中国细胞生物学学报 Chinese Journal of Cell Biology 2025, 47(2): 299–305
DOI: 10.11844/cjcb.2025.02.0016
CSTR: 32200.14.cjcb.2025.02.0016

运动通过调控BDNF/TrkB通路防治帕金森病研究进展

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摘要 帕金森病(Parkinson's disease, PD)是一种慢性进行性的神经系统疾病。脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)/酪氨酸激酶受体B(tyrosine kinase receptor B, TrkB)信号通路失调与PD发生发展有关。调控BDNF/TrkB信号通路已被认为是PD的一种治疗策略。运动疗法是一种无毒、低成本、普遍适用的非药理治疗手段, 不仅可以降低PD的发病风险, 而且在改善PD相关行为功能障碍方面均具有积极的作用, 其机制可能是通过调控BDNF/TrkB信号通路来实现的。该文从BDNF/TrkB通路视角入手, 对它在PD发生发展及PD运动防治中的可能作用等方面的研究进行综述。

关键词 运动; 帕金森病; BDNF/TrkB通路

Research Progress of Exercise in Prevention and Treatment of Parkinson's Disease by Regulating BDNF/TrkB Pathway

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Abstract PD (Parkinson's disease) is a chronic progressive neurological disorder. Dysregulation of BDNF (brain-derived neurotrophic factor)/TrkB (tyrosine kinase receptor B) signaling pathway is associated with PD development. Regulation of the BDNF/TrkB signaling pathway has been suggested as a therapeutic strategy in PD. Exercise therapy is a non-toxic, low-cost and generally applicable non-pharmacological treatment that not only reduces the risk of PD, but also has a positive effect in improving PD-related behavioral dysfunction, and its mechanism may be achieved by regulating the BDNF/TrkB signaling pathway. This article reviews the possible role of BDNF/TrkB pathway in the occurrence and development of PD and the prevention and treatment of PD exercise.

Keywords exercise; Parkinson's disease; BDNF/TrkB pathway

帕金森病(Parkinson's disease, PD)是世界上发病率仅次于阿尔茨海默病的第二常见慢性神经退行性疾病, 随着人口老龄化的加剧, 我国的PD患者人数逐年增加, 发展形势十分严峻, PD已成为继肿瘤、心脑血管疾病之后危害我国中老年人健康的"第三大杀手", 预计到2030年, 我国PD患者将达到490万(全球约870万)[1]。最初于1817年首先对PD进行了详细描述, 其临床表现主要包括静止性震颤、运动迟缓、肌强直和姿势步态障碍[2], 这显著影响了患者的日常生活活动, 并大大降低了他们的生活质量。PD的这些主要运动症状是由中脑黑质致密部(substantia nigra pars compacta, SNpc)多巴胺(dopamine, DA)能神经元的变性死亡, 从而引起纹状体DA含量显著性减少所致的[3]。然而, 面对这种疾病, PD患者的治疗选择非常有限, 根源在于PD背后的致病机理尚不

收稿日期: 2024-11-21 接受日期: 2024-12-24
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Received: November 21, 2024 Accepted: December 24, 2024
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明确。

脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)在外周和中枢神经系统的神经元分化、细胞存活和突触功能中起着关键作用[4]。BDNF通过激活酪氨酸激酶受体B(tyrosine kinase receptor B, TrkB)诱导下游各种信号通路的激活, 从而促进突触可塑性、抗凋亡活性、细胞骨架蛋白合成以及控制树突生长和分支[5]。研究表明, PD患者或PD模型动物BDNF/TrkB信号通路失调与PD发生发展密切联系[6-8]。研究发现, 调控BDNF/TrkB信号通路能够有效缓解PD相关行为功能障碍[9-10]。运动疗法是一种无毒、低成本、普遍适用的非药理治疗手段, 对PD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, 运动/体育锻炼是PD的一种治疗形式, 不仅可以降低PD的发病风险, 而且在改善PD相关行为功能障碍方面均具有积极的作用。动物实验结果证实, 运动干预可有效改善PD相关行为功能障碍。本文以BDNF/TrkB通路为切入点, 综述其在PD及PD运动防治中的可能作用, 以期为运动干预缓解PD相关行为功能障碍的潜在分子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 BDNF/TrkB

BDNF是神经营养因子蛋白家族的一员, 最初从猪脑中纯化[11]。人、大鼠和小鼠中BDNF由单个*BDNF*基因编码, 其转录受几个启动子调节[12]。BDNF在神经元中的积极作用是激活成熟BDNF的高亲和力受体TrkB。BDNF与TrkB受体高亲和力结合, 与p75受体的亲和力较低[13]。BDNF/TrkB信号通路的激活有助于神经发生、胶质生成以及神经元的生长和存活[14]。BDNF/TrkB活化主要启动丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)、磷脂酰肌醇3-激酶(phosphatidylinositol 3-kinase, PI3K)和磷脂酶Cγ(phospholipase Cγ, PLCγ)信号通路(图1)。TrkB细胞内酪氨酸残基的二聚化和自身磷酸化是多种细胞内信号激活所必需的[15]。TrkB活化(磷酸化)后, 其Tyr490和Tyr515残基处TrkB的激活募集Shc衔接蛋白(Src同源2结构域), 然后与生长因子受体结合蛋白2(growth factor receptor-bound protein 2, grb2)结合, 再与鸟苷三磷酸水解酶(guanosine triphosphate, GTP) Ras结合形成复合物, 启动细胞外信号调节激酶(extracellular regulated protein kinases, ERK)活化, 进而激活MAPK/ERK通路, 导致环磷酸腺苷效应元件结合蛋白(cAMP-response element binding protein, CREB)激活[16-17]。然后磷酸化的CREB易位到细胞核中, 通过与*BDNF*启动子结合诱导*BDNF*转录, CREB与*BDNF*启动子结合驱动BDNF表达, 调节神经元存活、分化和突触可塑性[18]。PI3K通路通过Ras在Tyr515残基的联合作用下被激活, 从而激活了多个级联反应, 即PI3/蛋白激酶B(protein kinase B, PKB)和丝裂原活化蛋白激酶(mitogen-activated protein kinase, MEK)/MAPK通路[19]。MAPK和PI3K信号转导均通过CREB发挥抗炎、抗氧化应激、调节神经递质表达及促进神经可塑性等神经保护功能。PLCγ/IP3途径的BDNF导致细胞内钙库释放钙, 激活依赖Ca^{2+}/钙调蛋白的蛋白激酶(Ca^{2+}/calmodulin-dependent protein kinase, CaMKs), 进而激活CREB磷酸化[20-21]。此外, 二酰甘油(diacylglycerol, DAG)激活蛋白激酶C(protein kinase C, PKC), PKC转位到膜上进一步激活和磷酸化ERK, 导致突触可塑性, 从而发挥神经保护作用[20,22]。总之, 在这些神经元反应中, BDNF/TrkB信号通路(包括下游细胞内信号)发挥着关键作用。研究表明, BDNF在神经退行性疾病[如PD、(Alzheimer's disease, AD)和(Huntington's disease, HD)等]中的表达情况错综复杂, 值得注意的是, 许多神经退行性疾病损害了大脑中BDNF的产生, 反过来, BDNF的下调加快了神经退行性疾病的发生发展[23]。

2 BDNF/TrkB与PD

在一项临床试验中, 尸检分析显示PD大脑黑质*BDNF* mRNA表达水平显著降低[24]。在一项涉及47例PD患者和23例健康对照者的病例研究中, 与健康对照组相比, PD患者早期BDNF血清水平显著降低[25]。后来, 随着PD神经病理学的发展, 发现血清BDNF水平升高可能与PD的严重程度相关[25]。在PD晚期BDNF血清水平升高可能是减少黑质DA能神经元变性和相关神经炎症的一种代偿机制[25]。此外, PD的发生发展还与外周BDNF/TrkB信号转导减弱有关[26]。与28例健康对照者相比, 28例PD患者外周血淋巴细胞BDNF和TrkB表达水平显著降低[26]。然而, PD患者长期使用左旋多巴治疗可增强BDNF和TrkB的表达[26]。有趣的是, 一项涉及48例PD患者和24例健康对照受试者的病例对照研究显示, 与

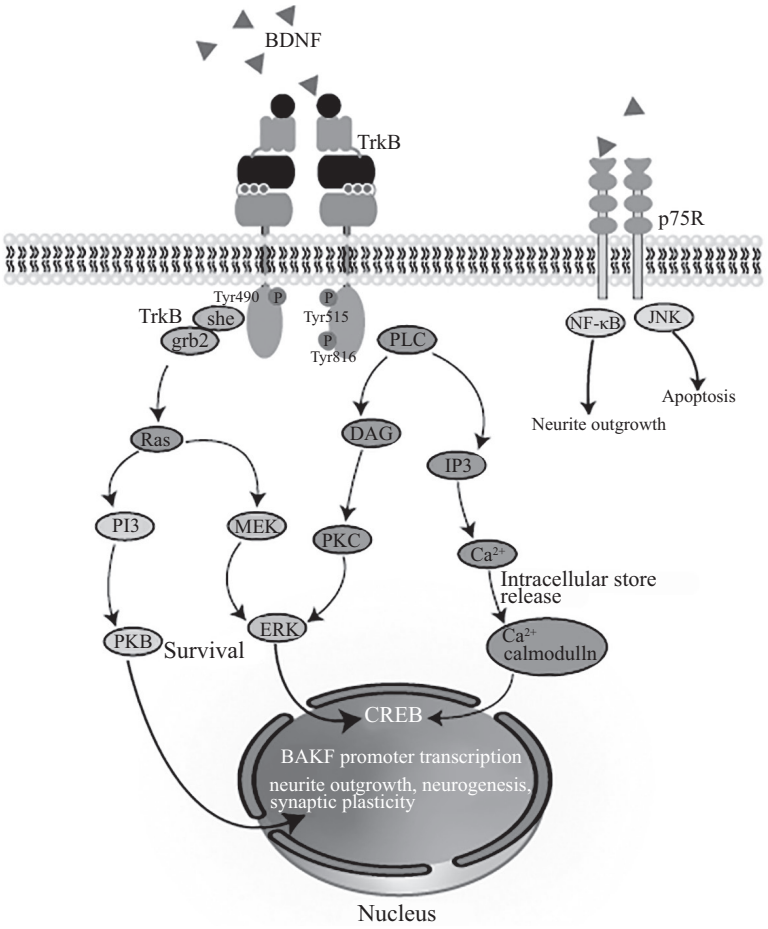

图1 BDNF/TrkB信号通路及其下游细胞内信号转导

Fig.1 BDNF/TrkB signaling pathway and its downstream intracellular signaling

对照组相比, PD患者的脑脊液(cerebro-spinal fluid, CSF) BDNF水平升高[27]。另外, 一项97例PD患者和102例健康对照者的病例研究表明, 与健康对照组相比, PD患者血清BDNF水平显著下降, 并与认知功能障碍相关[28]。因此, PD晚期BDNF/TrkB信号转导的增强可能是由左旋多巴的治疗引起的。此外, BDNF与PD患者的特异性表现(如不宁腿综合征和抑郁)相关。一项横断面研究纳入了53例伴有不宁腿综合征的PD患者、196例不伴有不宁腿综合征的PD患者和326例匹配的健康对照者, 结果显示伴有不宁腿综合征的PD患者BDNF血清水平显著降低[28-29]。一项对PD患者的队列研究表明, BDNF血清水平主要在伴有抑郁和运动功能障碍的PD女性患者中降低[28]。因此, 血清BDNF水平可能是检测PD患者抑郁是否发生的标志物。MILLER等[24]观察到PD患者死后α-突触核蛋白(α-aynucelin, α-Syn)的较高表达与BDNF表达下调有关。值得注意的是, α-Syn下调BDNF表达及其下游信号。在过表达α-Syn的神经元中BDNF和TrkB的逆行转运减少[30]。因此, 激活BDNF/TrkB信号通路可能会下调α-Syn的表达。大脑和胃肠道之间通过肠−脑轴存在紧密的联系。研究表明, α-Syn蓄积最初在肠神经系统中开始, 可通过迷走神经逆行转运到大脑。此外, 肠道微生态失调可能诱导PD神经炎症的发生。肠神经系统中积累的α-Syn可抑制肠道BDNF的表达, 动物和人的研究恰恰证实BDNF信号在肠道中减弱, 并通过诱导肠道炎症和肠道菌群失调影响PD胃肠道疾病的发生发展[31-33]。

BDNF/TrkB信号转导与PD发生发展密切相关。目前有证据表明, 增强BDNF活性在改善PD临床前模型的症状方面起着关键的作用[9-10]。GIBRAT等[34]研究发现, 半胱胺通过上调MPTP诱导的PD模型小鼠BDNF表达水平, 致使模型小鼠黑质TH免疫阳性细胞、纹状体TH免疫阳性纤维终末的平均光密度以及黑质*Nurr1* mRNA表达水平显著上调, 从而产生神经保护作用。CAO等[9]研究表明, 核因子E2相关因子2(nuclear factor erythroid derived 2-like 2, Nrf2)的激活和DNA甲

基结合蛋白2(methyl-CpG-binding protein 2, MeCP2)的抑制对BDNF表达水平的上调发挥调控作用。此外, 在MPTP诱导的PD模型小鼠中, MeCP2表达沉默致使BDNF和Nrf2表达水平显著上调, 模型小鼠在转棒实验中的持续时间显著增加[9]。ZHAO等[35]研究发现, 在司来吉兰(1.0 mg/kg·天, 持续14天)给药MPTP诱导的PD模型小鼠中, 模型小鼠BDNF蛋白和*BDNF* mRNA表达水平显著上调, 模型小鼠的步态功能障碍显著改善。KANDIL等[36]研究表明, 在阿米替林给药鱼藤酮诱导的PD模型大鼠中, 模型大鼠TrkB表达水平显著上调, 模型小鼠总移动距离显著增加(旷场实验), 在棒上的维持时间显著提高(转棒实验)。SALARI等[10]研究发现, 丝胶给药能够使鱼藤酮诱导的PD模型大鼠纹状体BDNF和TrkB蛋白表达水平显著上调, 模型大鼠在转棒实验中的潜伏时间显著增加, 在杆实验中停留在杆上的时间显著缩短。LI等[37]研究表明, 在7,8-二羟基黄酮给药MPTP诱导的PD模型小鼠中, 模型小鼠TrkB表达水平显著上调, 模型小鼠运动功能障碍显著改善, 表现为模型小鼠在棒上的维持时间显著增加(转棒实验), 下行时间显著缩短(极点实验), 到达平台的时间显著缩短(钢丝悬吊实验)。ZHAO等[38]研究发现, 电针能够使MPTP诱导的PD模型小鼠BDNF和TrkB表达水平显著上调, 模型小鼠在棒上的维持时间显著增加(转棒实验)。李媛媛等[39]研究表明, 电针可使MPTP诱导的PD模型小鼠纹状体BDNF蛋白表达水平显著上调, 模型小鼠悬挂时间显著缩短(悬挂实验), 旷场运动距离显著增加(旷场实验)。

综上, BDNF和TrkB表达水平在PD中显著下调, 可能会导致BDNF/TrkB信号通路活性在PD中减弱, 这与PD发生发展密切相关, 而BDNF/TrkB信号通路可能是PD的潜在治疗靶点及调控BDNF/TrkB信号转导是实现PD有效神经保护的策略之一。

3 运动与BDNF/TrkB

目前已有报道关注到健康机体(人和大鼠)在运动后BDNF表达水平升高, 这可能会增强BDNF/TrkB信号转导。LIU等[40]研究表明, 4周的跑步机训练(5天/周)能够使雄性BALB/c小鼠海马区BDNF表达水平在每次运动后1 h、2 h和4 h短暂的增加。SKUP等[41]研究发现, 4周的跑步机训练(5天/周)可使成年雄性Wistar大鼠神经元核周体内BDNF表达水平上调。SEIFERT等[42]研究表明, 5周的跑步机训练(5天/周)能够使小鼠海马区*BDNF* mRNA表达水平显著上调。ALOMARI等[43]研究发现, 6周的游泳训练(5天/周)可使雄性Wistar大鼠海马区BDNF表达水平显著升高。JIN等[44]研究表明, 6周的跑步机训练(7天/周)可使成年雄性Sprague-Dawley大鼠海马区BDNF表达水平显著上调。SO等[45]研究发现, 6周的跑步机训练(7天/周)可使雌性C57BL/6小鼠海马区BDNF表达水平显著升高。CASSILHAS等[46]研究表明, 8周的跑步机训练(5天/周)可使成年雄性Wistar大鼠海马区BDNF表达水平显著上调。COSTA等[47]研究发现, 8周的跑步机训练(60%~75% $VO2_{max}$, 1天/周、3天/周和7天/周, 3组频率)能够使年轻成年和中年雄性Wistar大鼠海马区BDNF表达水平均显著升高。除了健康机体外, 有关运动对BDNF和TrkB表达水平的影响, 在不同疾病状态下也有大量的研究报道。MAEJIMA等[48]研究发现, 4周的跑步机训练(5天/周)可使加速衰老小鼠海马区BDNF蛋白和*BDNF* mRNA表达水平显著上调。CHENG等[49]研究表明, 12周的游泳训练(30 min/天, 5天/周)能够使链脲佐菌素诱导的糖尿病模型小鼠大脑皮层BDNF和TrkB蛋白表达水平显著上调。CHEN等[50]研究发现, 连续14天的跑步机训练(12 m/min, 1 h/天, 1次/天)可使应激模型小鼠大脑皮层BDNF蛋白和mRNA表达水平显著上调, 模型小鼠的焦虑行为显著改善, 表现为模型小鼠在旷场实验和高架十字迷宫任务中的中央区持续时间显著增加, 开放臂持续时间也显著提高。LEE等[51]研究表明, 连续14天的跑步机训练(前5 min 2 m/min; 后5 min 3 m/min; 后20 min 4 m/min, 1 次/天, 30 min/天)可使脑缺血模型沙鼠海马区BDNF和TrkB表达水平显著上调, 模型沙鼠的记忆障碍显著改善, 表现为模型沙鼠在跳台回避任务的潜伏期显著增加。

总之, 不同方式、强度、持续时间的运动训练干预对健康机体和不同疾病状态下BDNF和TrkB活性和表达水平的影响具有一定的差异。但长期慢性运动对不同动物模型机体BDNF和TrkB活性和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运动方式组合(如耐力+抗阻运动)进行进一步的研究。

4 BDNF/TrkB介导的PD运动防治

研究发现, BDNF通过激活TrkB受体诱导下游

MAPK、PI3K和PLC-γ信号转导[52]。这些信号转导激活CREB, CREB促进突触可塑性、抗凋亡活性、细胞骨架蛋白合成以及控制树突生长和分支, 进而诱导神经退行性疾病的防治作用[52]。而ZHAO等[53]研究发现, 4周的振动训练可使MPTP诱导的PD模型小鼠纹状体BDNF表达水平显著上调, 模型小鼠在网格实验中的运动功能显著改善。张康等[54]研究表明, 5周跑台运动(12 m/min, 60 min/天, 5天/周)可使MPTP诱导的PD模型小鼠海马区BDNF和TrkB表达水平均显著上调。因此, 不难推测, 运动可能通过上调BDNF的表达激活TrkB, 从而激活下游信号通路MAPK、PI3K和PLC-γ, 这些信号的增强最终导致CREB激活, 进而通过抗炎、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功能介导PD相关行为功能障碍的改善[51]。BDNF/TrkB通路可能是运动防治PD的潜在分子靶点。靶向BDNF/TrkB通路的干预很可能成为未来一种有前景的新治疗方式, 而这需要做进一步的研究证实。

5 小结与展望

BDNF/TrkB通路与PD发生发展密切相关。促进BDNF/TrkB信号转导在PD神经保护和临床前模型的症状改善方面起着关键的作用; 运动在改善PD相关行为功能障碍方面具有积极的作用, 运动也能够影响BDNF/TrkB通路。运动在PD防治过程中表现的积极作用可能是BDNF/TrkB通路介导的。BDNF/TrkB通路可能是运动防治PD的潜在分子靶点。

运动疗法是一种无毒、低成本、普遍适用的非药理治疗手段, 不仅可以降低PD的发病风险, 而且在改善PD相关行为功能障碍方面均具有积极的作用, 其机制可能是通过调控BDNF/TrkB信号通路来实现的。但运动治疗因人而异, 运动方式、强度、时长也各有不同, 不同运动方式之间的对比和运动带来的长期影响又是怎样的呢? 这对阐释运动改善PD相关运动功能障碍的分子机制是极其重要的, 未来还需要做进一步的系统研究和更多的探索。

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