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运动改善炎性痛与抑郁共病作用机制的研究进展

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【摘要】 炎性痛与抑郁症是临床常见疾病,二者具有高共病率,且能够相互加剧彼此病程,严重降低患者生活质量。炎性痛与抑郁共病的发病机制极为复杂,为临床诊疗带来严峻挑战。近年研究发现,神经炎症的持续激活是炎性痛与抑郁共病的核心病理环节。运动作为一种非药物手段,可有效改善共病患者的疼痛和抑郁症状,然而其具体的作用机制尚未完全明确。本文对运动在抑制中枢炎症水平、调节小胶质细胞 M1/M2 极化平衡、调控神经元兴奋-抑制稳态以及促进海马神经发生方面的最新研究进行总结,系统综述运动调节神经炎症治疗炎性痛与抑郁共病的分子及神经机制,以期为临床运动治疗提供新的理论基础和实践参考。

【关键词】 运动;炎性痛;抑郁症;神经炎症
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Research progress on the mechanism of exercise in improving the comorbidity of inflammatory pain and depression

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【Abstract】 Inflammatory pain and depression are clinically common disorders with a high comorbidity rate. They mutually exacerbate their pathological processes and severely reduce the quality of life of patients. The pathogenesis of the comorbidity of inflammatory pain and depression is highly complex, posing significant challenges for clinical diagnosis and treatment. Recent studies have revealed that sustained activation of neuroinflammation is a central pathological link in the comorbidity of inflammatory pain and depression. As a non-pharmacological intervention, exercise can effectively improve both pain and depressive symptoms in patients with comorbidity. However, its specific mechanisms of action remain incompletely elucidated. This article summarizes recent research advances on the effects of exercise in inhibiting central inflammation, modulating the balance of microglial M1/M2

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polarization, regulating neuronal excitatory-inhibitory homeostasis, and promoting hippocampal neurogenesis. It systematically reviews the molecular and neural mechanisms by which exercise modulates neuroinflammation to treat the comorbidity of inflammatory pain and depression, with the aim of providing a theoretical basis and practical guidance for clinical exercise therapy.

【Keywords】 exercise; inflammatory pain; depression; neuroinflammation

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炎性痛患者以慢性炎症、痛觉超敏及焦虑抑郁等情绪障碍为特征[1]。流行病学研究表明,迁延不愈的炎性痛常与抑郁症共病,约 52%的疼痛患者具有抑郁症状,65%的抑郁症患者遭受疼痛困扰,二者形成“疼痛-抑郁”双向恶性循环,导致其病理机制更加复杂[2]。该共病现象在膝骨关节炎[3]、类风湿性关节炎[4]及慢性盆腔炎[5]等疾病中尤为突出,其临床治疗难度显著高于单一疾病。现有研究认为,神经炎症是炎性痛与抑郁共病发生及维持的重要病理基础。在慢性炎症状态下,促炎因子持续升高可导致中枢免疫细胞异常激活,破坏神经保护与稳态调控机制,并通过影响疼痛及情绪调节相关的神经环路,促进疼痛敏化并诱发抑郁障碍[6,7]。尽管现有药物治疗可在一定程度上缓解共病症状,但长期使用往往伴随耐受、依赖综合征及其他不良反应,限制了其持续干预效果。因此,探索能够有效调控神经炎症反应的非药物干预手段,被认为是同时改善炎性痛与抑郁共病的潜在关键策略。

在此背景下,运动作为一种安全、耐受性良好的干预方式,已被证实能够有效改善炎性痛与抑郁共病症状[8]。运动可下调 toll 样受体(toll-like receptor, TLR)信号通路和干扰素信号通路等活性,抑制神经胶质细胞过度激活并降低神经炎症水平,从而减轻疼痛感知并改善抑郁症状,其临床价值日益凸显[9]。然而,目前关于运动改善炎性痛与抑郁共病的作用机制尚缺乏系统整合。基于此,本文将从运动改善神经炎症的视角出发,系统分析运动调控神经炎症缓解炎性痛与抑郁共病的潜在机制,以期为临床运动治疗提供理论支持与科学依据。

1 炎性痛与抑郁共病的发生机制

炎性痛与抑郁共病通常表现为痛觉敏化、情绪低落、反应迟钝及精神萎靡,导致生活质量下降,病情严重者甚至放弃生命,造成沉重的社会负担[10]。临床研究表明,炎性痛患者常伴有焦虑、抑郁等负性情绪,且长期疼痛的患者在 14 年的随访期间患抑郁症的风险更高,疼痛与抑郁症之间存在正相关关系[11]。疼痛与抑郁共享重叠的大脑区域,包括前额叶皮层(prefrontal cortex, PFC)、前扣带皮层(anterior cingulate cortex, ACC)、杏仁核、海马体和中缝核等,这些脑区互相连接并协同调节,激活负责疼痛处理的大脑区域也会导致抑郁症等异常情绪,且编码促炎因子的基因在这些脑区中表达显著增加[12]。

炎性痛与抑郁共病的核心病理变化与神经炎症密切相关,尤以肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)、白细胞介素(interleukin,IL)-1β 和 IL-6 等促炎因子的激活为特征[12]。在慢性炎症状态下,维持内皮结构和功能完整性的 Claudin-5 表达降低,血脑屏障完整性被破坏,不仅直接诱导中枢炎症反应,其通透性增高可进一步促进炎症细胞浸润到中枢神经系统(central nervous system, CNS)[13]。TNF-α、IL-1β 等炎症因子直接浸润至海马体,能够激活中枢小胶质细胞,通过与神经元交互作用使得神经元过度兴奋,进而加剧神经炎症并诱导抑郁[14]。对于炎性痛与抑郁共病,目前常见的治疗方法为镇痛和抗抑郁药物联合使用,但长期服用存在副作用多、药物成瘾等缺点,因此,寻找能够有效缓解疼痛与抑郁症状,改善患者生活质量的干预措施极为重要。

2 运动对炎性痛与抑郁共病的影响

目前,多种运动形式已被应用于炎性痛与抑郁共病的治疗,包括有氧运动(如跑步、骑行)、抗阻运动(如力量训练、举重)以及身心运动(如瑜伽、太极拳)等。YAN 等[15]研究表明,有氧运动在膝骨关节炎等炎性痛患者中可稳定缓解疼痛、

改善功能并提升生活质量。抗阻运动通过增强肌肉力量与耐力,不仅改善关节稳定性,还可抑制炎症反应并缓解疼痛与抑郁症状[16]。身心运动通过整合姿势控制、呼吸调节和心理放松等要素,在缓解疼痛和抑郁症状方面亦显示出良好效果[17]。值得注意的是,有氧与抗阻运动的联合干预在改善疼痛、情绪及整体功能方面优于单一运动方式,其协同效应可能与机体神经炎症反应的综合调控密切相关[18]。

除运动形式外,运动频率、持续时间及强度同样是影响疗效的重要因素。针对炎性痛的研究表明,每周 5 次以上,持续超过 12 周的有氧运动在疼痛缓解方面效果最为显著,而短于 8 周的运动方案往往难以达到临床显著性[19]。在抑郁治疗方面,短期和长期有氧运动均可改善抑郁,其中每周 3 次,每次 40 min,持续 11 周的中等强度运动方案疗效最为显著[20]。综上所述,长期运动较短期干预在疼痛和抑郁改善方面更为稳定和持久。在运动强度方面,中低强度运动在中老年炎性痛患者中具有较好的耐受性和依从率,并可有效缓解疼痛[21]。而在疾病控制良好的患者中,高强度运动可带来更显著且持久的疼痛缓解和抑郁改善,其对身体功能的促进作用可持续 6 个月以上,这可能与更持久的神经炎症抑制相关[21,22,8]。综上所述,在炎性痛与抑郁共病的运动干预中,应综合考虑运动方式、频率、持续时间及强度与患者个体特征的匹配程度,遵循循序渐进和个性化原则,以实现长期稳定的综合获益。

3 运动改善炎性痛与抑郁共病的神经炎症机制

越来越多的证据表明,神经炎症可能是运动改善炎性痛与抑郁共病的关键环节。神经炎症是神经系统对损伤、感染或炎性刺激的先天免疫反应,其特征是常驻神经胶质细胞如小胶质细胞和星形胶质细胞的激活,以及细胞因子和趋化因子的释放[23]。基于炎性痛与抑郁共病模型的转录组学研究显示,海马脑区的差异表达基因主要富集于神经炎症相关通路,提示神经炎症是共病的核心驱动因素[24]。

3.1 运动减轻中枢炎症水平

慢性炎性痛主要表现为免疫耐受失衡引起的促炎和抗炎介质的异常表达,此类患者 TNF-α 和 C-反应蛋白(C-reactive protein, CRP)等促炎标志物水平显著高于健康人群,这种炎症因子对 CNS 的持续刺激被认为是抑郁症的重要触发机制[25]。在疼痛与抑郁共病状态下,CNS 的小胶质细胞和星型胶质细胞异常激活,导致与情绪调控和疼痛处理相关的脑区(海马、杏仁核、ACC 和 PFC)释放核因子-κB(nuclear factor-κB, NF-κB)、信号转导及转录激活因子(signal transducer and activator of transcription, STAT)、TNF-α、IL-1β、IL-6 等促炎介质,引发这些脑区的神经元损伤并加剧神经炎症[12]。

规律运动能有效减轻慢性腰痛、膝骨关节炎等多种疾病的疼痛症状,降低炎症标志物表达,改善抑郁严重程度并提升患者生活质量[26]。与一次性高强度运动干扰细胞稳态并可能引起的炎症波动相比,持续中等强度运动可显著且稳定的降低 IL-6、CRP 和 TNF-α 等炎症生物标志物水平[27]。GOMES 等[28]研究发现,连续 10 d,每天 30 min 的跑台运动可显著降低小鼠海马脑区促炎与抗炎因子的比值,提示运动在调节海马炎症因子平衡方面具有积极作用。定期有氧运动可降低多种促炎因子如 CRP、TNF-α、可溶性肿瘤坏死因子受体(soluble tumor necrosis factor receptor, sTNFR)1 和 sTNFR2 的水平,并促进抗炎因子如 IL-4、IL-1 受体拮抗剂(IL-1 receptor antagonist, IL-1RA)和转化生长因子-β(transforming growth factor-β, TGF-β)的产生[29]。针对炎性痛模型的研究表明,为期 12 周的跑台运动能有效减轻小鼠 CNS 关键区域(包括脑干、下丘脑和海马体)的神经炎症,具体表现为促进抗炎因子 IL-10 表达,同时抑制促炎因子 IL-1β、IL-6 和 TNF-α 等表达,这一神经炎症的减轻不仅直接缓解疼痛,还能有效改善伴随的情绪障碍[30]。上述证据提示,长期规律运动对于稳定调控中枢炎症反应、实现共病症状的持久改善具有关键作用。

3.2 运动调节小胶质细胞极化平衡

小胶质细胞作为 CNS 的主要免疫细胞,在炎性痛与抑郁共病的神经炎症机制中发挥关键作用。WU 等[31]空间转录组学研究表明,小胶质细胞是抑郁症首先响应的神经胶质细胞类型,其最早对炎症信号做出反应。小胶质细胞介导的神

经炎症具有双重调控特性,M1 型小胶质细胞释放促炎因子诱导神经炎症并加剧组织损伤,而 M2 型小胶质细胞释放抗炎介质促进组织再生和修复[32]。在炎性痛与抑郁状态下,相关脑区(海马、PFC)小胶质细胞向 M1 型极化,极化的小胶质细胞大量分泌 TNF-α、IL-1β、趋化因子、活性氧(reactive oxygen species, ROS)、诱导型一氧化氮合酶(inducible nitric oxide synthase, iNOS)等炎症介质,引起细胞和组织损伤[33,34]。这种极化破坏小胶质细胞 M1/M2 表型平衡,导致神经炎症不断恶化,进一步刺激疾病发展。

运动可通过重塑小胶质细胞极化状态缓解神经炎症。研究表明,单次 30 min 急性跑台运动可抑制小鼠小胶质细胞过度激活,而长期中等强度跑台运动则能够逆转海马小胶质细胞的数量及形态异常,并促进其由 M1 向 M2 表型转变[35,36]。WANG 等[37]研究表明,6 周高强度间歇训练通过抑制 Janus 激酶 2(Janus kinase 2, JAK2)/STAT3 通路促进小胶质细胞 M1 向 M2 表型转变,减少炎症因子释放。此外,4 周中等强度跑台运动可通过激活脂联素(adiponectin)/脂联素受体 1(adiponectin receptor 1, AdipoR1)依赖性腺苷酸活化蛋白激酶(adenosine monophosphate-activated protein kinase, AMPK)/NF-κB/STAT3 信号通路,促使抑郁小鼠海马小胶质细胞 M1 向 M2 表型转变[35]。跑台运动还通过减少 STAT3 磷酸化激活降低磷酸化 STAT3(p-STAT3)和总 STAT3(t-STAT3)比值,抑制小胶质细胞炎症因子的释放并促进其向 M2 表型转变[38]。这种表型转变减少了 TNF-α、干扰素-γ(interferon-γ, IFN-γ)、IL-1β 和 IL-18 等促炎因子的产生,同时增加了 IL-10 和 TGF-β 等免疫抑制细胞因子的释放,减轻神经炎症,并缓解炎性痛及抑郁症状[39]。上述研究提示,长期规律运动对于稳定调控小胶质细胞结构功能、恢复其极化平衡具有重要意义。

3.3 运动调控神经元兴奋/抑制平衡

当机体处于炎症状态时,异常活化的小胶质细胞可破坏中枢谷氨酸(glutamate, Glu)和 γ-氨基丁酸(γ-aminobutyricacid, GABA)系统间的动态平衡,导致神经元兴奋/抑制(excitation/inhibition, E/I)稳态失衡,诱发焦虑、抑郁等情绪障碍[40]。HAROON 等[41]研究发现,M1 型小胶质细胞释放的炎症因子可干扰中枢 Glu 的释放和再摄取,致使基底神经节和 ACC 突触间隙中 Glu 浓度显著升高,引发神经元过度兴奋。SHAO 等[42]采用化学遗传学技术特异性激活 ACC 区域 GABA 能神经元,通过增强抑制性突触传递降低锥体神经元的兴奋性,缓解共病症状。此外,神经元过度兴奋引发的神经炎症可损伤疼痛与情绪调节相关的关键神经回路,如激活基底外侧杏仁核(basolateral amygdala, BLA)-ACC 通路,造成少突胶质细胞数量减少和髓鞘形成受损,最终驱动共病病理进程[43]。

运动能够降低 Glu 浓度减轻兴奋性毒性,同时上调 GABA 介导的抑制性调控,恢复神经递质稳态并调节神经元 E/I 平衡,其调控作用具有时间效应和剂量依赖性[44]。磁共振波谱研究发现,单次 20 min 高强度间歇运动后健康成人感觉运动皮层 GABA 浓度增加 20%,且浓度在 1 h 内持续性高表达[45]。长期中等强度的运动更利于 E/I 稳态重塑,其效果也更为稳定和持久,这一过程与 GABA 能中间神经元功能增强及谷氨酸转运体表达上调等结构性适应相关[46,47]。在突触可塑性层面,14 d 的跑台运动可降低兴奋性突触活动,增加突触前囊泡的释放和突触小泡的密度,优化突触结构和功能[48]。值得注意的是,运动对神经元 E/I 平衡的调控不仅体现在单个神经元或突触水平,还体现在整个神经网络的功能上。运动能够通过调节神经回路中的兴奋性和抑制性输入,维持整个神经网络的稳态。研究表明,每天运动 1 h,持续 14 d 的跑台运动可以选择性激活内侧前额叶前边缘皮层(prelimbic cortex, PrL)-初级运动皮层(primary motor cortex, M1)-腹内侧丘脑(ventromedial thalamus, VM)神经回路,并可抑制内侧前额叶皮层(medial prefrontal cortex, mPFC)-BLA 神经回路的过度兴奋,恢复关键脑区的正常 E/I 平衡,最终缓解负面情绪[49,50]。

3.4 运动调节海马神经发生

海马神经发生,即终生在海马中产生新神经元的过程,作为维持认知和情绪调节的重要生理机制,在炎性痛与抑郁共病中具有关键作用[51]。FANG 等[52]研究表明,增加海马新生神经元数量可缓解慢性炎性痛小鼠的热痛和机械痛阈值,反之,给予神经发生抑制剂则导致伤害性感受增强

并加剧小鼠抑郁症状。M1 型小胶质细胞释放的 IL-1β、TNF-α、IL-6、环氧化酶 2(cyclooxygenase-2, COX-2)等促炎因子可直接阻碍新生神经细胞增殖存活,导致神经发生受损[53]。持续性炎症还通过下调脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)表达,抑制神经发生并损伤海马突触可塑性,最终诱发抑郁症等负性情绪[54]。

运动是促进成体神经发生的重要因素,运动强度通常与神经发生程度呈反比,且短期运动促进细胞增殖,而长期运动除了促进细胞增殖外,还进一步促进神经元分化和存活[55]。CHOI 等[56]研究发现,4 周中等强度跑台运动能够通过海马鸢尾素/纤连蛋白Ⅲ型结构域蛋白 5(fibronectin type Ⅲ domain containing 5, FNDC5)介导的 BDNF/环腺苷酸反应元件结合蛋白(cAMP-responsive element-binding protein, CREB)通路促进新生神经元生成。XU 等[57]研究发现,10 周中等强度跑台运动通过抑制鸢尾素/TLR4/髓样分化因子 88(myeloid differentiation factor 88, MyD88)/NF-κB 通路减轻神经炎症并改善海马成体神经发生所需的微环境。此外,运动介导的鸢尾素信号通过上调神经细胞抗凋亡因子 B 淋巴细胞瘤-2(B-cell lymphoma-2, Bcl-2),下调促凋亡因子 Bcl-2 相关 X 蛋白(Bcl-2-associated X protein, BAX)和活化的 Caspase-3,增强神经保护作用并提高新生神经元存活率[58,59]。上述研究表明,运动通过调节鸢尾素依赖的神经发生促进与凋亡抑制机制,在缓解炎性痛的同时改善抑郁症状(图 1)。

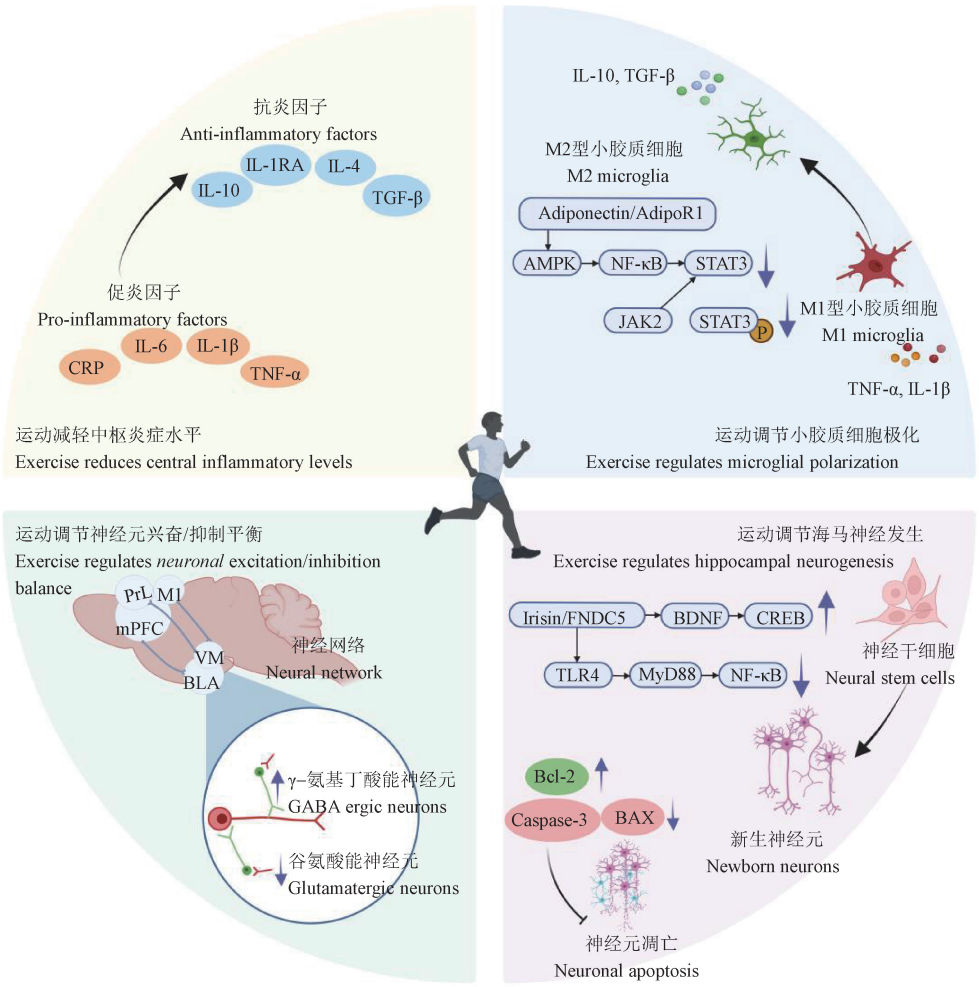

图 1 运动改善炎性痛与抑郁共病的神经炎症机制

Figure 1 Neuroinflammatory mechanisms underlying exercise-induced amelioration of comorbid inflammatory pain and depression

4　小结与展望

炎性痛患者常伴有不同程度的抑郁症状,神经炎症是介导这一共病现象的关键病理环节。作为一种安全有效的干预方式,运动可通过抑制中枢炎症反应、恢复小胶质细胞极化平衡、调节神经元兴奋-抑制稳态以及促进海马神经发生等多种途径发挥作用,从而抑制神经炎症并改善疼痛与抑郁症状。然而,当前研究仍存在局限性,首先,炎性痛与抑郁共病的病理机制较复杂,不同运动方案对神经炎症的调节可能涉及不同的信号通路,多条通路之间的交互作用及其在共病发生发展中的级联调控网络仍有待系统阐明。其次,关于不同运动强度、频率及持续时间与不同类型共病治疗之间的匹配关系尚未完全明确,仍需深入细化相关研究,以实现治疗效益的最大化。未来研究应推动临床与基础研究的深度融合,实施更严谨的临床试验和机制探索,进一步明确运动干预的临床转化潜力并挖掘其在防治共病中的关键作用靶点。

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