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运动与多巴胺的交叉对话:作用与相关机制

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摘 要:多巴胺是调控运动、奖赏、情绪和认知的关键神经递质,其功能失调关联多种疾病。运动作为一种安全有效的干预手段,展现出调节多巴胺系统的显著潜力。本文系统综述了运动对多巴胺系统的多层次调节机制,包括促进多巴胺合成释放、增强突触可塑性、提升抗氧化及神经营养能力;探讨了多巴胺对运动执行、学习及动机的反馈调节;重点分析了运动在帕金森病、抑郁症、高血压及骨代谢异常等多巴胺相关疾病中的干预作用,强调了多巴胺在运动介导的疾病修复中的核心地位。未来需结合多组学等技术推动精准运动干预研究,为构建“运动-多巴胺-疾病”调控网络及优化临床康复提供理论基础。

关键词:多巴胺;运动干预;神经可塑性;奖赏系统;分子机制
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The cross-talk between exercise and dopamine: roles and related mechanisms

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Abstract: Dopamine is a key neurotransmitter involved in the regulation of motor control, reward processing, emotion, and cognition. Dysregulation of dopamine signaling is implicated in various neurological, psychiatric, and metabolic disorders. As a safe and effective intervention, exercise has demonstrated significant potential in modulating the dopaminergic system. This review provides a comprehensive overview of the multi-level mechanisms by which physical activity influences dopamine function, including enhanced synthesis and release, improved synaptic plasticity, and increased antioxidant and neurotrophic support. It further explores the reciprocal role of dopamine in regulating motor performance, learning, and motivation. Special attention is given to the therapeutic effects of exercise in dopamine-related conditions such as Parkinson's disease, depression, hypertension, and bone metabolic disorders. Finally, the review underscores the central role of dopamine in exercise-mediated disease modulation and highlights the need for integrating multi-omics and individualized approaches to advance precision exercise interventions and inform clinical rehabilitation strategies.

Key words: dopamine; exercise intervention; neuroplasticity; reward system; molecular mechanisms

运动作为一种非药物干预方式,近年来在中枢神经系统疾病的预防与康复中展现出显著疗效。大量研究表明,规律的身体活动不仅有助于改善认知功能、缓解情绪障碍,还能延缓如帕金森病(Parkinson's disease,PD)及抑郁症等神经退行性疾病的进程。尽管运动干预的临床效果已获得充分肯定,但其作用机制仍未完全阐明,特别是在分子与神经调控层面。

多巴胺(dopamine,DA)作为中枢神经系统中的关键神经递质,与多种神经精神疾病密切相关。它不仅参与调节运动控制、情绪反应、奖赏机制及认知加工,其功能异常更与帕金森病、抑郁症等多种神经系统疾病的发生发展密切相关。运动与多巴胺之间存在多维度的交互机制,包括神经通路调节、奖赏系统激活及突触可塑性增强等方面。然而,系统性总结二者交互关系的研究尚不充分,尤其在分子机制

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与神经调控路径方面仍有待深入探讨。因此,本文旨在系统梳理多巴胺在运动调节中的作用机制,重点探讨其在运动控制、奖赏系统激活以及相关神经系统疾病中的调节功能,为后续运动干预的机制研究与临床应用提供理论支撑与参考依据(图1)。

1　运动对多巴胺系统的调节作用

1.1　运动促进多巴胺合成与突触释放

运动通过激活多条生物信号通路,显著促进多巴胺的合成与突触释放。多巴胺的生物合成由两种关键限速酶介导:酪氨酸羟化酶(tyrosine hydroxylase,TH)将酪氨酸转化为L-多巴(L-DOPA),芳香族L-氨基酸脱羧酶(aromatic L-amino acid decarboxylase,AADC)进一步催化其生成多巴胺[1]。有氧运动及高强度间歇训练已被证实可上调TH与DDC的基因表达与酶活性,加速多巴胺合成[2]。

在分子信号调控层面,运动可上调胰岛素与胰岛素样生长因子-1(insulin-like growth factor-1,IGF-1)水平,增强其与下丘脑及中脑区域胰岛素受体(insulin receptors,InsRs)的结合能力,进而激活磷脂酰肌醇3激酶/蛋白激酶B(phosphoinositide 3-kinase/protein kinase B,PI3K/Akt)信号通路。该通路通过促进转录因子cAMP反应元件结合蛋白(cAMP response element-binding protein,CREB)的磷酸化,上调TH与DDC的基因表达和酶活性,从而直接增强多巴胺的生物合成效率。此外,PI3K/Akt通路还调控多巴胺转运蛋白(dopamine transporter,DAT)在突触前膜的定位与功能状态,提高突触间隙中多巴胺的再摄取速率与代谢周转效率,进一步优化多巴胺系统的动态稳态调节[3,4]。此外,运动可增强纹状体胆碱能中间神经元(cholinergic interneurons,ChIs)的放电活动,促进其释放乙酰胆碱(acetylcholine,ACh)[5],并激活定位于多巴胺能轴突末梢的烟碱型乙酰胆碱受体(nicotinic acetylcholine receptors,nAChRs)[6]。该过程通过引发膜去极化及电压门控钙通道(voltage-gated calcium channels,VGCCs)开放,促使多巴胺囊泡融合并实现钙依赖性快速释放,是纹状体多巴胺动态调控的重要机制之一[6,7]。

运动还提高脑源性神经营养因子(brain-derived neurotrophic factor,BDNF)和IGF-1水平,这些因子分别通过原肌球蛋白受体激酶B(tropomyosin receptor kinase B,TrkB)和胰岛素样生长因子-1受体(insulin-like growth factor-1 receptor,IGF1R)活化下游细胞外信号调节激酶/丝裂原活化蛋白激酶通路(extracellular signal-regulated kinase/mitogen-activated protein kinase,ERK/MAPK)与Akt通路,增强多巴胺神经元的能量代谢、轴突生长和突触可塑性,从而实现对多巴胺系统的结构性重塑[8]。

1.2　运动诱导多巴胺系统的功能适应性与可塑性

长期运动训练可显著提升多巴胺系统的结构与

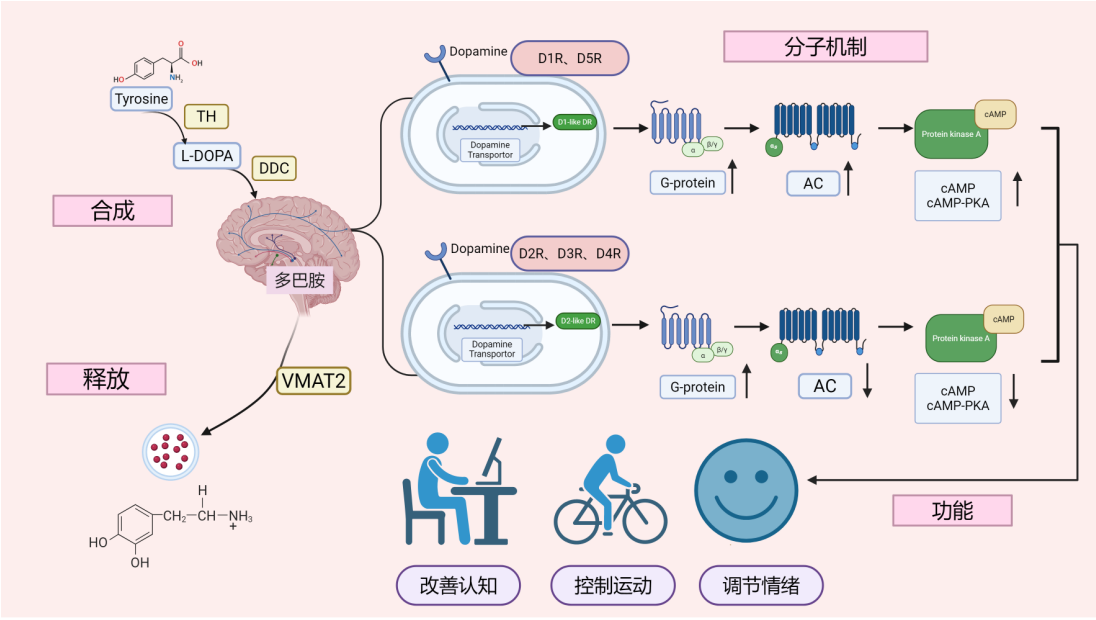

图1　多巴胺生物合成、释放与受体信号通路

Figure 1　Dopamine biosynthesis, release and receptor signaling pathways

功能可塑性。在转录水平,运动促进DAT在纹状体与前额叶皮层中的转录表达,改善多巴胺再摄取功能,提高突触间隙多巴胺的稳态调节能力[9]。该过程依赖于CREB磷酸化及cAMP/PKA[10]、PI3K/Akt[4]、MAPK[11]等经典信号轴的协同激活,从而增强DAT合成与膜定位能力。BDNF、IGF-1及纤维连接蛋白Ⅲ型结构域包含蛋白5(fibronectin type Ⅲ domain-containing protein 5,FNDC5)等运动诱导的神经营养因子在多巴胺系统中具有突出的调节作用。它们通过激活TrkB与IGF1R,增强多巴胺神经元存活率、突触形成能力及活动依赖性突触可塑性,构建更加稳定而高效的多巴胺信号网络[3,12]。

此外,运动激活内源性抗氧化系统如超氧化物歧化酶(superoxide dismutase,SOD)、过氧化氢酶(catalase,CAT),清除自由基,抑制活性氧(reactive oxygen species,ROS)对黑质多巴胺神经元的氧化损伤,保护其线粒体功能,减缓年龄相关或病理性退行性变化[13]。

1.3 运动在成瘾与认知障碍中的多巴胺调节机制

多巴胺系统功能紊乱是药物成瘾、抑郁障碍、注意力缺陷多动障碍(ADHD)等疾病的重要病理基础。慢性滥用成瘾物质(如可卡因)会造成伏隔核多巴胺持续升高、DAT功能障碍与奖赏系统去敏化,表现为动机缺失、执行障碍与情绪波动[14,15]。运动通过调节多巴胺与谷氨酸的协同通路,降低突触兴奋毒性[16];上调钙信号促进TH表达,并激活多巴胺合成通路;通过运动诱导的多巴胺释放激活奖赏系统,模拟天然奖赏体验,从而减弱对药物奖赏的依赖[17]。此外,运动可修复染色质重塑异常,稳定与奖赏记忆、冲动控制相关的多巴胺回路,为神经精神疾病的非药物干预提供了理论支撑[18]。

综上,不同类型、强度及持续时间的运动均可通过多层级机制调节多巴胺系统,从分子、细胞到神经环路水平形成综合性调控。为了更系统地展示运动参数与多巴胺系统间的关系,本文整理了近年动物及人体研究的主要发现(表1)。

2 多巴胺对运动功能的调控作用

2.1 多巴胺介导的运动指令编码与执行

多巴胺作为中枢神经系统的核心神经递质,通过构建精密的运动调节网络,在运动指令的生成、传导与执行中发挥关键作用。在基底节运动环路中,D1类受体(D1R)激活直接通路中的中等棘状神经元(medium spiny neurons,MSNs),抑制苍白球内节(globus pallidus internus,GPi)与黑质网状部(substantia nigra pars reticulata,SNpr),释放丘脑对运动皮层的兴奋性输入,从而促进运动启动;D2类受体(D2R)则抑制间接通路,减少对运动皮层的抑制信号,优化运动输出模式[28-30]。多巴胺还通过调节突触后膜受体敏感性、突触前递质释放以及离子通道活动(如D1受体促进Na^+内流并引发去极化),提高突触传递效率与神经元兴奋性[31]。在信号转导层面,多巴胺激活腺苷酸环化酶(AC)-cAMP-蛋白激酶A(PKA)通路,调控运动关键蛋白的磷酸化状态,从而维持直接与间接通路的平衡与协调[32]。尽管多巴胺不直接作用于骨骼肌,但可通过黑质-纹状体通路调节运动皮层输出的强度与时序,间接影响神经肌肉接头ACh的释放及其受体活性[33]。高水平多巴胺可抑制ACh释放、降低肌肉收缩反应,并通过调节肌质网Ca^{2+}的释放与再摄取,精确控制肌肉张力与舒张节律[34]。

2.2 多巴胺参与运动学习与神经可塑性重构

多巴胺不仅是运动执行的关键调控者,更在动态的神经可塑性重构过程中扮演核心角色,其通过调控长时程增强(LTP)与长时程抑制(LTD)的平衡,深刻影响运动技能的学习与巩固[35]。

在分子机制层面,多巴胺通过D1与D2受体的双向作用,构成突触可塑性的基本调控逻辑。在初级运动皮层(M1)与纹状体中,D1受体的激活通过启动cAMP/PKA信号通路,促进突触后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)受体中谷氨酸受体1亚基(glutamate receptor subunit 1,GluR1)的磷酸化,从而驱使更多AMPA受体插入突触后膜,增强突触传递效能,形成LTP,以此强化与成功行为相关的神经连接[36]。相反,D2受体的激活则通过抑制cAMP/PKA通路,或招募其他磷酸酶,促进AMPA受体的内吞,支持LTD的发生,实现对无效或错误运动策略的“突触修剪”[37]。此外,D4受体表现出更为复杂的“可塑性门控”特性,能够依据局部微环境的状态双向调节LTP/LTD的诱导阈值,从而动态调整学习速率,这在快速适应性运动与技能迁移过程中尤为关键[38]。

多巴胺系统的精妙之处更在于其卓越的时空编

表1　不同运动参数对多巴胺系统的调节效应及潜在神经机制

Table 1　Regulatory effects of different exercise parameters on the dopamine system and underlying neural mechanisms

研究对象	运动方式	运动频率	运动强度	影响的脑区/多巴胺系统环节	主要调节效应	潜在分子/细胞/信号机制	参考文献
C57小鼠	有氧运动	30 d	中等强度	纹状体	DA表达增加	BDNF/TrkB信号上调;突触可塑性增强;释放效率提高	[6]
C57小鼠	有氧运动	60 min/次,6 d/w,4 w	中等强度	伏隔核	中型多棘神经元兴奋性降低	运动诱导神经适应	[19]
High-Runner(HR)小鼠	有氧运动	2 w	中等至高强度	海马体、前额叶皮层和小脑	D1/D5受体表达降低,DAT表达增加	调节多巴胺能突触传递	[20]
Long-Evans大鼠	有氧运动	30 min/d,6 d	低至中等强度	海马、蓝斑和腹侧被盖区	酪氨酸羟化酶阳性神经元激活	激活背侧海马体,触发突触和细胞可塑性	[21]
Wistar大鼠	有氧运动	11 m/min,30 min/d	中等强度	纹状体	DA表达增加	调节多巴胺信号传导	[22]
SD大鼠	有氧运动	15 m/min,60 min/d,5 d/w	中等强度	海马	E、NE和DA表达增加	神经保护性海马结构突触可塑性增强	[23]
SD大鼠	有氧运动	60 min/d,5 d/w,共4 w	中等强度	前额叶皮层	DA、5-HT表达增加	改善突触结构可塑性损伤	[24]
Lewis大鼠	高强度间歇训练	7 d/w,共6 w	高强度	腹侧尾状壳核、伏隔核	D2受体表达增加	调节多巴胺信号传导	[25]
健康人类	有氧运动	中等强度运动	中等强度	纹状体、基底节、奖赏相关区域	DA表达增加	运动诱发DA释放促进提升认知反应速度	[26]
帕金森病患者	高强度运动	6个月	高强度	黑质、纹状体	DAT表达增加	运动诱导神经元功能改善	[9]
帕金森病患者	多模式运动(抗阻训练、有氧运动和平衡)	5 d/w,共12 w	中等强度	全脑	BDNF、GDNF表达增加	神经营养因子支持、多层神经可塑性作用	[27]

注:min,分钟;d,天;w,周;m,米。

Note: min, minute; d, day; w, week; m, meter.

码特异性。多巴胺神经元在运动执行后短暂且局部地“相位性”释放,为突触可塑性设定了一个关键的“资格痕迹”时间窗。这意味着,突触活动会留下一个短暂的分子印记;如果多巴胺信号(作为奖励或成功完成的信号)在此时间窗内抵达,就能选择性地强化或弱化这个“刚刚活跃过”的特定突触,从而将奖赏信号与导致该奖赏的具体神经活动精确关联。最新研究还揭示,多巴胺在纹状体等区域的释放可以达到亚细胞级别的精准度,形成局部的“热点”,使得表达不同受体(如高亲和力D2受体)的神经元能够对多巴胺进行空间解码,实现对单个树突棘的独立调控[39]。

上述受体与信号通路最终汇聚于对运动皮层可塑性的调控。源自中脑腹侧被盖区(ventral tegmental area,VTA)并投射至M1的多巴胺能神经末梢,是运动技能学习所必需的结构基础。阻断M1区的D1/D2受体可显著削弱LTP的诱导[40],这从功能上印证了多巴胺信号在运动皮层可塑性中的核心地位。在信号转导层面,除了经典的cAMP/PKA通路,磷脂酶C(phospholipase C,PLC)-Ca^{2+}-Ca^{2+}/钙调蛋白依赖性蛋白激酶Ⅱ(calcium/calmodulin-dependent protein kinase Ⅱ,CaMKⅡ)信号轴同样在D1受体介导的LTP与LTD诱导过程中扮演核心角色,共同调控运动技能的学习[41]。

2.3　多巴胺调节运动中的奖赏机制与动机维持

中脑边缘系统(mesolimbic system,MLS)是多巴胺调控运动动机与行为强化的核心环路,由VTA多巴胺能神经元投射至伏隔核(nucleus accumbens,NAc)、前额叶皮层(prefrontal cortex,PFC)、纹状体及海马等区域构成。在积极刺激下,VTA释放多巴胺,产生奖赏反应,显著增强运动积极性[42]。NAc作为奖赏信号整合枢纽,接收谷氨酸能输入并受多巴胺调节,影响神经元兴奋性与奖赏预期相关的行为输出,其下游信号进一步投射至腹侧苍白球等区域,驱动奖赏相关运动行为[43]。背侧纹状体则主要

参与动作选择与执行，其多巴胺释放呈现与任务同步的“波浪式”动态模式，为奖赏预期提供时空编码基础[44]。多巴胺还通过调节局部γ-氨基丁酸（gamma-aminobutyric acid，GABA）能中间神经元对MSNs的前馈抑制作用，协调奖赏信号传递与整合，并调节神经肽表达，从而参与奖赏敏感性和长期行为适应性变化[45]。最新研究显示，多巴胺在奖赏学习中可与5-羟色胺系统协同作用，在慢性运动干预下重塑奖赏通路可塑性，增强动机维持与行为坚持能力[46]（图2）。

3 运动在多巴胺相关疾病中的分子干预机制

3.1 帕金森病：从线粒体稳态到突触可塑性的多通路调控

PD是一种以黑质致密部（substantia nigra pars compacta，SNpc）多巴胺能神经元进行性退化为核心病理特征的神经退行性疾病，其临床表现包括运动迟缓、肌强直、震颤和姿势障碍等[47,48]。多巴胺缺乏导致基底节-丘脑-皮质回路功能紊乱，直接通路受阻、间接通路过度活跃，从而抑制运动启动。运动干预被证明可通过多层机制对PD病理过程产生有益调控。临床研究采用的干预方式多样，主要包括持续性有氧运动（如跑步、蹬车）与多模式运动。后者通常指结合有氧、抗阻、平衡及柔韧性训练的综合性方案，旨在从多维度改善PD患者的运动与非运动症状。

在分子层面上，规律运动可显著上调TH和DDC的表达，增强多巴胺的生物合成能力[22]。与此同时，运动通过刺激BDNF和GDNF的表达[49]，激活TrkB[50]，进而启动下游ERK1/2、PI3K/Akt及哺乳动物雷帕霉素靶蛋白（mammalian target of rapamycin，mTOR）信号通路，促进多巴胺能神经元

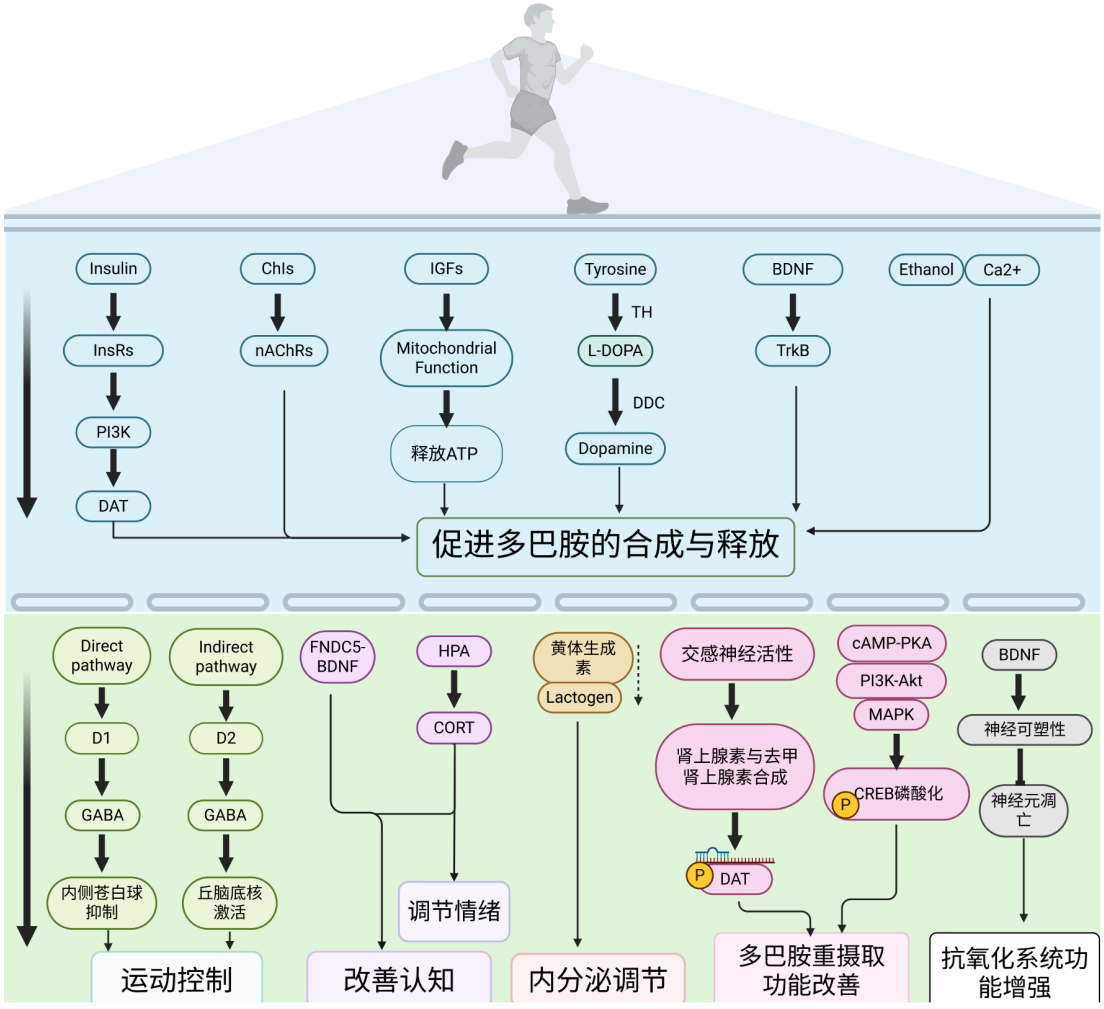

图2 运动干预对多巴胺系统的多层次调节机制

Figure 2 Multi-level regulatory mechanisms of exercise intervention on the dopamine system

的存活与突触连接修复[51]。特别是在6-羟多巴胺(6-hydroxydopamine,6-OHDA)诱导的PD模型中,这一机制可显著逆转多巴胺神经元凋亡与轴突萎缩现象[52]。氧化应激是PD发病的核心驱动因子之一。运动激活核因子E2相关因子2/抗氧化反应元件(nuclear factor erythroid 2-related factor 2/antioxidant response element,Nrf2/ARE)通路,促进抗氧化酶如血红素氧合酶1(heme oxygenase-1,HO-1)、NAD(P)H醌氧化还原酶1(NAD(P)H quinone oxidoreductase 1,NQO1)和SOD2的表达,显著减轻ROS积聚对线粒体的损伤[53]。此外,运动可上调线粒体关键调控蛋白过氧化物酶体增殖物激活受体γ辅激活因子-1α(peroxisome proliferator-activated receptor gamma coactivator-1 alpha,PGC-1α)与线粒体转录因子A(mitochondrial transcription factor A,TFAM),增强线粒体复制及能量代谢功能,恢复ATP生成,维持神经元代谢稳态[2]。2024年的研究表明,运动还可诱导线粒体自噬相关分子如PTEN诱导的激酶1(PTEN-induced putative kinase 1,PINK1)与Parkin蛋白上调,从而清除损伤线粒体,增强细胞应激适应能力[54]。此外,运动能够调节小胶质细胞的极化状态,促使其从促炎M1型向抗炎M2型转变,显著减少炎症因子如白细胞介素-1β(interleukin-1 beta,IL-1β)、肿瘤坏死因子-α(tumor necrosis factor-alpha,TNF-α)及环氧合酶-2(cyclooxygenase-2,COX-2)的表达,从而缓解中枢炎症反应[55]。与此同时,运动通过激活CaMKⅡα-ERK/MAPK通路与CREB磷酸化,促进突触后密度蛋白95(postsynaptic density protein-95,PSD-95)的表达[56],增强突触可塑性,改善基底节通路功能耦合。有氧运动与高强度运动主要在改善基础分子代谢和诱导特异性突触可塑性方面作用突出,而多模式运动则可能通过其综合性,在提供广泛的神经营养支持、改善平衡功能及促进全脑网络适应性重构方面展现出独特优势,进一步促进PD患者的运动能力恢复[57,58]。

3.2　抑郁症:奖赏通路重建与受体信号的调节机制

抑郁症被广泛认为是由多巴胺及5-羟色胺系统功能障碍共同驱动的情绪与认知障碍。多巴胺系统的失衡,尤其是在VTA-NAc-PFC奖赏通路中,多巴胺的合成、释放及受体敏感性下降,是导致快感缺失、动机减退及情绪低落的关键分子基础[59]。

运动能够激活中脑边缘系统,提高VTA神经元兴奋性,增强多巴胺在伏隔核与前额叶的释放,改善奖赏敏感性。具体机制上,运动上调神经递质转运蛋白VMAT2(vesicular monoamine transporter 2,囊泡单胺转运蛋白2)和DAT的表达,提高多巴胺的储存与再摄取效率[60],并通过PI3K/Akt通路增强多巴胺突触稳态[4]。有研究进一步指出,运动还可提升D2受体在NAc壳区的表达密度,使其更高效地响应多巴胺信号,从而增强奖赏驱动性行为[25]。在突触可塑性方面,运动通过上调BDNF表达,提高海马与前额叶皮层神经元的突触连接密度,改善认知与情绪调节能力[61]。此外,运动可通过与5-HT系统协同激活AMPA受体[62],调节mTOR和ERK信号通路[63],这一神经可塑性变化与运动抗抑郁效应显著相关。运动还通过下丘脑-垂体-肾上腺轴(hypothalamic-pituitary-adrenal axis,HPA轴)促进皮质酮(corticosterone,CORT)释放,适度激活前额叶皮层的D1受体,增强个体的压力应对能力,具有应激缓冲作用[64]。

3.3　高血压:肾脏多巴胺系统与交感神经调节的协同机制

在高血压的病因学机制中,肾脏钠排泄障碍与交感神经系统的过度活跃被认为是关键因素[65]。多巴胺作为肾内局部合成的重要激素(尤其是D1和D5受体在近曲小管中大量表达),其激活可抑制钠钾泵(Na^+/K^+-ATPase)与钠氢交换蛋白3(sodium-hydrogen exchanger 3,NHE3)的活性,促进钠排泄并维持血压稳态[66]。

运动通过增强TH表达,提升肾脏多巴胺水平,同时上调D1和D5受体的蛋白表达与膜定位,改善高盐摄入引发的盐敏感性血压升高[65,67]。D5受体还通过下调肾素-血管紧张素-醛固酮系统(renin-angiotensin-aldosterone system,RAAS)中血管紧张素Ⅱ 1型受体(angiotensin Ⅱ type 1 receptor,AT1R)表达,抑制醛固酮释放,进一步减少钠重吸收,从而达到降压效果[68]。在中枢层面,运动刺激多巴胺在PVN和NTS中的释放,抑制交感神经输出,减少去甲肾上腺素(norepinephrine,NE)和肾素(renin)分泌[69]。运动还可下调脑干中的氧化应激水平,维持交感-副交感动态平衡[70]。此外,运动通过多巴胺介导内皮细胞SOD活性上调,减少NADPH氧化酶(nicotinamide adenine dinucleotide phosphate oxidase,NOX)诱导的ROS产生,增强血管内皮功能,改善动

脉僵硬[71,72]。

3.4 骨代谢紊乱:多巴胺受体介导的骨重建与免疫调节机制

近年来的研究逐步揭示,骨组织亦为多巴胺能系统调控的外周靶器官[73]。成骨细胞与破骨细胞均表达多巴胺D1~D5类受体,其中D1和D2受体尤为关键[74]。运动通过系统性地激活多巴胺信号轴从而促进骨代谢稳态的分子基础日益明确。

在成骨方面,多巴胺通过多巴胺D1受体-细胞外信号调节激酶1/2-Runx2(dopamine D1 receptor-extracellular signal-regulated kinase 1/2-Runt-related transcription factor 2,D1R-ERK1/2-Runx2)信号通路促进成骨细胞的增殖、分化及矿化过程。研究发现,运动可增强该通路活性,有效逆转雌激素缺乏与糖皮质激素诱导的骨质疏松模型中的成骨抑制现象[75]。2023年,体外研究发现,多巴胺还可通过促进碱性磷酸酶(alkaline phosphatase,ALP)和骨钙素(osteocalcin,OCN)表达,增强骨基质合成[76]。另一方面,多巴胺通过D2R-cAMP-PKA-CREB通路抑制破骨细胞分化[77],减少活化T细胞核因子1(nuclear factor of activated T-cells 1,NFATc1)与癌基因c-Fos(cellular proto-oncogene Fos)的表达,从而抑制骨吸收。运动可放大该抑制效应,尤其是在类风湿性关节炎或骨关节炎模型中,表现出显著的抗炎性骨保护作用[78]。此外,多巴胺通过调节骨内免疫微环境,抑制促炎因子如IL-1β、IL-6与TNF-α的释放,改善骨髓局部炎症状态[79];运动还可诱导血管内皮生长因子(vascular endothelial growth factor,VEGF)与内皮型一氧化氮合酶(endothelial nitric oxide synthase,eNOS)表达升高,促进骨微血管新生,增强营养供应与细胞修复[80](图3)。

尽管动物与体外实验已取得大量进展,临床层面仍需进一步验证。部分研究显示,帕金森病患者与长期使用D2受体拮抗剂的精神分裂症患者骨密度下降,提示多巴胺-骨轴在人体中同样发挥作用[76,81]。此外,在类风湿性关节炎与骨关节炎患者滑液中多巴胺含量下降、D2受体表达减少,进一步支持多巴胺的临床相关性[82]。而运动干预可提升多巴胺水平与骨代谢指标,为未来多巴胺靶向治疗骨代谢紊乱提供了新思路。

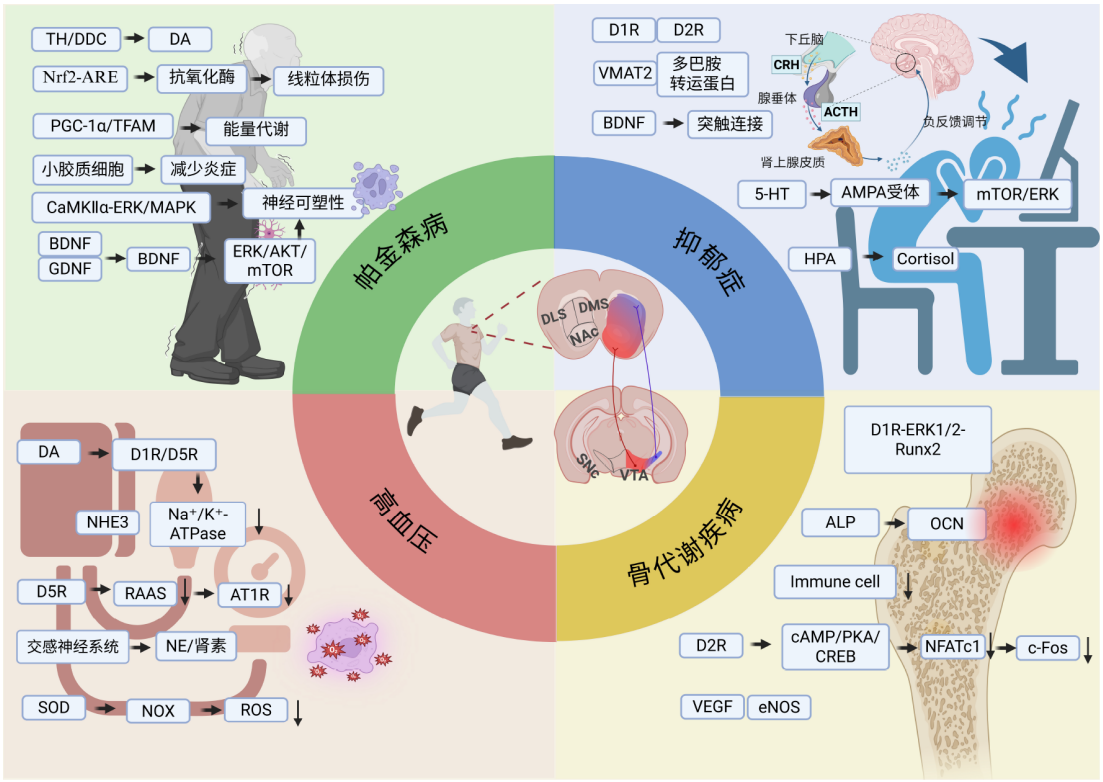

图3 运动干预多巴胺通路在帕金森病、抑郁症、高血压及骨代谢疾病中的跨疾病调控机制

Figure 3 Cross-disease regulatory mechanisms of exercise intervention on dopamine pathways in Parkinson's disease, depression, hypertension and bone metabolic diseases

3.5 整合性机制总结:多巴胺轴在运动干预中的统一分子逻辑

多巴胺作为中枢与外周功能调控的核心神经递质,其信号轴在多种慢性疾病的发生与进展中发挥关键作用。尽管帕金森病、抑郁症、高血压及骨代谢紊乱呈现不同临床表型,但从分子层面看,均可归因于多巴胺能系统功能障碍所致的组织稳态失衡。

运动干预以其系统性、生理性和可调控性优势,能够多层面激活并重塑多巴胺信号轴,形成跨病种的整合性调控网络。在神经递质代谢方面,运动可增强多巴胺合成、储存与再摄取,从而在帕金森病中补偿神经元缺陷,在抑郁症中强化奖赏通路,在高血压与骨代谢紊乱中改善外周稳态。在受体信号层面,运动通过调节不同多巴胺受体亚型,实现中枢与外周作用的动态平衡。这一调控不仅改善神经传导与情绪反应,也有助于血压、骨代谢等外周生理功能的恢复。此外,运动还能广泛激活神经营养、抗氧化及能量代谢相关通路,促进神经修复、线粒体功能维持及免疫炎症平衡。这些效应共同构建了以多巴胺信号为核心的多维调控体系。

运动干预在多巴胺相关疾病中展现出"统一中有差异、共通中有特异"的特征:其统一性体现在对多巴胺轴的系统性激活与稳态重建,其特异性则源于不同靶器官和疾病背景下受体及下游通路的差异性响应。该整合性分子网络为多病种共通的运动治疗提供了理论支撑,也为精准运动医学的发展奠定了基础。

4 讨论与展望

多巴胺作为中枢神经系统中功能最为多样的神经递质之一,广泛参与运动控制、奖赏感知、情绪维持及认知加工等关键神经过程。近年来,随着分子神经科学与运动医学的交叉融合,越来越多研究证实,运动干预可通过多层级、多通路的机制深度调节多巴胺系统功能,尤其在帕金森病、抑郁症、高血压及骨代谢紊乱等多巴胺相关疾病的预防与康复中展现出显著的干预潜力。本文围绕运动对多巴胺系统的调控作用,系统梳理了其在神经递质合成、受体信号转导、突触可塑性、氧化应激、神经营养因子表达及炎症调节等方面的分子基础,并进一步探讨了多巴胺作为"枢纽型因子"在多种疾病中的跨系统整合机制。

值得强调的是,运动对多巴胺系统的调节呈现出高度的脑区特异性。中脑-纹状体通路中多巴胺的动态变化直接影响运动程序的生成与执行,中脑-边缘系统介导奖赏动机与情绪行为,运动皮层中的多巴胺则参与运动技能学习与可塑性维持。在不同脑区内,D1与D2受体激活所触发的信号通路存在显著差异,由此产生的生理效应在功能上也呈现出明显的分化。此外,组织多巴胺含量的增加未必等同于突触前膜"功能性多巴胺释放"的提升。因此,在解读运动对多巴胺系统的调控效应时,应警惕因指标维度混淆而导致的机制误判。

当前证据多来源于动物实验与人体研究两类路径。动物模型具有变量控制严谨、机制解析深入的优势,广泛采用微透析、电化学、qPCR、Western blot等技术,从细胞、分子与电生理层面系统揭示运动对多巴胺系统的调控路径。但动物模型在情绪、社会行为与认知结构方面无法完全模拟人类特征,其外推性存在明显限制。相较之下,人体研究更侧重使用fMRI、PET、行为任务等非侵入性方法,在生态效度和实际干预验证方面具备更高的价值。然而,这类研究在脑区定位精度与分子机制揭示方面存在局限。因此,如何在动物与人类研究之间建立机制与证据的桥梁,成为未来该领域研究发展的关键。

除多巴胺系统本身外,运动对神经功能的调节还涉及与5-羟色胺、去甲肾上腺素等单胺类递质的协同作用[83]。研究显示,运动可同时上调多种单胺递质的合成与释放,并协同激活如cAMP/PKA[84]、PI3K/Akt[85]、BDNF/mTOR等信号通路[86],形成互补性神经调控网络。在帕金森病与抑郁症中,这种递质间的交互作用不仅促进突触可塑性重构,也增强了个体对外部奖赏与内在情绪的适应能力。值得注意的是,VTA神经元的共释放现象提示神经递质调控模式已从传统的"分区分工"向"整合协同"转变[83],为理解运动干预的多通路效应提供了新的视角。

此外,运动参数(如强度、频率、持续时间、类型)与个体生理特征(如年龄、性别、代谢状态、基因背景)对多巴胺系统调节具有显著影响。不同形式的运动可能激活不同的信号通路和脑区适应模式,有氧运动更倾向于激活神经营养因子相关通路,抗阻训练则可能更倾向于促进多巴胺回收机制与受体表达。因此,未来应加强对"运动刺激-多巴胺反应"之间非线性关系的系统研究,探索量化的"运动剂量反

应曲线”,推动个体化运动干预策略的精准制定。

综上所述,运动作为一种低成本、高可及、无药物依赖性的干预手段,在调控多巴胺系统及相关神经功能中展现出重要的应用前景。将运动视为一种“精准神经调节工具”,以多巴胺系统为核心建立“运动-神经递质-疾病”调控网络,是实现运动干预从经验处方向机制导向转变的关键路径。未来研究需聚焦多模态检测技术的集成、多递质系统协同调控模型的构建,以及动物机制研究向临床转化的可行策略,进一步推动运动神经科学走向精准化、机制化与整合化。

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