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综 述

Kalirin-7在运动改善神经退行性疾病中的作用研究进展

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摘 要：中枢神经系统鸟嘌呤核苷酸交换因子Kalirin-7 (Kal-7)是突触可塑性的关键因子，在大脑中发挥重要调控作用。突触功能异常可导致学习记忆等认知功能减弱，并伴随Kal-7异常表达，进而诱发多种神经退行性疾病。运动可上调相关脑区Kal-7表达，预防或减轻脑部神经退行性疾病。本文通过对Kal-7与神经退行性疾病及其运动干预研究进展的文献梳理，归纳Kal-7在运动改善神经退行性疾病中的作用及其可能机制，为运动防控神经退行性疾病的基础与临床研究提供新视野和新靶点。

关键词：Kalirin-7 (Kal-7)；神经退行性疾病；突触可塑性；运动

Progress on the role of Kalirin-7 in exercise intervention-mediated improvement of neurodegenerative diseases

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Abstract: Guanine nucleotide exchange factor Kalirin-7 (Kal-7) is a key factor in synaptic plasticity and plays an important regulatory role in the brain. Abnormal synaptic function leads to the weakening of cognitive functions such as learning and memory, accompanied by abnormal expression of Kal-7, which in turn induces a variety of neurodegenerative diseases. Exercise can upregulate the expression of Kal-7 in related brain regions to alleviate neurodegenerative diseases. By reviewing the literature on Kal-7 and neurodegenerative diseases, as well as the research progress of exercise intervention, this paper summarizes the role and possible mechanism of Kal-7 in the improvement of neurodegenerative diseases by exercise and provides a new rationale for the basic and clinical research on the prevention and treatment of neurodegenerative diseases by exercise.

Key words: Kalirin-7 (Kal-7); neurodegenerative diseases; synaptic plasticity; exercise

神经退行性疾病是指因神经元和(或)其髓鞘丧失累积所致的功能障碍，如阿尔茨海默病(Alzheimer disease, AD)、帕金森病 (Parkinson's disease, PD)、抑郁症、亨廷顿病 (Huntington's disease, HD)和精神分裂症 (schizophrenia, SCZ) 等，属于老年性疾病，其发病率逐年增高，严重危害人类健康和生活质量[1, 2]，其发病原因未完全阐明。近年来发现中枢氧化应激、炎症等引起的树突、树突棘及其突触可塑性损害，是神经退行性疾病发生和发展的核心环节[3, 4]。鸟嘌呤核苷酸交换因子 Kalirin-7 (Kal-7)是 Kalirin 基因的选择性剪切变体之一，主要在大脑皮层和海马区兴奋性神经元的突触后膜表达，具有营养和支持神经元、调节突触可塑性等作用。诸多文献表明，运动通过降低氧化应激、炎症和细胞凋亡改善慢性非传染性疾病，如心梗[5, 6]；还可增加大脑皮层、前额叶和海马等区域 Kal-7 蛋白表达，改善脑梗患者神经炎症、神经元坏死程度和海马萎缩等[7, 8]。因此，运动不仅可以改善心血管等慢性

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疾病，还可通过 Kal-7 介导改善神经退行性疾病。本文通过梳理 Kal-7 与神经退行性疾病及其运动干预新近文献，归纳 Kal-7 在运动改善神经退行性疾病中的作用及其可能机制，为进一步阐释运动防控神经退行性疾病的可能机制，寻找运动防治该类疾病的手段与方法及其靶标筛选提供思路。

1 Kal-7分子结构、组织分布及功能

1.1 Kal-7分子结构与组织分布

Kalirin 属于 Rho 鸟嘌呤核苷酸交换因子亚类，最早在弥漫性 B 细胞淋巴瘤中发现 [9]，主要分布在大脑、肠道、心脏、脂肪、肾上腺及肾脏、脾脏和肝脏等器官组织 [10]。Fagerberg 等 [11] 在 2014 年文献附件数据库中报道了不同器官组织 Kalirin 表达情况 (见图 1)。

Kalirin 表达多种蛋白，分子量一般在 100~500 kDa 不等，如 Kalirin-5 (Kal-5)、Kal-7、Kalirin-9 (Kal-9) 和 Kalirin-12 (Kal-12) 等，其中 Kal-5 是 Kalirin 亚型中分子量最小的蛋白，主要在成年大鼠脑组织中表达。Kal-9 在中枢之外表达最丰富，如人主动脉、肝脏、骨骼肌等 [12]，在培养的平滑肌细胞、内皮细胞和巨噬细胞也有表达 [13]。Kal-12 分子量最大，广泛分布于骨骼肌、垂体、神经元、肝脏、主动脉等组织及胚胎的发育过程中 [14]。Kal-7 在大脑认知相关区域 (额叶、海马、纹状体等) 高度表达，与神经发育密切相关，Kal-Duet 亚型定位于肌动蛋白相关的细胞骨架元件，结构与 Kal-7 相似，调节突触可塑性 [15] (见表 1)。

Kalirin 主要亚型的分子结构特征见图 2。Kal-7 仅在中枢神经系统中表达，且在大脑皮层和海马体中表达水平最高。Kal-7 结构各区域可结合多种蛋白发挥作用，其 N 端 Sec14p 样结构域 [23] 可与磷脂酰肌醇 -3- 磷酸 (inositol 1,4,5-triphosphate, IP3) 互作 [24]，随后的 9 个 Spectrin 重复结构可与亨廷顿关

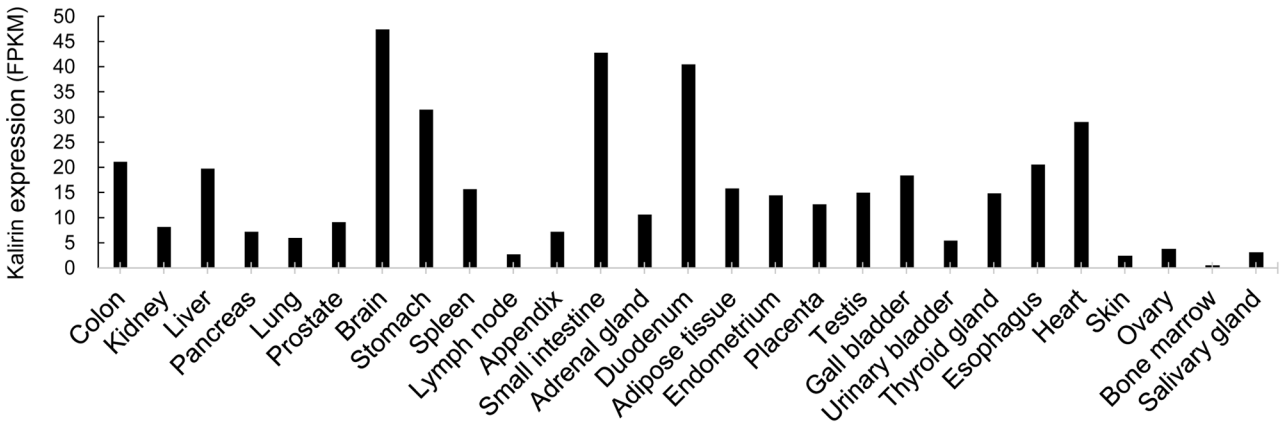

图 1. Kalirin的组织特异性分布(参考文献[11]和NCBI数据库绘制)

Fig. 1. Tissue-specific distribution of Kalirin (Drawn by reference [11] and NCBI database). FPKM: fragments per kilobase of exon model per million mapped reads.

表1. Kalirin亚型、组织分布与功能

Table 1. Subtypes, tissue distribution and function of Kalirin

Kalirin subtype	Molecular weight	Tissue distribution	Function
Kal-5	115 kDa	Brain [16, 17]	Regulate the morphology of dendritic spines [18]
Kal-7	190 kDa	Brain [19]	Maintain dendritic morphology and function [18]
Kal-9	270 kDa	Aorta, liver, skeletal muscle, cultured smooth muscle cells, endothelial cells and macrophages [12, 20]	Participate in cytoskeleton dynamics, which is essential for cell movement and proliferation [13]
Kal-12	470 kDa	Skeletal muscle, pituitary, neuron, liver, aorta, embryonic development [12, 20]	Regulate the number and length of neurites to facilitate the maturation of dendritic spines in early development [21]
Kal-Duet	144 kDa	Cerebral cortex, cerebellum [15]	Involved in cytoskeleton dependent cell function [22]

联蛋白 1 (huntingtin-associated protein 1, HAP1)、肽基甘氨酸 α 酰胺化单加氧酶 (peptidyl-glycine alpha-amidating monooxygenase, PAM)、ADP 核糖基化因子 6 (ADP ribosylation factor 6, Arf6)、SCZ 破坏蛋白 1 (disrupted in schizophrenia 1, DISC1)、诱导型一氧化氮合酶 (inducible nitric oxide synthase, iNOS) 等蛋白结合 [17]。GEF1 域 (DH-PH 结构域) 通过脑源性神经营养因子 (brain-derived neurotrophic factor, BDNF) 参与树突棘形态调节。Kal-7 独有的 C 端 PDZ 相互作用段可与多种 PDZ 结构域蛋白互作，如突触后致密蛋白 95 (postsynaptic density protein-95, PSD-95)、p21 激活激酶 (p21 activated kinase, PAK)、支架蛋白 (discs large MAGUK scaffold protein 3，DLG3，即 SAP-102)、谷氨酸突触支架蛋白 (synapse-associated protein 97, SAP-97)、iNOS 等 [25] 突触后蛋白 (见图 2)，调节膜蛋白和细胞骨架肌动蛋白的信号转导。

1.2 Kal-7与突触可塑性

突触可塑性是指神经细胞间突触连接强度可调节的特性，反映中枢中单个突触强度的变化，是认知功能的细胞基础。突触可塑性主要机制涉及突触后膜谷氨酸受体 (*N*-methyl-*D*-aspartic acid receptor, NMDAR) [26]。Kal-7 通过含有 NMDA(2B) 的 NMDAR 以不依赖 PDZ 结合的方式与 NMDA 直接相互作用 [27]，参与突触后膜谷氨酸兴奋性信号传递，同时树突棘动力学依赖细胞骨架高水平肌动蛋白的动态变化。谷氨酸受体通过 α- 肌动蛋白与细胞骨架的肌动蛋白结合，借助 Kal-7 参与神经元细胞骨架肌动蛋白的动态调节，改变树突棘形态大小和密度，调节神经可塑性和突触传递，表明 Kal-7 是调节突触强度的关键因子。另有研究表明，Kal-7 在啮齿动物出生后 1~7 天的海马中表达水平极低，第 14 天开始显著升高，与神经元突触发生时间相一致 [15]。Kalirin 功能障碍与树突棘病变存在较高相关性 [28]，

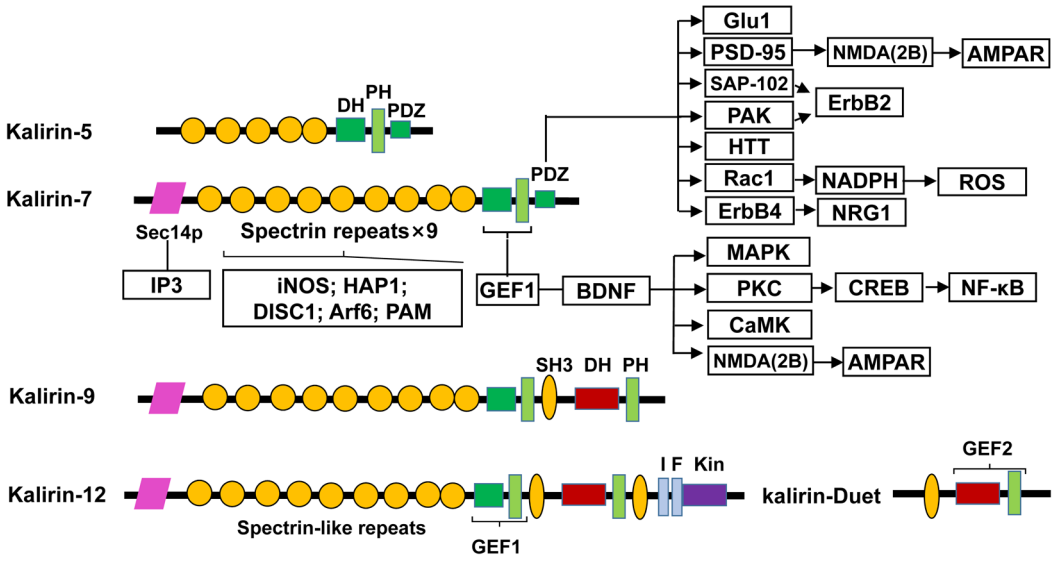

图 2. Kalirin主要亚型的分子结构特征及Kalirin-7分子信号通路[8, 17, 24, 25]

Fig. 2. Molecular structure characteristics of major subtypes of Kalirin and molecular signaling pathway of Kalirin-7 [8, 17, 24, 25]. DH, Dbl homology; F, Fibronectin III-like structure; GEF1, guanine nucleotide exchange factor 1; GEF2, guanine nucleotide exchange factor 2; I, Immunoglobulin-like structure; PH, Plexstrin homology; SH3, Src homology domain 3; PDZ, post-synaptic density; Kin, kinase; IP3, inositol 1,4,5-triphosphate; iNOS, inducible nitric oxide synthase; HAP1, Huntingtin-associated protein 1; DISC1, disrupted in schizophrenia 1; Arf6, ADP ribosylation factor 6; PAM, peptidyl-glycine alpha-amidating monooxygenase; BDNF, brain-derived neurotrophic factor; Glu1, glutamate 1; SAP-102, discs large MAGUK scaffold protein 3; PAK, p21 activated kinase; HTT, Huntingtin; Rac1, Rac family small GTPase 1; ErbB4, epidermal growth factor receptor 4; MAPK, mitogen-activated protein kinase; PKC, protein kinase C; CaMK, calmodulin dependent protein kinase; NMDA(2B), *N*-methyl-*D*-aspartic acid receptor 2B; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazole propionate receptor; ErbB2, epidermal growth factor receptor 2; NADPH, nicotinamide adenine dinucleotide phosphate binding domain; ROS, reactive oxygen species; NRG1, neuregulin 1; CREB, cAMP-response element binding protein; NF-κB, nuclear factor kappa-B.

各类神经退行性疾病与Kal-7异常表达关系密切[29]。这些研究表明Kal-7依赖性树突棘形成和增强在神经元突触调节、树突棘可塑性和认知行为变化中发挥重要介导作用。

1.3 Kal-7与神经递质

神经系统中突触可传递不同类型的脑神经递质(brain neurotransmitter, BNT)，如5-羟色胺(5-hydroxytryptamine, 5-HT)、肾上腺素、γ-氨基丁酸(γ-aminobutyric acid, GABA)和多巴胺(dopamine, DA)等。5-HT在功能和遗传多态性上与SCZ和自闭症等疾病相关[30]。在培养的皮质神经元中激活5-HT受体后，通过Kal-7及其受体PAK诱导树突棘瞬时增加，该依赖性机制影响神经元突触结构的可塑性[31]。Kal-7也在中脑DA能神经元中表达，而多巴胺D2受体(dopamine D2 receptor, D2Rs)可调节Kal-7表达[32]，缺乏Kal-7可影响神经元的谷氨酸能信号传导过程。GABA属于抑制神经元活动的神经递质，Kal-7与谷氨酸受体、GABA受体和其他鸟苷酸结合蛋白共同维持大脑兴奋性与抑制性突触传递之间的平衡[33]。以上研究表明Kal-7参与BNT的生物学效应。

1.4 Kal-7与神经营养支持

神经元生长、分化与存活均依赖神经营养因子(neurotrophic factors, NTFs)，如神经生长因子(nerve growth factor, NGF)、BDNF、神经营养因子3(neurotrophic factor 3, NT-3)和神经营养因子4(neurotrophic factor 4, NT-4)等。Kal-7参与NTFs对神经的保护作用，并与BDNF作用密不可分。BDNF可通过酪氨酸激酶受体B(tyrosine kinase receptor B, TrkB)促进神经突的形成，发挥营养作用，但特异性抑制Kalirin的GEF1结构域，细胞内BDNF/TrkB信号传导被阻断。小鼠神经元敲除Kalirin后也无法激活Rac家族小GTP酶1(Rac family small GTPase 1, Rac1)对BDNF的响应[34]。BDNF通过与NMDA(2B)结合调节突触传递[35]，而Kal-7可与NMDA(2B)等突触后膜蛋白相互作用，表明Kal-7可能是BDNF的下游信号。神经调节蛋白1(neuregulin 1, NRG1)的受体有4个亚型，包括表皮生长因子受体1~4(epidermal growth factor receptor 1–4, ErbB1–4)，Kal-7与其中的ErbB4相互作用，参与NRG1/ErbB4信号通路对成熟海马中间神经元生长过程的调节，共同发挥神经保护作用[36]。因此认为Kal-7通过NTFs参与神经营养和保护作用。

2 Kal-7与神经退行性疾病

2.1 Kal-7与AD

AD是常见神经退行性疾病之一，多发于老年人群，预计到2050年全球AD病例将达到1.15亿[37]。AD发病机制包括淀粉样蛋白β肽(amyloid β-protein, Aβ)斑块相关神经变性[38]、神经原纤维变性[39]、突触功能障碍和BNT失衡[40]、基因突变[41]、神经炎症和氧化应激等假说[42]，目前临床多采用Aβ肽聚集而成的斑块和过度磷酸化tau蛋白组成的神经原纤维缠结进行AD诊断。脑内斑块和缠结聚集可导致反应性氧化应激现象，周围小胶质细胞募集活化，出现局部炎症反应，进一步加剧AD病理进程[43]。在AD病理发生与发展中Kal-7的作用至关重要。一方面，神经炎症发生时，Kal-7与NMDA(2B)结合，增强还原型烟酰胺腺嘌呤二核苷酸磷酸氧化酶(NADPH oxidase, NOX)活性，导致超氧自由基增加，抑制Kalirin信号通路，可减少Rac1-NADPH氧化酶活化和随后产生的促炎细胞因子[44]，表明Kal-7对AD发病后的神经炎症和氧化应激反应起抑制作用。另一方面，AD模型小鼠海马中活性剪接转录因子X-Box结合蛋白1(X-Box binding protein 1, XBP1)可在功能上调节树突棘密度并改善突触可塑性，改善AD发病后的认知功能障碍，这在很大程度上抵消Aβ聚集引起的海马认知功能损害。Kal-7由XBP1转录激活，同时Kal-7作为XBP1发挥有益作用的介质，当内源性敲低Kal-7时，AD模型小鼠XBP1有效作用降低[45]，因此推断，在AD中Kal-7信号的传导在促进树突棘形成、降低Aβ水平中有一定作用，Kal-7的减少可能导致Aβ的积累加剧[46]，但其具体正向作用还有待进一步研究。

2.2 Kal-7与PD

PD是神经退行性疾病中发展最快的一种，其患病率、致残率和死亡率仅次于AD[47]。中脑黑质的DA能神经元渐进变性死亡，α-突触核蛋白错误折叠和聚集导致路易小体形成是PD的标志性病理特征。PD的运动功能障碍表现为平衡功能和步态障碍，运动迟缓，静止性震颤和肌肉僵直以及认知功能障碍等[48]。目前认为PD病理机制主要涉及氧化应激、线粒体损伤、铁蓄积及自噬、基因突变和NTFs缺乏等[49]。α-突触核蛋白是PD发病机制中的关键蛋白，Kal-7以组蛋白脱乙酰酶6(histone deacetylase 6, HDAC6)依赖方式降解α-突触核蛋白聚集体，可能是改善PD的重要途径之一[50]。在

AD 和 PD 等脑疾病中细胞周期蛋白依赖性激酶 5 (cyclin dependent kinase 5, Cdk5) 活性失调，引起神经元细胞骨架重塑和突触丢失，最终导致神经退行性变，而 Cdk5 可靶向 Kal-7 [51]，提示进一步探索通过改善 Cdk5 活性促进 Kal-7 水平升高，可能为揭示运动防控 PD 机制提供新思路。

2.3 Kal-7与SCZ

SCZ 属于慢性精神性障碍疾病，可导致行为和认知障碍。SCZ 受多因素影响，具有不同临床表现，属于异质性疾病，病因尚不明确。目前认为，遗传与环境 [52, 53]、线粒体功能障碍 [54]、DA 传递紊乱、神经炎症 [55]、氧化应激 [56] 和神经可塑性 [57] 等均与 SCZ 发生和发展相关。认知功能障碍是 SCZ 核心症状之一，SCZ 患者大脑树突棘减少，突触功能障碍，包括突触后神经元的树突棘、树突和细胞体中的神经递质受体和突触后支架蛋白的突变 [58]。DISC1 是 SCZ 枢纽蛋白，Kal-7 重复片段与 DISC1 结合介导其与 NMDAR 的相互作用，从而促进 Kal-7/Rac-1 引起的活动依赖性树突棘伸长。DISC1 基因多态性与 SCZ 易感性密切相关，当 SCZ 发作时，DISC1 突变导致其蛋白表达减少，DISC1/Kal-7/Rac1 信号级联反应紊乱促使疾病恶化 [59, 60]。另有文献表明，Kal-7 与 SCZ 的神经炎症和氧化应激水平有关 [61]。在神经炎症时，Rac-1 产生活性氧 (reactive oxygen species, ROS) 可导致NADPH氧化酶过量产生ROS [62]，加重炎症与氧化应激损伤。文献表明，大脑的单胺系统在 SCZ 病理学机制中起主要作用 [63]，SCZ 皮质下突触的 DA 增加，临床普遍使用有效剂量阻断剂阻断 D2Rs 受体作为抗精神病药物。谷氨酸和 GABA 等递质变化在一定程度上引起 DA 分泌变化，SCZ 期间脑脊液以及血浆中谷氨酸和 GABA 浓度减少，且前额叶谷氨酸及其受体信号传递失调，过度激活 D2Rs，Kal-7 可能通过与谷氨酸受体的结合抑制 DA 的过量产生，减缓 SCZ 症状 [64, 65]。以上研究表明 Kal-7 或通过 DA 系统，或通过兴奋性神经递质谷氨酸系统间接影响 DA 的释放，与 SCZ 关系密切。

2.4 Kal-7与HD

HD 是由编码亨廷顿蛋白 (Huntingtin, HTT) 基因中 CAG 三重重复扩增引起的神经退行性疾病，表现为亨廷顿舞蹈症，包括进行性运动功能障碍、认知能力下降和精神障碍，其发病机制包括 NMDAR 介导的兴奋性毒性 [66]、DA 和线粒体功能障碍、氧化应激和 NTFs 缺失等 [67]。HD 小鼠早期的大脑皮质 Kal-7 水平特异性降低，皮质树突棘发生变化，增加 BDNF 水平可显著改善 HD 表型 [68]。HTT 异常是导致 HD 发生的关键因素 [69]，而 Kalirin 的 C-末端具有 HTT 结合部位，两者结合后可降低 HTT 诱导产生的细胞毒性。上调 Kalirin 表达可降低细胞毒性，改善 HD 症状 [70]。HAP1 功能障碍也可导致 HD，而 Kalirin 与 HAP1 相互作用，共同调节纹状体神经元、树突棘形状和大小。分析 HD 模型皮层突触相关蛋白后发现 Kal-7 特异性减少 [68]，过表达 Kal-7 可恢复成熟培养的 HD 皮质神经元中谷氨酸能突触的数量 [71]。以上研究提示 Kal-7 水平升高可改善 HD 的发生与发展。

2.5 Kal-7与抑郁症

抑郁症患者常表现出情绪低落、精力下降、认知和记忆损害等，一般情况下伴随多种其他疾病而产生，如脑部疾病、心血管疾病、代谢综合征和免疫系统疾病等 [72]，并与性别、年龄和社会因素等多因素相关，其病理生理学机制涉及神经内分泌系统改变和神经可塑性降低等多种机制。有文献表明，抑郁样行为小鼠海马区 BDNF 与 Kal-7 水平同步降低 [73]，大鼠模型也表现出 Kal-7 表达减少 [74]，且与 BDNF 和 α- 氨基 -3- 羟基 -5- 甲基 -4- 异恶唑丙酸 (α-amino-3-hydroxy-5-methyl-4-isoxazole propionate, AMPA) 受体亚基 GluA1 有关 [73]。DA 和 5-HT 与抑郁症发病机制相关 [75]，突触后神经元 DR2 通过信号通路可调节 Kal-7 表达，参与突触可塑性调节。Kal-7 主要在树突棘处维持兴奋性神经递质谷氨酸的传递，通过拮抗 5-HT 受体维持突触兴奋与抑制的动态平衡，发挥抗抑郁作用 [76]。

2.6 Kal-7与癫痫(epilepsy)

癫痫发病与神经系统兴奋和抑制性神经递质失衡及突触功能异常有关。海马区是人类和实验性癫痫中研究最广泛的大脑区域 (海马硬化症)。海马区 Kal-7 通过增强 Rac1 活性，上调下游靶蛋白表达，维持正常树突棘和分支 [77]，而癫痫大鼠海马区 Kal-7 表达减少，尽管其相关蛋白表达增加，但 Kal-7 与 PSD-95 突触相关蛋白的结合减少，蛋白表达异常影响神经元结构功能，加重癫痫发作，导致认知功能障碍，此时增加 Kal-7 表达可能是抗癫痫的关键 [78, 79]。神经递质 GABA 相对浓度与癫痫直接相关 [80]，癫痫雌性小鼠海马 CA1 区和 CA3 区 Kalirin 与 GABA 受体相互作用 [81]，调节海马树突

长度，参与兴奋性神经递质传递。根据以上研究推测，Kal-7 表达变化与癫痫发生和发展有关，但 Kal-7 与癫痫的具体因果关系尚缺乏进一步报道。

以上研究均表明，Kal-7 功能的丧失与神经退行性疾病密切相关，通过观察 Kal-7 末端外显子缺失、Kal-7 缺失以及 Kalirin 的 GEF1 敲除小鼠，发现前脑和海马总 Kalirin 蛋白减少，并伴随着树突棘密度的特异性降低和焦虑样行为的出现 [82]，在抑郁症和癫痫患者中发现的海马 Kal-7 表达减少、树突棘密度和形状的异常可能与 Kal-7 的缺失有潜在联系 [38]。此外，重复测序与关联研究表明，Kalirin 错义突变也可能是 AD 和 SCZ 的危险因素。PD 与 HD 患者脑内 Kal-7 表达降低，α- 突触核蛋白聚合体作为 PD 的易感因素，Kal-7 对聚合体的降解作用是预防 PD 的关键 [83]，尽管 Kal-7 在 PD 与 HD 中的直接作用尚未被阐述，但两者最突出的病理特征为树突棘变化，这很可能是 Kal-7 特定的突变、修饰和翻译过程错误而导致的 [17]。

2.7 Kal-7与雌激素缺乏相关疾病

雌激素缺乏可引起抑郁症、AD 等神经退行性疾病 [84]，雌激素参与调节诸多脑区突触联结、调节神经内分泌功能、抗氧化应激和炎症等功能。雌激素治疗可增加去卵巢大鼠海马区树突棘密度，增加兴奋性突触的数量，并伴随 Kal-7 及其相关蛋白 PSD、GluR1 和 N- 粘连蛋白的增加。雌二醇治疗慢性不可预测应激模型 (chronic unpredictable mild stress, CUMS) 大鼠，可逆转海马 Kal-7 下降，改善抑郁样行为 [85]。相反，当内源性 Kal-7 表达减少时，雌激素治疗不再增加海马 NMDAR 激活以及神经元突触形成 [86]。以上研究表明，神经可塑性是 Kal-7 与雌激素相互作用的枢纽，共同在增强兴奋性突触功能和神经保护中起作用。

3 Kal-7在运动改善神经退行性疾病中的作用和机制

不同类型的神经退行性疾病均伴随突触功能障碍、神经可塑性变化、BNT 分泌和兴奋与抑制失衡、神经细胞缺乏营养支持等病理过程，其中 Kal-7 扮演着重要角色。运动作为改善神经退行性疾病的防控手段，与其他药物治疗相比，经济实惠、方便简单、灵活个性化。因此，中枢 Kal-7 在运动改善神经退行性疾病中的作用和机制值得探索。

3.1 Kal-7在运动改善突触可塑性中的作用

运动是改善抑郁症等神经退行性疾病广泛应用的非药物处方。有研究发现，抑郁症患者海马、前额叶皮质和伏隔核体积及突触数量减少 [87]，而运动可缓解 CUMS 大鼠抑郁样行为 [88]。大鼠自主轮转运动可调节生长激素的表达水平，诱导海马神经发生、神经元活化和增加海马 CA3 区树突棘密度 [88, 90]，运动促进 PSD-95 与其下游 Kal-7 和 Rac1 信号通路结合，参与应激后的神经元突触重塑。低氧环境可导致神经损伤，包括海马神经元树突棘发生进行性减少或丢失，Kal-7 在其中参与树突形态发生和神经功能调控 [76]。强化运动锻炼可增加认知相关脑区 Kal-7 表达，通过调节神经可塑性改善神经退行性疾病症状 [91]。这些研究表明运动介导了 Kal-7 参与的有益神经可塑性。

3.2 Kal-7在运动调节神经内分泌免疫中的作用

抑郁症患者脑脊液中 5-HT 及其代谢产物 5- 羟吲哚乙酸显著减少 [92]，抑郁症模型小鼠脑内单胺类神经递质水平降低。Kal-7 是调节树突棘结构与功能的关键因子，而运动可提高大鼠脑内 5-HT 水平，增加 Kal-7 蛋白表达，影响与之联系的 BNT 分泌与传递，改善 BNT 紊乱等引起的精神类疾病。神经退行性疾病发生后，中枢和外周的炎症因子水平升高，中枢谷氨酸含量增多，促使不断激活的小胶质细胞释放炎症因子，产生潜在神经毒性。谷氨酸过度产生导致超氧自由基刺激 iNOS 过量合成 NO，损伤神经细胞膜，神经细胞凋亡或坏死，Kalirin 不仅依赖 PDZ 结构域与 NR2B 亚基的相互作用，而且在酵母双杂交测定中发现 Kalrin 与 iNOS 也存在特异性相互作用，Kalirin 表达上调可抑制 iNOS 活性。提示 Kal-7 参与调节脑内局部炎症反应 [93]。在炎症后期，Kal-7 抑制海马小胶质细胞的增殖与活化，星形胶质细胞增加谷氨酸吸收，维持细胞间隙谷氨酸正常浓度，而合理的运动锻炼调节 Kal-7 表达，可能通过突触微环境参与神经炎症发展，发挥神经保护作用 [44]。

3.3 Kal-7在运动促进NTFs分泌中的作用

NTFs 支持神经可塑性，促进神经元生长、分化和存活。运动改善认知与各类 NTFs 关系密切 [94]，运动通过提高相关 NTFs 水平预防神经退行性疾病 [95]。BDNF 是 NTFs 家族成员，在中枢和周围神经系统的发育、维持和可塑中起重要作用。Kal-7 与 BDNF 关系密切，在神经发生退行性变化后，谷

氨酸受体可将两者联系起来。当采用适中至高强度运动时，激活神经生理反应，诱导 BNT 合成 [96]，BDNF 通过刺激谷氨酸与受体结合，激活钙调蛋白激酶 (calmodulin dependent protein kinase, CaMK)、蛋白激酶 C (protein kinase C, PKC) 和丝裂原活化蛋白激酶 (mitogen-activated protein kinase, MAPK)，进而激活环磷腺苷效应元件结合蛋白 (cAMP-response element binding protein, CREB) 和核因子 κB (NF-κB)，反过来激活 BDNF 受体并诱导自身表达 [97]，或直接通过 TrkB 参与磷脂酶 Cγ (phospholipase Cγ, PLC-γ)、PI3K 和 MAPK 等细胞内信号通路，参与调节神经元存活、可塑性、细胞能量平衡和线粒体生物发生 [95]。短时间低强度运动通过蛋白激酶 B、CREB 和 BDNF 信号参与海马神经元的可塑性，改善衰老大鼠的空间学习和记忆能力 [98]，而急性和定期运动均对 BDNF 水平产生显著影响 [99]。抑制黑质小胶质细胞激活可减少与年龄相关的 DA 能神经元丢失和运动缺陷。小鼠跑步运动可上调 BDNF、TrkB 信号，抑制小胶质细胞激活和 DA 能神经元丢失，改善 PD 相关病症 [100]。运动干预抑郁小鼠后，BDNF 的增加伴随 Kal-7 降低的逆转，且两者变化呈现相关性 [101] (见表 2)。提示，Kal-7 参与运动促进 NTFs

表2. 神经退行性疾病与运动干预下Kal-7表达

Table 2. Neurodegenerative diseases and Kal-7 expression under motor intervention

Neurodegenerative disease	Pathogenic site	Kal-7	Exercise intervention	Kal-7 after exercise intervention	References
Depression	Hippocampus, prefrontal cortex	↓	Aerobics	↑	[74, 102]
Alzheimer disease	Hippocampus, parietal lobe, frontal lobe	↓	Aerobics	↑	[103]
Parkinson's disease	Substantia nigra, striatum of midbrain	↓	Aerobics	↑	[51, 92]
Schizophrenia	Frontal and temporal lobes	↓	Resistance movement	↑	[61, 104]
Huntington's disease	Caudate nucleus, putamen, striatum	↓	Aerobics	↑	[70]
Epilepsy	Frontal, parietal and temporal lobes of the brain	↓	Aerobics	↑	[105]

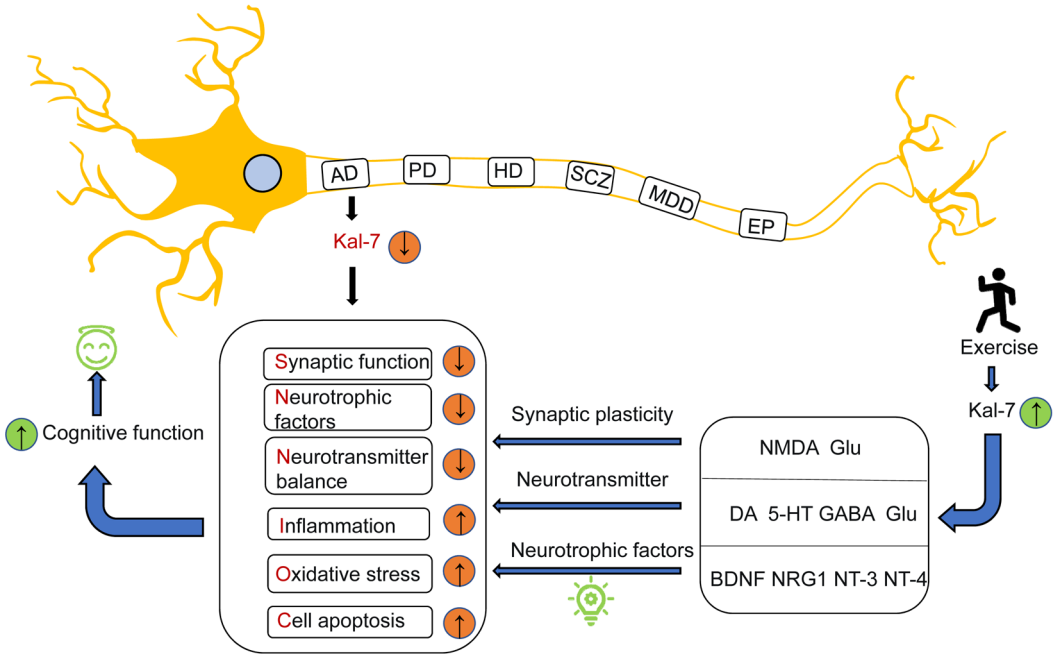

图 3. 运动通过Kal-7改善神经退行性疾病的机制

Fig. 3. Mechanism of exercise improving neurodegenerative diseases through Kal-7. AD, Alzheimer disease; BDNF, brain-derived neurotrophic factor; DA, dopamine; EP, epilepsy; GABA, γ-aminobutyric acid; Glu, glutamic acid; HD, Huntington's disease; MDD, major depressive disorder; NMDA, *N*-methyl-*D*-aspartic acid; NRG1, neuregulin 1; NT-3, neurotrophic factor 3; NT-4, neurotrophic factor 4; 5-HT, 5-hydroxytryptamine; PD, Parkinson's disease; SCZ, schizophrenia

的表达和分泌。

4 总结与展望

Kal-7 作为调节中枢神经突触可塑性的关键因子，通过与不同突触后蛋白结合参与神经细胞的生长、发育、营养支持和 BNT 调控机制等过程，维持大脑兴奋与抑制平衡并与多种神经退行性疾病密切相关。运动训练可作为针对神经退行性疾病防治和康复的有效手段，其应用可适当减少患者的药物使用和经济负担。运动可促进中枢 Kal-7 表达，改善神经突触可塑性和脑部疾病导致的学习记忆退化 (见图 3)。

但调节中枢 Kal-7 表达水平的最佳运动方式与持续时间缺乏系统研究，Kal-7 介导运动改善神经退行性疾病的具体机制尚未完全阐明。因此，进一步探究 Kal-7 介导运动改善神经退行疾病的机制，将对揭示运动改善神经退行疾病提供理论和临床治疗新靶点。

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