纹状体星形胶质细胞EAATs介导的帕金森病运动防治研究进展

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摘要 帕金森病(parkinson's disease, PD)是第二大神经退行性疾病, 主要发生于中老年人。中脑黑质致密部(substantia nigra pars compacta, SNpc)多巴胺(dopamine, DA)能神经元的变性丢失导致向基底神经节(basal ganglia, BG)纹状体释放的DA大量减少, 致使与PD进展有关的纹状体内谷氨酸(glutamate, Glu)能信号过度传导, 而纹状体星形胶质细胞上的兴奋性氨基酸转运蛋白(excitatory amino acid transporters, EAATs)可以调节Glu的清除, 因此成为治疗PD的一个潜在靶点。运动干预作为PD的一种辅助治疗手段, 能够有效缓解PD相关的行为功能障碍, 其机制可能是通过调节纹状体星形胶质细胞EAATs表达水平来介导的。该文从纹状体星形胶质细胞EAATs入手, 对它在PD神经退行性病变及PD运动防治中的作用等方面的研究进行综述, 以期为运动干预缓解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。

关键词 运动防治; 帕金森病; EAATs

Progress of Exercise in Prevention and Treatment of Parkinson's Disease through Striatal Astrocyte EAATs

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Abstract PD (Parkinson's disease) is the second most common neurodegenerative disease and occurs mainly in middle-aged and elderly people. Degeneration and loss of dopaminergic neurons in the SNpc (substantia nigra pars compacta) of the midbrain leads to a large reduction in DA (dopamine) release to the BG (basal ganglia) striatum, resulting in excessive Glu (glutamate) energy signal transduction in the striatum associated with PD progression, while EAATs (excitatory amino acid transporters) on striatal astrocytes can regulate Glu clearance and therefore become a potential target for the treatment of PD. Exercise intervention, as an adjunct to PD, can effectively alleviate PD-related behavioral dysfunction, and the mechanism may be mediated by regulating EAATs expression levels in striatal astrocytes. This article reviews the research on the role of striatal astrocyte EAATs in PD neurodegeneration and exercise prevention and treatment of PD, in order to provide necessary theoretical basis and new ideas for the study of neurobiological mechanism of exercise intervention in relieving PD-related behavioral dysfunction and targeted intervention.

Keywords exercise intervention; Parkinson's disease; EAATs

帕金森病(Parkinson's disease, PD)是一种复杂的多系统神经退行性疾病, 在60岁以上的老年人中占比约为1%[1]。根据2016年全球疾病负担(global burden of disease, GBD)数据库的分析结果, 1990年至2016年间全球PD的疾病负担已增加一倍多, 且中国PD患病率的增幅在全世界中最大[2]。由于人口

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老龄化等因素的影响, 据预测, 到2030年, 中国的PD患者人数将增加到世界PD患者人数的一半以上[3]。PD的病理特征是中脑黑质致密部(substantia nigra pars compacta, SNpc)多巴胺(dopamine, DA)能神经元的变性和死亡, 以及DA含量的显著减少诱发大量的运动障碍(如四肢无力、僵硬、肌动过速和姿势不稳)[4-7]。PD的发病机制尚不明确, 大部分学者认为, 黑质DA能神经元变性、坏死导致基底神经节(basal ganglia, BG)纹状体神经递质DA大量减少, 致使皮层-BG-丘脑–皮层环路传导异常, 是PD运动功能障碍出现的主要原因[8-9]。在生理状态下, 来自SNpc的DA能神经元投射到纹状体, 其释放的DA通过与纹状体中等多棘神经元(medium spiny neurons, MSNs)上的DA I型受体(dopamine I type receptor, D_1R)和DA II型受体(dopamine II type receptor, D_2R)相结合, 分别作用于直接和间接通路。作用于这两条通路的DA抑制苍白球内侧部(globus pallidus internus, GPi)和黑质网状部(reticular part of substantia nigra, SNr)(GPi/SNr)复合体的电活动, 从而使接受大脑底部BG投射的靶核团去抑制, 引起运动效应。在PD中, SNpc DA能神经元退化, 导致向纹状体释放的DA水平降低, 造成纹状体向GPi/SNr复合体释放的γ-氨基丁酸(γ-aminobutyric acid, GABA)能减少, 向苍白球外侧部(globus pallidum external segment, GPe)释放的GABA能增加。总的结果是维持运动的直接通路活性减弱, 而抑制多余动作的间接通路活性增强, 造成震颤、肌强直, 并且难以控制其运动, 最终引起运动迟缓和步态异常等PD相关行为功能障碍。目前认为, PD发病与环境因素、氧化应激、遗传因素、老龄化、蛋白质稳态失衡及代谢稳态失衡等多因素相关; 由于其致病机理仍不清楚, 因此缺乏对因治疗的有效药物。药物治疗(*L*-多巴)和脑深部电刺激(deep brain stimulation, DBS)是目前PD治疗的主要手段, 可以有效地改善肢体震颤等运动症状, 但无法阻止PD的进展。因此, 寻找能够延缓PD进程或预防PD发生的有效方法是目前研究所关注的热点问题。

谷氨酸(glutamate, Glu)是大脑中枢神经系统(central nervous system, CNS)中主要的兴奋性神经递质, 在正常BG功能的破坏中起着关键作用[10-11]。在PD状态下, 黑质–纹状体DA的减少致使皮层–纹状体Glu通路过度激活, 突触前膜释放过多的Glu或Glu的再摄取功能受损, 导致突触间隙Glu浓度增加[12-13]。细胞外Glu水平过高触发神经元损伤或死亡, 这一过程被称为Glu兴奋毒性作用[14-15]。因此, 清除细胞外高浓度的Glu可以达到降低Glu兴奋毒性作用的目标。降低Glu兴奋毒性作用也可以通过调节纹状体星形胶质细胞上的兴奋性氨基酸转运蛋白(excitatory amino acid transporters, EAATs)的表达水平来实现[16-17]。身体活动作为PD治疗的一种辅助手段, 对其预防和治疗起着积极的作用。流行病学研究和临床观察表明, 经常持续规律地参加体力活动可以降低PD的发病风险, 改善PD相关行为功能障碍[18-19]。动物实验结果证实, 运动干预可以显著改善PD相关行为/运动功能障碍[20-24]。该文从纹状体星形胶质细胞EAATs入手, 对其在PD神经退行性病变及PD运动防治中的作用等方面的研究进行综述, 以期为运动干预缓解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。

1 纹状体星形胶质细胞

星形胶质细胞是CNS中一种常见的神经胶质细胞, 体积大且数量多, 在与神经代谢、神经活动调节、突触生成因子产生、胶质细胞界膜控制以及血脑屏障控制等相关的神经发育和内稳态方面发挥着重要作用[25-26]。这些神经内稳态机制对于维持正常的CNS生理功能十分重要, 内稳态异常会导致神经系统疾病的发生, 而且在疾病状态下, 星形胶质细胞具有促进CNS病理进程的功能[27-28]。

纹状体是BG最大的核团, 是一组可参与运动和行动以及产生多种神经精神状况的皮质下核团[29]。NAGARAJAN等[30]使用显微镜观察到纹状体星形胶质细胞是由胞体、从胞体发出的6个左右初级分支、多个二级和三级分支、一个或多个足突末端的水通道蛋白-4(aquaporin-4, AQP4)以及无数的小枝和小叶组成。包含的这些小枝和小叶是CNS中健康星形胶质细胞的重要特征[31]。纹状体最主要的投射神经元是表达D_1R和D_2R的MSNs。MARTIN等[32]研究表明, 背侧纹状体中的星形胶质细胞与D_1-MSNs和D_2-MSNs相互作用, 星形胶质细胞亚群以回路特异性方式运作。纹状体中的星形胶质细胞已成为突触生理学的主动调节因子, 应对不同神经递质, 星形胶质细胞会经历细胞内Ca^{2+}的波动, 从而感知和整合突触活动[33], 星形胶质细胞释放调节神经元兴奋性、突触可塑性和突触传递(Glu能和GABA能)的胶质递质(包括*D*-丝

氨酸、Glu或ATP/腺苷); 在病理状态下, *D*-丝氨酸增加, 加上细胞外Glu水平升高, 可能导致神经元兴奋毒性和死亡[34]。星形胶质细胞也表达不同的膜受体, 包括Glu、GABA和内源性大麻素受体, 当它们的激动剂参与突触信号传递时, 这些受体可以直接激活星形胶质细胞, 这种激活可以反过来介导递质释放的逆向调节, 控制神经元兴奋性, 并调节或介导不同大脑区域的突触可塑性[35]。纹状体星形胶质细胞还可对G蛋白偶联受体(G protein coupled receptors, GPCPs)的超家族成员代谢型Glu受体(metabotropic glutamate receptors, mGluRs)(mGluR1/5)的激活产生反应, 致使细胞内Ca^{2+}水平升高从而激活催化酶, 导致细胞内产生毒性自由基, 损害细胞能量的产生, 最终可能导致细胞死亡[36]。目前研究发现, 包括PD在内的多种神经和精神疾病涉及纹状体功能障碍[37-39]。这些纹状体功能障碍均与纹状体中的星形胶质细胞有关[30,40], 它们构成了大脑免疫应答的一部分。

2 纹状体星形胶质细胞EAATs

当兴奋性神经传递异常时, 细胞外Glu水平升高可引起细胞损伤[41-42]。然而, 由于缺乏胞外酶, 突触的Glu摄取主要通过位于神经元和神经胶质质膜的EAATs实现[17]。已发现5种不同的EAATs, 这些转运蛋白的氨基酸序列同源性为50%~60%[43]。EAATs具有8种跨膜结构, 且具有羧酸末端和氨基末端[44]。EAATs最有可能以三聚物形式存在[45-46]。特异性EAAT谷氨酸天冬氨酸转运体(glutamateaspartate transporter, GLAST)也被称为兴奋性氨基酸转运体1(excitatory amino acid transporter 1, EAAT1)[47-48], EAAT谷氨酸转运体1(glutamate transporter-1, GLT-1)也被称为兴奋性氨基酸转运体2(excitatory amino acid transporter 2, EAAT2)。研究表明, GLAST在新生大鼠海马的细胞中高表达[49-50]。GLAST是一种膜结合转运体, 转运突触间隙的Glu以及3个Na^+、1个H^+以及1个K^+, 从而介导细胞对Glu的再摄取[51]。尽管GLT-1被认为是清除突触间隙中过量Glu的主要转运蛋白亚型, 但GLAST在预防兴奋毒性神经元损伤中也发挥着关键作用。大约90%的Glu转运由EAAT2介导, 这些转运蛋白与每个谷氨酸盐(或天冬酰胺酶)分子协同转运2~3个Na^+和1个质子, 并协同逆向转运1个K^+[52]。GLT-1和GLAST主要存在于星形胶质细胞中[53-54]。星形胶质细胞通过高亲和力EAAT1和EAAT2从突触间隙清除细胞外高浓度的Glu, EAAT2对Glu稳态、突触可塑性和神经元存活起着关键作用[55-56]。在许多其他细胞(如少突胶质细胞和巨噬细胞)中也发现了这些转运蛋白[57-58]。每个EAAT都有特定的表达模式, EAATs的一些功能特征可归因于其不同的时空定位[59]。GLT-1不仅在星形胶质细胞中表达; 其剪接变体GLT-1a也在海马神经元的轴突中表达, 这可能会显著促进Glu被摄取进入轴突末端[60-62]。EAAT家族的两个成员兴奋性氨基酸转运体3(excitatory amino acid transporter 3, EAAT3)和兴奋性氨基酸转运体4(excitatory amino acid transporter 4, EAAT4)是神经元转运体[53]; 然而, 在许多神经元中, 它们似乎位于突触后膜上, 表明它们不像单胺转运蛋白那样参与递送循环[63-64]。已证明EAAT3在海马和皮质锥体神经元以及GABA能神经元[53]、少突胶质细胞[65]和其他Glu神经元中表达。EAAT3还介导神经元中半胱氨酸(cysteine, Cys)的转运[66], 为谷胱甘肽(glutathione, GSH)的合成提供Cys底物。EAAT4是高亲和力Na/K依赖性Glu转运蛋白家族的成员, 主要在小脑GABA能浦肯野细胞中表达[67]。兴奋性氨基酸转运体5(excitatory amino acid transporter 5, EAAT5)的表达局限于视网膜视杆细胞光感受器和双极细胞中[68](图1)。

综上所述, 这些发现有助于阐明EAATs的生理功能以及星形胶质细胞EAAT1和EAAT2对调节细胞外Glu浓度的重要作用。

3 纹状体星形胶质细胞EAATs与PD

研究表明, PD与线粒体功能障碍[70]、氧化应激[71]、免疫功能异常[72]、Glu兴奋毒性作用[73]等因素有关。目前, 尚无安全有效的预防Glu兴奋毒性的药物。研究发现, 与健康受试者相比, PD患者血小板中的Glu摄取量减少了50%[74]。因此, 预防Glu兴奋毒性作用的一种潜在方法是增强Glu再摄取。

胶质Glu转运体EAAT1和EAAT2主要存在于与兴奋性突触接触密切相关的星形胶质细胞中, 负责维持低水平的细胞外Glu。在PD患者中, EAAT2功能异常可能导致兴奋毒性, 上调EAAT2表达水平会立即降低细胞外Glu的水平, 以防止神经元损伤[75]。SINGH等[76]研究发现, 乙酰左旋肉碱可以减少ROS的积累量, 上调EAAT2表达水平, 从而达到保护DA能神经元的目的。而有证据表明头孢曲松可以上调EAAT2表达水平, 降低细胞外Glu含量从而保护

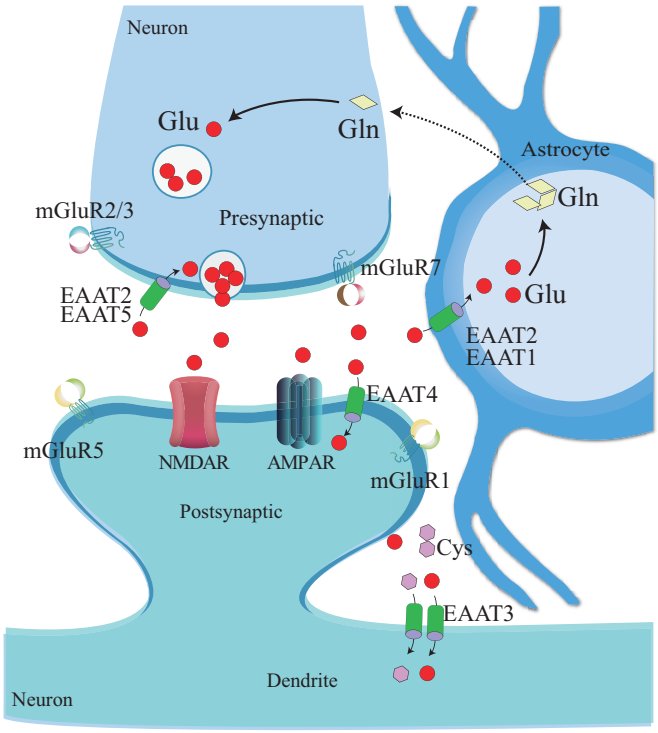

图1 EAATs蛋白亚型的分布及EAAT1和EAAT2参与Glu摄取的途径(根据参考文献[69]修改)

Fig.1 Distribution of EAATs protein isoforms and pathways involved in Glu uptake by EAAT1 and EAAT2 (modified from the reference [69])

DA能神经元[77]。此外, WEI等[78]研究证明, Wnt信号通路通过调节星形胶质细胞EAAT2表达水平介导了星形胶质细胞对DA能神经元细胞的保护作用。ZHOU等[79]研究发现, 人参皂苷可通过NF-κB通路上调EAAT2蛋白表达水平, EAAT2蛋白表达水平上调可降低Glu兴奋毒性作用, 达到防治PD的目的。这些研究表明, Wnt信号通路和NF-κB通路之间的交互对话参与了EAAT2表达的调控。因此, 调节EAAT2表达水平可能是预防神经兴奋毒性的潜在手段。在PD模型动物中, 已经有很多的研究调控EAAT2表达水平, 并寻找PD治疗的潜在靶点。CHOTIBUT等[77]研究发现, 在6-OHDA(6-hydroxydopamine hydrobromide)诱导的单侧损毁[内侧前脑束(medial forebrain bundle, MFB)注射] PD模型大鼠中, 当EAAT2表达水平上调时, 左旋多巴(levodopa, L-DOPA)诱导的运动功能障碍显著改善。HOLMER等[80]研究表明, MPTP(1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)诱导的PD模型小鼠纹状体EAAT2蛋白表达水平显著下调。ZHANG等[81]研究发现, 在MPTP诱导的PD模型小鼠中, GLT-1的异常泛素化会导致GLT-1蛋白表达水平显著下调和模型小鼠出现运动功能障碍以及DA能神经元细胞丢失。而后又有研究发现星形胶质细胞GLT-1缺失可诱导小鼠PD表型、进行性运动缺陷和黑质DA能神经元死亡[82]。IOVINO等[83]研究表明, 在含有亮氨酸重复激酶2(leucine repetitive kinase 2, LRRK2)致病变体(G2019S)的人脑和PD模型小鼠中, EAAT2蛋白表达水平显著下调, 这与胶质细胞增生有关。据报道, MPTP诱导的PD模型小鼠中miR-543-3p和miR-342-3p水平的增加与GLT-1的表达量和功能下降以及细胞外Glu的积累增加有关, 抑制任一miRNA都可以逆转PD对GLT-1表达和功能的影响, 改善PD相关行为功能障碍[84]。近年来, 关于EAAT1与PD的研究也有相关报道。JOHNSON等[85]研究发现, 上调EAAT1蛋白和mRNA表达水平可导致小鼠对锰诱导的神经毒性产生抵抗。换句话说, EAAT1调节Glu的水平以抵抗神经毒性, 包括发生在PD中的神经毒性。另一项研究还表明, 上调星形胶质细胞EAAT1的基因和蛋白表达水平可降低Glu兴奋毒性[86]。研究发现, 急性MPTP模型小鼠纹状体EAAT1的免疫反应性和基因表达水平均降低[80]。EL ARFANI等[87]研究表明, 6-OHDA损伤(MFB注

射) PD模型大鼠纹状体EAAT1的免疫反应性和基因表达水平也降低。WU等[84]研究发现, MPTP诱导的PD模型小鼠纹状体GLAST蛋白表达水平显著下调。此外, LI等[88]研究表明, 在MPTP诱导的PD模型小鼠中, 上调EAAT1表达水平可能是DA能神经元通过降低兴奋毒性而受到保护的潜在机制。

综上所述, 纹状体星形胶质细胞EAAT1和EAAT2的表达水平在PD中发生了改变, 调节EAAT1与EAAT2表达水平可能是PD治疗的一种新策略。

4 纹状体星形胶质细胞EAATs介导的PD运动防治

PD中脑SNpc的DA能神经元变性丢失导致向BG纹状体传递的DA大量减少, 造成纹状体Glu能传递显著升高, 纹状体星形胶质细胞EAAT1和EAAT2表达水平降低, 最终加剧了DA能神经元丢失以及PD进展, 使得PD相关行为功能障碍进一步恶化。

4.1 EAAT2介导的PD运动防治

有关运动通过改变PD患者BG纹状体星形胶质细胞EAAT2的表达水平来介导PD相关行为/运动功能障碍改善的研究还未见报道, 而运动通过改变PD模型动物BG纹状体星形胶质细胞EAAT2的表达水平来介导PD相关行为/运动功能障碍改善的研究已有相关报道。时凯旋等[89]研究发现, 4周跑台训练干预能够使神经毒素6-OHDA诱导的偏侧损毁(MFB注射) PD模型大鼠纹状体GLT-1表达水平显著上调, 纹状体神经元胞外Glu浓度显著降低, 阿扑吗啡诱导的旋转圈数显著降低, 左侧前肢接触壁次数(圆桶实验)显著增加。FENG等[90]研究表明, 11周跑台训练干预(30米/分钟, 5分钟/天, 4天/周, 共1周)能够使6-OHDA诱导的偏侧损毁(MFB注射) PD模型大鼠*GLT-1* mRNA和GLT-1蛋白表达水平显著上调, 平衡木潜伏期和总时间明显缩短, 前爪在金属丝上的停留时间明显延长。SCONCE等[91]研究发现, 4周跑轮运动能够使MPTP诱导的PD模型小鼠GLT-1表达水平显著上调, 模型小鼠运动功能障碍显著改善。综上, 运动能够通过调节EAAT2的表达水平介导PD相关行为功能障碍的改善(表1)。

4.2 EAAT1介导的PD运动防治

有关运动通过改变PD患者和PD模型动物纹状体星形胶质细胞EAAT1的表达水平来介导PD相关行为/运动功能障碍改善的研究还未见报道, 而通过药物调控BG纹状体星形胶质细胞EAAT1表达水平已显示出一定的抗PD相关行为功能障碍作用。马利芳等[92]研究表明, 复方地黄颗粒能够使6-OHDA注射损伤黑质法诱导的阴虚动风证PD模型大鼠纹状体*GLAST* mRNA和GLAST蛋白表达水平显著上调, 模型大鼠旋转圈数显著减少, 悬挂时间及移动格数显著增加。ZHANG等[81]研究发现, 雷帕霉素能够使MPTP诱导的PD模型小鼠纹状体星形胶质细胞*GLAST* mRNA和GLAST蛋白表达水平显著上调, 模型小鼠在抓握实验和爬杆实验中的行为表现显著改

表1 不同运动方案对PD模型动物EAAT2的调控

Table 1 Regulation of EAAT2 in PD model animals by different exercise regimens

运动方案 Exercise protocol	PD动物模型 PD animal model	GLT-1表达水平的变化 Changes in GLT-1 expression levels	行为学变化 Behavioral changes	参考文献 Reference
Four weeks treadmill training	6-OHDA-induced PD model rats	GLT-1 expression level↑	Significant decrease in the number of turns and significant increase in the number of contacts of the left forelimb with the wall (barrel test)	[89]
Eleven weeks treadmill training	OHDA-induced PD model rats	*GLT-1* mRNA and GLT-1 protein expression level↑	The latency and total time of the balance beam were significantly reduced, the residence time of the forepaw on the wire was significantly prolonged, and the maximum lifting of the head and trunk was significantly increased	[90]
Four weeks running wheel exercise	MPTP-induced PD model mice	GLT-1 expression level↑	Motor dysfunction significantiy improved	[91]

↑: 指标的水平上调。

↑: Up-regulated level of indicator.

善。米超等[93]研究表明, 利鲁唑能够使MPTP诱导的PD模型小鼠纹状体星形胶质细胞*GLAST* mRNA和GLAST蛋白表达水平显著上调, 纹状体神经元胞外Glu浓度显著降低, 模型小鼠转棒潜伏期、疲劳耐力时间及跑步距离均显著增加。而运动干预对PD纹状体星形胶质细胞EAAT1表达水平的影响是怎样的, 这对阐释运动干预缓解PD相关行为功能障碍的神经生物学分子机制是极其重要的, 未来还需要做进一步的研究。

5 纹状体星形胶质细胞EAATs介导PD运动防治的可能胞内分子机制

在PD状态下, 纹状体胞外Glu浓度升高。Glu与α-氨基-3-羟基-5-甲基-4-异恶唑丙酸(α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid, AMPA)受体和红藻氨酸(kainic acid, KA)受体结合后, 使Ca^{2+}通道打开, Na^{+}内流可导致快速兴奋性突触传递反应, 导致突触后膜部分去极化, 使原来阻断*N*-甲基-*D*-天冬氨酸(*N*-methyl-*D*-aspartate, NMDA)受体通道开放的Mg^{2+}离子移除, 大量Ca^{2+}内流。此外, 部分mGluRs(如mGluR1/5)也分布在皮层–纹状体突触后膜上, 且位于突触后膜上的离子通道型GluR的边缘, 可与Gq/11结合并促进多磷酸肌醇(polyphospho inositide, PI)水解, 致使IP3和DAG的生成量显著增加。DAG的生成量增加导致蛋白激酶C(protein kinases C, PKC)激活, 从而使Ca^{2+}通道过度打开以及离子型GluR磷酸化作用增强, 进一步诱导Ca^{2+}大量内流, 最终导致神经元胞内Ca^{2+}浓度的显著上升。异常高水平的胞内Ca^{2+}激活催化酶(包括激酶、磷脂酶、一氧化氮合酶和蛋白酶等), 产生毒性自由基如超氧阴离子和过氧化亚硝酸离子, 并使CREB信号强度降低, 线粒体受到氧化损伤, 膜电位丢失, ATP耗竭, 进而对神经元产生Glu兴奋毒性作用, 并最终使正常BG功能破坏而导致PD相关行为功能障碍(图2)[94]。

在轴突中, Glu储存在突触囊泡中。在充分去极化后, Glu通过电压门控Ca^{2+}通道的突触释放, 从而导致突触Glu浓度显著升高。II组mGluRs(mGluR2/3)定位于皮层–纹状体突触前末梢[95-96]。mGluR2/3的激活或者上调能够调控EAAT1和EAAT2表达水平[97-98]。Glu与突触后的NMDA和AMPA受体结合, 刺激Na^{+}和Ca^{2+}流入神经元[99-100], 导致突触后膜部分去极化和动作电位的产生, 这时EAAT1和EAAT2迅速将Glu从突触间隙中清除, 以防止Glu受体受到过度刺激, 突触周围星形胶质细胞的Glu将被谷氨酰胺合成酶转化为谷氨酰胺(Glutamine, Gln), 之后Gln会转移到神经元, 然后Gln转化为Glu, Glu再被囊泡Glu转运体摄取到突触囊泡中[101](图1)。而已有研究发现, 跑台运动可使PD模型动物纹状体mGluR2/3的mRNA和蛋白表达水平显著上调, 纹状体神经元胞外Glu浓度显著降低, PD相关行为功能障碍显著改善[21-22]。

综上, 运动可能一方面通过上调*GLT-1* mRNA和GLT-1蛋白表达水平, 使得EAAT2清除突触间隙高浓度的Glu, 降低PD纹状体神经元胞外Glu浓度; 另一方面可能通过上调定位于皮层纹状体突触前末梢的II组mGluRs(mGluR2/3)的mRNA和蛋白表达水平, 致使星形胶质细胞*GLAST* mRNA和GLAST蛋白表达水平上调, 使得EAAT1清除突触间隙高浓度的Glu, 最终降低Glu兴奋性神经毒性, 重建BG功能并改善PD相关行为功能障碍。

6 结语和展望

纹状体星形胶质细胞EAATs表达水平在PD中发生了改变, 对于PD的发生和进程展现出重要的作用。总的来说, PD纹状体星形胶质细胞EAATs表达水平显著下降, 导致Glu再摄取量减少, 突触间隙Glu浓度显著升高, 造成Glu兴奋毒性作用, 并使BG功能紊乱以及PD相关行为功能障碍进一步恶化, 从而加重了PD病理状况, 加快了疾病的进程。

运动干预作为PD的一种辅助治疗手段, 显著改善了PD患者和PD模型动物相关行为功能障碍。这一积极的影响效应可能一方面通过上调*GLT-1* mRNA和GLT-1蛋白表达水平, 降低PD纹状体神经元胞外Glu浓度; 另一方面可能通过上调mGluR2/3的mRNA和蛋白表达水平, 从而导致纹状体星形胶质细胞*GLAST* mRNA和GLAST蛋白表达水平上调来介导的。而这仍需要做进一步的研究来证实。因此, 探索运动对PD纹状体星形胶质细胞EAATs表达水平的影响可能是未来防治PD新的关注点。

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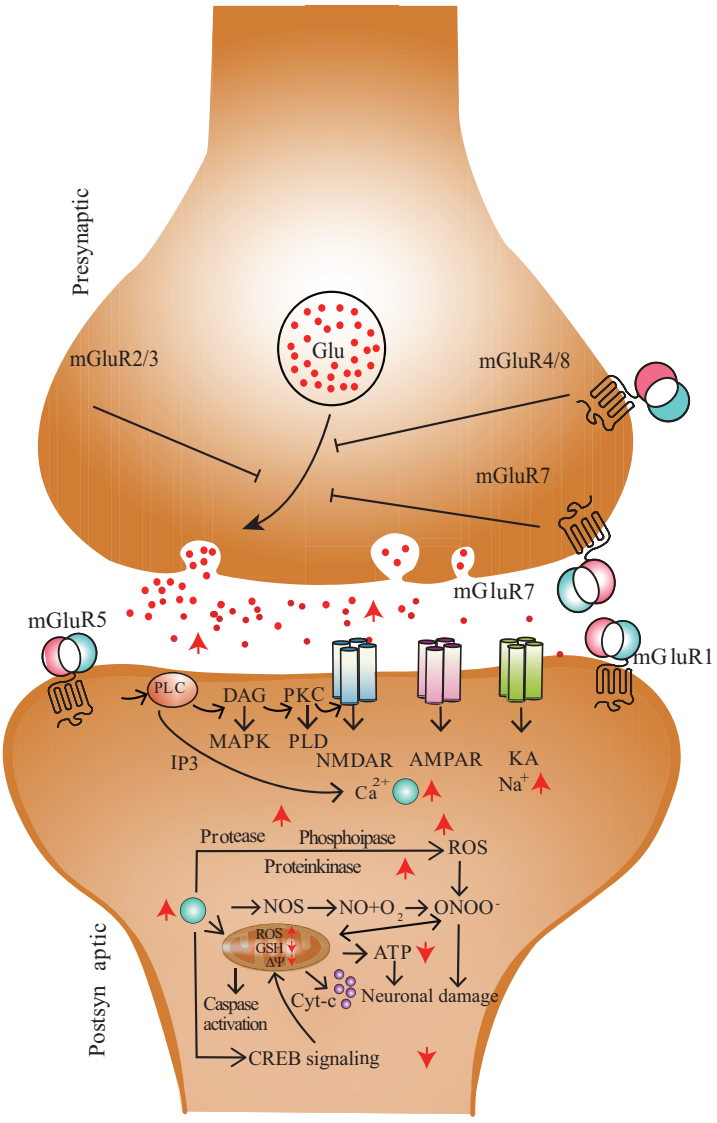

图2 PD纹状体内Glu兴奋性毒作用启动胞内一系列信号级联反应(根据参考文献[94]修改)

Fig.2 Excitotoxicity of Glu in PD striatum initiates a series of intracellular signaling cascades (modified from the reference [94])

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