临床证据证实, 运动作为PD最广泛采用的非药物补充治疗方法之一, 对PD患者的运动障碍和非运动障碍均有积极效应。

6 纹状体$A_{2A}R$与PD运动防治

研究表明, Glu兴奋性毒作用[84]、DA的耗竭[85]和胆碱能神经功能失衡[86]等因素均与PD风险增加及发生发展有关。而这些因素所涉及的Glu能系统、胆碱能系统和单胺能系统均与$A_{2A}R$有潜在的联系。2周跑台运动(8 m/min, 40 min/天)通过调节$A_{2A}R$的表达水平来减弱鱼藤酮诱导的PD模型大鼠神经细胞变性, 表现在运动增加了PD模型大鼠黑质(substantia nigra, SN)中DA表达水平, 下调了Glu、GSH、IL-1β等蛋白的表达量, 改善了PD模型大鼠运动功能障碍(从转棒上跌落的潜伏期延长, 阿扑吗啡诱导的旋转次数减少, Morris水迷宫实验中在目标象限停留的时间延长, 穿越平台的次数增加, 逃避潜伏期缩短), 而运动+$A_{2A}R$激动剂(CGS21680)却逆转了以上益处[87]。HOU等[88]研究证实,

4周电动跑步机训练(11 m/min, 30 min/天, 5天/周)可使PD模型大鼠MSN中$A_{2A}R$ mRNA减少, 上调A_1R mRNA表达, 改善动物模型运动功能障碍。刘晓莉等[89]研究表明, 4周运动干预(11 m/min, 30 min/天, 5天/周)减轻了神经毒素6-OHDA对大鼠SN DA能神经元的毒性损伤, 使纹状体$A_{2A}R$ mRNA及蛋白表达显著下调, 改善了PD模型大鼠运动功能障碍。上述研究表明, 运动可通过下调纹状体$A_{2A}R$蛋白表达水平来调控D_2-MSNs活性, 但运动通过下调$A_{2A}R$调控纹状体D_2-MSNs的活性来改善PD的文献报道尚少, 但结合上述$A_{2A}R$与PD发生发展、运动与$A_{2A}R$以及运动与PD的相关研究, 可以推测出, 运动下调$A_{2A}R$表达水平, 抑制D_2-MSNs过度兴奋, 继而调控D_2-MSNs活动来改善PD相关行为功能障碍。因此, 靶向$A_{2A}R$的干预成为未来一种有前景的PD治疗方式, 而这需要做进一步的研究证实。

7 小结与展望

$A_{2A}R$特异性表达于纹状体D_2-MSNs上, 其过表达可增强D_2-MSNs兴奋性, 与PD相关行为功能障碍有关。靶向调控$A_{2A}R$的表达水平可显著改善PD患者和或模型动物的运动功能障碍。运动在PD防治过程中表现的积极作用可能是$A_{2A}R$介导的。$A_{2A}R$可能是运动防治PD的潜在分子靶点。

科学运动(如有氧运动、抗阻运动和平衡运动等)是PD患者综合防控的重要组成部分。但运动有助于PD神经保护和临床前模型症状改善的神经生物学机制尚未完全知晓。时至今日, 研究者主要从神经炎症、胆碱能系统、钙超载、Glu兴奋性毒作用和自噬等不同视角探讨运动防治PD的可能神经生物学机制。结合上述$A_{2A}R$在PD防治中的作用和运动对$A_{2A}R$的影响以及运动在PD防治中的作用, 推测$A_{2A}R$调控纹状体D_2-MSNs可塑性可能是介导PD运动防治的可能机制之一。在接下来的研究中, 可利用药理学和遗传学(如$A_{2A}R$拮抗剂或激动剂、光遗传学和化学遗传学等)的实验方法, 并结合包括Cre-LoxP和$A_{2A}R$-Cre在内的基因编辑技术及先进的细胞和分子成像技术, 在纹状体D_2-MSNs上特异性敲除或过表达$A_{2A}R$, 探索$A_{2A}R$调控纹状体D_2-MSNs可塑性在PD运动防治中的作用, 以证实纹状体$A_{2A}R$调控D_2-MSNs可塑性可能是运动防治PD相关行为功能障碍的可能机制之一。这可为运动干预缓解PD相关行为功能障碍的神经生物学机制的研究以及靶向干预提供必要的理论依据和新的思路。

参考文献 (References)

[1] WANG M, LIU H, MA Z. Roles of the cannabinoid system in the basal ganglia in Parkinson's disease [J]. Front Cell Neurosci, 2022, 16: 832854.

[2] SUAREZ L M, SOLIS O, SANZ-MAGRO A, et al. Dopamine D1 receptors regulate spines in striatal direct-pathway and indirect-pathway neurons [J]. Mov Disord, 2020, 35(10): 1810-21.

[3] MA L, DAY-COONEY J, BENAVIDES O J, et al. Locomotion activates PKA through dopamine and adenosine in striatal neurons [J]. Nature, 2022, 611(7937): 762-8.

[4] CHEN J F. Adenosine receptor control of cognition in normal and disease [J]. Int Rev Neurobiol, 2014, 119: 257-307.

[5] HE Y, HUANG L, WANG K, et al. α-synuclein selectively impairs motor sequence learning and value sensitivity: reversal by the adenosine A2A receptor antagonists [J]. Cereb Cortex, 2022, 32(4): 808-23.

[6] FENG Y S, YANG S D, TAN Z X, et al. The benefits and mechanisms of exercise training for Parkinson's disease [J]. Life Sci, 2020, 245: 117345.

[7] MÜLLER T. The role of istradefylline in the Parkinson's disease armamentarium [J]. Expert Opin Pharmacother, 2023, 24(7): 863-71.

[8] LIN F, LIN Y, CHEN L, et al. Association of physical activity pattern and risk of Parkinson's disease [J]. NPJ Digit Med, 2024, 7(1): 137.

[9] LIU M, HE P, YE Z, et al. Association of handgrip strength and walking pace with incident Parkinson's disease [J]. J Cachexia Sarcopenia Muscle, 2024, 15(1): 198-207.

[10] DOMENICI M R, FERRANTE A, MARTIRE A, et al. Adenosine A2A receptor as potential therapeutic target in neuropsychiatric disorders [J]. Pharmacol Res, 2019, 147: 104338.

[11] 刘军, 乔德才, 刘晓莉. 咖啡因延缓运动疲劳作用及机制研究进展[J]. 中国运动医学杂志(LIU J, QIAO D C, LIU X L. Research progress on the effect and mechanism of caffeine in delaying exercise fatigue [J]. Chinese Journal of Sports Medicine), 2018, 37: 791-6.

[12] CIRUELA F, GOMEZ-SOLER M, GUIDOLIN D, et al. Adenosine receptor containingoligomers: their role in the control of dopamine and glutamate neurotransmission in the brain [J]. Biochim Biophys Acta, 2011, 1808: 1245-55.

[13] WU Z, CUI Y, WANG H, et al. Neuronal activity-induced, equilibrative nucleoside transporter-dependent, somatodendritic adenosine release revealed by a GRAB sensor [J]. Proc Natl Acad Sci USA, 2023, 120(14): e2212387120.

[14] CHEN J F, ELTZSCHIG H K, FREDHOLM B B. Adenosine receptors as drug targets: what are the challenges [J]? Nat Rev Drug Discov, 2013, 12(4): 265-86.

[15] FREDHOLM B B. Purinoceptors in the nervous system [J]. Pharmacol Toxicol, 1995, 76(4): 228-39.

[16] LIU Y J, CHEN J, LI X, et al. Research progress on adenosine in central nervous system diseases [J]. CNS Neurosci Ther, 2019, 25(9): 899-910.

[17] LI Y, HE Y, CHEN M, et al. Optogenetic activation of adenosine A2A receptor signaling in the dorsomedial striatopallidal neurons

suppresses goal-directed behavior [J]. Neuropsychopharmacology, 2016, 41(4): 1003-13.

[18] WANG Q, ZHOU F M. cAMP-producing chemogenetic and adenosine A2a receptor activation inhibits the inwardly rectifying potassium current in striatal projection neurons [J]. Neuropharmacology, 2019, 148: 229-43.

[19] KHEDR R M, AHMED A A E, KAMEL R, et al. Sitagliptin attenuates intestinal ischemia/reperfusion injury via cAMP/PKA, PI3K/Akt pathway in a glucagon-like peptide 1 receptor-dependent manner [J]. Life Sci, 2018, 211: 31-9.

[20] LIU Y J, CHEN J, LI X, et al. Research progress on adenosine in central nervous system diseases [J]. CNS Neurosci Ther, 2019, 25(9): 899-910.

[21] FERRE S, CIRUELA F. Functional and neuroprotective role of striatal adenosine A2A receptor heterotetramers [J]. J Caffeine Adenosine Res, 2019, 9: 89-97.

[22] CHEN J F, CHOI D S, CUNHA R A. Striatopallidal adenosine A2A receptor modulation of goal-directed behavior: homeostatic control with cognitive flexibility [J]. Neuropharmacology, 2023, 226: 109421.

[23] MELANI A, PUGLIESE A M, PEDATA F. Adenosine receptors in cerebral ischemia [J]. Int Rev Neurobiol, 2014, 119: 309-48.

[24] LEDENT C, VAUGEOIS J M, SCHIFFMANN S N, et al. Aggressiveness, hypoalgesiaand high blood pressure in mice lackingtheadenosine A2A receptor [J]. Nature, 1997, 388: 674-8.

[25] BAI Y, ZHANG X, ZHENG J, et al. Overcoming high level adenosine-mediated immunosuppression by DZD2269, a potent and selective A2aR antagonist [J]. J Exp Clin Cancer Res, 2022, 41(1): 302.

[26] RIVAS-SANTISTEBAN R, RICO A J, MUÑOZ A, et al. Boolean analysis shows a high proportion of dopamine D2 receptors interacting with adenosine A2A receptors in striatal medium spiny neurons of mouse and non-human primate models of Parkinson's disease [J]. Neurobiol Dis, 2023, 188: 106341.

[27] CARMO M, GONÇALVES F Q, CANAS P M, et al. Enhanced ATP release and CD73-mediated adenosine formation sustain adenosine A2A receptor over-activation in a rat model of Parkinson's disease [J]. Br J Pharmacol, 2019, 176(18): 3666-80.

[28] MENG F, GUO Z, HU Y, et al. CD73-derived adenosine controls inflammation and neurodegeneration by modulating dopamine signalling [J]. Brain, 2019, 142(3): 700-18.

[29] GONÇALVES F Q, MATHEUS F C, SILVA H B, et al. Increased ATP release and higher impact of adenosine A2A receptors on corticostriatal plasticity in a rat model of presymptomatic Parkinson's disease [J]. Mol Neurobiol, 2023, 60(3): 1659-74.

[30] HU Q, REN X, LIU Y, et al. Aberrant adenosine A2A receptor signaling contributes to neurodegeneration and cognitive impairments in a mouse model of synucleinopathy [J]. Exp Neurol, 2016, 283: 213-23.

[31] VILLAR-MENÉNDEZ I, PORTA S, BUIRA S P, et al. Increased striatal adenosine A2A receptor levels is an early event in Parkinson's disease-related pathology and it is potentially regulated by miR-34b [J]. Neurobiol Dis, 2014, 69: 206-14.

[32] LI P, RIAL D, CANAS P M, et al. Optogenetic activation of intracellular adenosine A2A receptor signaling in the hippocampus is sufficient to trigger CREB phosphorylation and impair memory [J]. Mol Psychiatry, 2015, 20(11): 1339-49.

[33] JOE E H, CHOI D J, AN J, et al. Astrocytes, microglia, and Parkinson's disease [J]. Exp Neurobiol, 2018, 7(2): 77-87.

[34] 李丹, 黄译腺, 罗蔚锋, 等. 腺苷2A受体、亲代谢谷氨酸受体对异动症可塑性改变的影响[J]. 国际神经病学神经外科学杂志(LI D, HUANG Y X, LUO W F, et al. Effects of adenosine 2A receptors and metabolophile glutamate receptors on the plasticity of dyskinesia [J]. Journal of International Neurology and Neurosurgery), 2010, 37(2): 135-40.

[35] BAKSHI R, MACKLIN E A, HUNG A Y, et al. Associations of lower caffeine intake and plasma urate levels with idiopathic Parkinson's disease in the harvard biomarkers study [J]. J Parkinsons Dis, 2020, 10(2): 505-10.

[36] LUAN Y, REN X, ZHENG W, et al. Chronic caffeine treatment protects against α-synucleinopathy by reestablishing autophagy activity in the mouse striatum [J]. Front Neurosci, 2018, 12: 301.

[37] FDA approves nourianz, new add-on drugto treat off episodes in adults with Parkinson's disease [EB/OL]. https://www.fda.gov/news-events/press-announcements/ fda-approves-new-add-drug-treat-episodes-adults parkinsons-disease.

[38] HODGSON R A, BEDARD P J, VARTY G B, et al. Preladenant, a selective A2A receptor antagonist, is active in primate models of movement disorders [J]. Exp Neurol, 2010, 225(2): 384-90.

[39] LUNDBLAD M, VAUDANO E, CENCI M A, et al. Cellularand behavioural effects of the adenosine A2a receptor an tagonist KW-6002 in a rat model of L-DOPA-induced dyskinesia [J]. J Neurochem, 2010, 84: 1398-410.

[40] FERREIRA D G, BATALHA V L, VICENTE MIRANDA H, et al. Adenosine A2A receptors modulate α-synuclein aggregation and toxicity [J]. Cereb Cortex, 2017, 27(1): 718-30.

[41] FERREIRA D G, TEMIDO-FERREIRA M, VICENTE MIRANDA H, et al. α-synucleininteracts with PrPC to induce cognitive impairment through mGluR5 and NMDAR2B [J]. Nat Neurosci, 2017, 20(11): 1569-79.

[42] LAHIRI A K, BEVAN M D. Dopaminergic transmission rapidly and persistently enhances excitability of d1 receptor-expressing striatal projection neurons [J]. Neuron, 2020, 106(2): 277-90.

[43] ZHAO Y, ZHOU Y G, CHEN J F. Targeting the adenosine A2A receptor for neuroprotection and cognitive improvement in traumatic brain injury and Parkinson's disease [J]. Chin J Traumatol, 2024, 27(3): 125-33.

[44] HUANG S Y, SU Z Y, HAN Y Y, et al. Cordycepin improved the cognitive function through regulating adenosine A2A receptors in MPTP induced Parkinson's disease mice model [J]. Phytomedicine, 2023, 110: 154649.

[45] BEGGIATO S, TOMASINI M C, BORELLI A C, et al. Functional role of striatal A2A, D2, and mGlu5 receptor interactions in regulating striatopallidal GABA neuronal transmission [J]. J Neurochem, 2016, 138(2): 254-64.

[46] NADAL L, GARCIA N, HURTADO E, et al. Presynaptic muscarinic acetylcholine autoreceptors (M1, M2 and M4 subtypes), adenosine receptors (A1 and A2A) and tropomyosin-related kinase B receptor (TrkB) modulate the developmental synapse elimination process at the neuromuscular junction [J]. Mol Brain, 2016, 9(1): 67.

[47] PASQUINI S, CONTRI C, MERIGHI S, et al. Adenosine receptors in neuropsychiatric disorders: fine regulators of neurotransmission and potential therapeutic targets [J]. Int J Mol Sci, 2022,

23(3): 1219.

[48] EL-SHAMARKA M E A, KOZMAN M R, MESSIHA B A S. The protective effect of inosine against rotenone-induced Parkinson's disease in mice; role of oxido-nitrosative stress, ERK phosphorylation, and A2AR expression [J]. Naunyn Schmiedebergs Arch Pharmacol, 2020, 393(6): 1041-53.

[49] TRITSCH N X, SABATINI B L. Dopaminergic modulation of synaptic transmission in cortex and striatum [J]. Neuron, 2012, 76(1): 33-50.

[50] EL-GHAIESH S H, BAHR H I, IBRAHIEM A T, et al. Metformin protects from rotenone-induced nigrostriatal neuronal death in adult mice by activating AMPK-FOXO3 signaling and mitigation of angiogenesis [J]. Front Mol Neurosci, 2020, 13: 84.

[51] CLARK P J, GHASEM P R, MIKA A, et al. Wheel running alters patterns of uncontrollable stress-induced cfos mRNA expression in rat dorsal striatum direct and indirect pathways: a possible role for plasticity in adenosine receptors [J]. Behav Brain Res, 2014, 272: 252-63.

[52] BAUER E E, BUHR T J, REED C H, et al. Exercise-induced adaptations to the mouse striatal adenosine system [J]. Neural Plast, 2020, 2020: 5859098.

[53] 刘军, 刘晓莉, 乔德才. 力竭运动过程中大鼠苍白球局部场电的动态变化及A2AR拮抗剂和D2DR激动剂的干预研究[J]. 北京体育大学学报(LIU J, LIU X L, QIAO D C, et al. Dynamic change of pallidal local field potentials and A2AR antagonists and D2DR agonists intervention for rats in exhaustive exercise process [J]. Journal of Beijing Sport University), 2017, 40(7): 36-42,105.

[54] 曾馨怡, 赵旭东, 马婧, 等. 纹状体A2AR/D2DR拮抗效应在运动功能调节中的研究进展[J]. 生命科学(ZENG X Y, ZHAO X D, MA J, et al. Review on A2AR/D2DR antagonistic effect in regulation of motor function in striatum [J]. Chinese Bulletin of Life Sciences), 2020, 32(9): 972-8.

[55] LEEM Y H, JANG J H, PARK J S, et al. Exercise exerts an anxiolytic effect against repeated restraint stress through 5-HT2A-mediated suppression of the adenosine A2A receptor in the basolateral amygdala [J]. Psychoneuroendocrinology, 2019, 108: 182-9.

[56] COSTA M S, ARDAIS A P, FIOREZE G T, et al. Treadmill running frequency on anxiety and hippocampal adenosine receptors density in adult and middle-aged rats [J]. Prog Neuropsychopharmacol Biol Psychiatry, 2012, 36(1): 198-204.

[57] LLAMAS-VELASCO S, CONTADOR I, MÉNDEZ-GUERRERO A, et al. Physical activity and risk of Parkinson's disease and parkinsonism in a prospective population-based study (NEDICES) [J]. Prev Med Rep, 2021, 23: 101485.

[58] WU H, GU Y, DU W, et al. Different types of screen time, physical activity, and incident dementia, Parkinson's disease, depression and multimorbidity status [J]. Int J Behav Nutr Phys Act, 2023, 20(1): 130.

[59] DE DOMENICO E, D'ARCANGELO G, FARAONI I, et al. Modulation of GDF11 expression and synaptic plasticity by age and training [J]. Oncotarget, 2017, 8(35): 57991-8002.

[60] AZEVEDO K P M, DE OLIVEIRA V H, MEDEIROS G C B S, et al. The effects of exercise on bdnf levels in adolescents: a systematic review with meta-analysis [J]. Int J Environ Res Public Health, 2020, 17(17): 6056.

[61] ZHEN K, ZHANG S, TAO X C, et al. A systematic review and meta-analysis on effects of aerobic exercise in people with Parkinson's disease [J]. NPJ Parkinsons Dis, 2022, 8(1): 146.

[62] MAK M K Y, WONG-YU I S K. Six-month community-based brisk walking and balance exercise alleviates motor symptoms and promotes functions in people with Parkinson's disease: a randomized controlled trial [J]. J Parkinsons Dis, 2021, 11(3): 1431-41.

[63] DAWSON R A, SAYADI J, KAPUST L, et al. Boxing exercises as therapy for Parkinson disease [J]. Top Geriatr Rehabil, 2020, 36(3): 160-5.

[64] KHUZEMA A, BRAMMATHA A, ARUL SELVAN V. Effect of home-based Tai Chi, Yoga or conventional balance exercise on functional balance and mobility among persons with idiopathic Parkinson's disease: an experimental study [J]. Hong Kong Physiother J, 2020, 40(1): 39-49.

[65] LI G, HUANG P, CUI S S, et al. Mechanisms of motor symptom improvement by long-term Tai Chi training in Parkinson's disease patients [J]. Transl Neurodegener, 2022, 11(1): 6.

[66] SALTYCHEV M, BÄRLUND E, PALTAMAA J, et al. Progressive resistance training in Parkinson's disease: a systematic review and meta-analysis [J]. BMJ Open, 2016, 6(1): e008756.

[67] 曹海豪, 孙文玉, 席晓明, 等. 五禽戏对帕金森病患者平衡功能、步行能力及生活质量的效果[J]. 中国康复理论与实践(CAO H H, SUN W Y, XI X M, et al. Effects of Wuqinxi on balance, walking and quality of life for patients with Parkinson's disease [J]. Chinese Journal of Rehabilitation Theory and Practice), 2021, 27(9): 1087-92.

[68] OTSUKA Y, YAMADA Y, MAEDA A, et al. Effects of resistance training intensity on muscle quantity/quality in middle-aged and older people: a randomized controlled trial [J]. J Cachexia Sarcopenia Muscle, 2022, 13: 894-908.

[69] DANI C, PROENÇA I T, MARINHO J, et al. Aquatic exercise program-modulated oxidative stress markers in patients with Parkinson's disease [J]. Neural Regen Res, 2020, 15(11): 2067-72.

[70] SILVA-BATISTA C, DE BRITO L C, CORCOS D M, et al. Resistance training improves sleep quality in subjects with moderate Parkinson's disease [J]. J Strength Cond Res, 2017, 31(8): 2270-7.

[71] KANEGUSUKU H, SILVA-BATISTA C, PEÇANHA T, et al. Effects of progressive resistance training on cardiovascular autonomic regulation in patients with parkinson disease: A randomized controlled trial [J]. Arch Phys Med Rehabil, 2017, 98(11): 2134-41.

[72] DANESHVAR P, GHASEMI G, ZOLAKTAF V, et al. Comparison of the effect of 8-week rebound therapy-based exercise program and weight-supported exercises on the range of motion, proprioception, and the quality of life in patients with Parkinson's disease [J]. Int J Prev Med, 2019, 10: 131.

[73] BRIENESSE L A, EMERSON M N. Effects of resistance training for people with Parkinson's disease: a systematic review [J]. J Am Med Dir Assoc, 2013, 14(4): 236-41.

[74] VIEIRA DE MORAES FILHO A, CHAVES S N, MARTINS W R, et al. Progressive resistance training improves bradykinesia, motor symptoms and functional performance in patients with Parkinson's disease [J]. Clin Interv Aging, 2020, 15: 87-95.

[75] HIRSCH M A, TOOLE T, MAITLAND C G, et al. The effects of

balance training and high-intensity resistance training on persons with idiopathic Parkinson's disease [J]. Arch Phys Med Rehabil, 2003, 84(8): 1109-17.

[76] ALLEN N E, SHERRINGTON C, PAUL S S, et al. Balance and falls in Parkinson's disease: a meta-analysis of the effect of exercise and motor training [J]. Mov Disord, 2011, 26(9): 1605-15.

[77] SEGURA C, ERASO M, BONILLA J, et al. Effect of a high-intensity tandem bicycle exercise program on clinical severity, functional magnetic resonance imaging, and plasma biomarkers in Parkinson's disease [J]. Front Neurol, 2020, 11: 656.

[78] ESCULIER J F, VAUDRIN J, BÉRIAULT P, et al.Home-based balance training programme using Wii Fit with balance board for Parkinsons's disease: a pilot study [J]. J Rehabil Med, 2012, 44(2): 144-50.

[79] GARCÍA-MUÑOZ C, GONZÁLEZ-GARCÍA P, CASUSO-HOLGADO M J, et al. Are movement-based mindful exercises (QIGONG, TAI CHI, AND YOGA) beneficial for stroke and Parkinson's disease? A scoping review [J]. Complement Ther Med, 2023, 72: 102912.

[80] ARCOLIN I, PISANO F, DELCONTE C, et al. Intensive cycle ergometer training improves gait speed and endurance in patients with Parkinson's disease: a comparison with treadmill training [J]. Restor Neurol Neurosci, 2016, 34: 125-38.

[81] DUARTE J D S, ALCANTARA W A, BRITO J S, et al. Physical activity based on dance movements as complementary therapy for Parkinson's disease: effects on movement, executive functions, depressive symptoms, and quality of life [J]. PLoS One, 2023, 18(2): e0281204.

[82] MORATELLI J A, ALEXANDRE K H, BOING L, et al. Dance rhythms improve motor symptoms in individuals with Parkinson's disease: a randomized clinical trial [J]. J Dance Med Sci, 2022, 26: 1-6.

[83] FENG H, LI C, LIU J, et al. Virtual reality rehabilitation versus conventional physical therapy for improving balance and gait in Parkinson's disease patients: a randomized controlled trial [J]. Med Sci Monit, 2019, 25: 4186-92.

[84] 陈平, 李刚强, 周文辉. 谷氨酸受体在帕金森病中的作用及其介导的帕金森病运动防治研究进展[J]. 体育科学(CHEN P, LI G Q, ZHOU W H, et al. Role of GluR in PD and the research progress of exercise regulated GluR in PD treatment [J]. China Sport Science), 2022, 42(9): 72-81.

[85] CUI Y, SU D, ZHANG J, et al. Dopaminergic versus anticholinergic treatment effects on physiologic complexity of hand tremor in Parkinson's disease: a randomized crossover study [J]. CNS Neurosci Ther, 2024, 30(4): e14516.

[86] CHUNG S J, KIM Y J, KIM Y J, et al. Association between white matter networks and the pattern of striatal dopamine depletion in patients with Parkinson disease [J]. Neurology, 2022, 99(24): e2672-82.

[87] LI R, JIN S, HE J, et al. Exercise attenuates neuronal degeneration in Parkinson's disease rat model by regulating the level of adenosine 2A receptor [J]. Folia Neuropathol, 2023, 61(2): 217-23.

[88] HOU L, CHEN W, LIU X, et al. Exercise-induced neuroprotection of the nigrostriatal dopamine system in Parkinson's disease [J]. Front Aging Neurosci, 2017, 9: 358.

[89] 刘晓莉, 赵刚, 王弘, 等. 运动通过调节纹状体A2AR/D2DR表达改善帕金森病模型大鼠行为功能障碍[J]. 中国运动医学杂志(LIU X L, ZHAO G, WANG H, et al. Exercise regulates striatum A2AR/D2DR expression to improve behavioral dysfunction of PD rats [J]. Chinese Journal of Sports Medicine), 2020, 39(5): 381-9.