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运动改善代谢性炎症：BDNF的潜在调节作用*

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摘要 代谢性炎症是代谢性疾病发生、发展的重要机制，主要表现为免疫细胞激活和促炎因子水平升高。脑源性神经营养因子（BDNF）在调节免疫与代谢功能中的作用日益受到关注。BDNF通过其受体酪氨酸激酶受体B（TrkB）在中枢神经系统中抑制胶质细胞激活、调节炎症反应，并在外周组织中通过影响巨噬细胞极化缓解局部炎症。运动可有效诱导中枢（下丘脑、海马体、前额叶皮质及脑干）和外周（肝脏、脂肪组织、肠道及骨骼肌）组织器官表达BDNF，进而参与炎症抑制与代谢改善。尽管早期已有学者提出BDNF可能参与运动介导的炎症调节，但系统性证据仍显不足。随着对运动生理机制认识的深化，亟需从多系统整合视角出发，系统梳理BDNF在运动调控代谢性炎症中的潜在作用与机制，以期为代谢性疾病的干预策略提供理论支持与实践依据。

关键词 运动，代谢性炎症，脑源性神经营养因子，脑源性神经营养因子前体
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近年来，代谢性疾病（如肥胖、2型糖尿病）的全球患病率显著上升，且发病年龄呈现年轻化趋势，已成为影响公众健康和生活质量的重要公共卫生问题。代谢性炎症（metaflammation）是机体代谢紊乱造成的慢性低度炎症状态，被认为是代谢性疾病发生和发展的重要机制，其主要特征包括免疫细胞的异常激活和促炎因子的持续升高。已有研究表明，营养过剩、脂质沉积、内质网应激及线粒体功能障碍等代谢异常是诱发代谢性炎症的重要因素[1]。脑源性神经营养因子（brain-derived neurotrophic factor，BDNF）作为一类关键的神经营养因子，在代谢与免疫调控中发挥重要作用。BDNF通过激活其高亲和性受体酪氨酸激酶受体B（tropomyosin receptor kinase B，TrkB），在中枢神经系统中可抑制小胶质细胞和星形胶质细胞的过度激活，减少促炎因子释放，促进抗炎因子表达，从而发挥抗炎作用[2]。此外，BDNF亦在外周组织（如肝细胞、白色脂肪细胞等）中表达并调节巨噬细胞极化，缓解局部炎症反应[3]。

运动作为一种非药物干预手段，被广泛应用于改善代谢性疾病，其发挥作用的重要途径之一是运动能够显著诱导BDNF表达，调节炎症反应、改善代谢状态，进而延缓疾病进展[4-5]。因此，BDNF被视为运动-代谢调控轴中的关键分子。2014年，Papathanassoglou等[6]首次归纳了BDNF参与运动介导炎症调节的研究证据，但由于彼时相关研究有限，尚未明确定论。此后，该领域仍缺乏与之相关的系统性总结与探讨。随着运动生理学研究的深入发展，学界逐渐认识到运动是一种多系统协调的复杂活动，其作用效果取决于运动类型、强度与频次等多因素的协同[7]。因此，亟需突破以往仅聚焦局部效应与单一机制的研究模式，转向对运动全身性效益的整体理解。

综上所述，鉴于BDNF在中枢及外周多个组织器官中广泛参与炎症反应调节，并与代谢过程关系紧密，故系统梳理其在运动调控代谢性炎症中的潜在作用与机制，将为深入揭示代谢性疾病的病理基础及优化运动干预策略提供理论支撑与实践依据。

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1　BDNF的结构与功能

BDNF由247个氨基酸组成，是Barde等[8]于1982年首次从猪脑中分离并发现的一种蛋白质。因其最初被发现能够促进鸡胚胎背根神经节的生长与存活，故被鉴定为除神经生长因子（nerve growth factor）外的另一种神经营养因子[9]。BDNF主要在神经元[10]、神经胶质细胞[11]及骨骼肌[12]中产生，其合成与成熟涉及多个生理过程。首先，BDNF基因转录后，在内质网中合成并折叠成前体原BDNF（pre-pro-BDNF），这是一种由“信号肽序列”、“前体区域”和“成熟区域”组成的蛋白质；随后，前体原BDNF被转运至高尔基体，“信号肽序列”被迅速切割生成BDNF前体蛋白（pro-BDNF）；pro-BDNF在纤溶酶或基质金属蛋白酶作用下被进一步分解，最终产生成熟BDNF（mBDNF）。

BDNF在神经发育、学习、记忆、突触可塑性及神经元存活等多个生物学过程中发挥作用。在循环系统中，它有两种形式：mBDNF和pro-BDNF，两者在功能和作用机制上存在显著差异[13-14]。mBDNF以二聚体形式存在，主要与高亲和力受体TrkB结合激活磷脂酰肌醇3激酶（phosphoinositide 3-kinase，PI3K）/蛋白激酶B（protein kinase B，PKB）、核因子κB（nuclear factor kappa-B，NF-κB）和哺乳动物雷帕霉素靶蛋白（mammalian target of rapamycin，mTOR）等下游信号通路，促进神经元存活、增强突触可塑性、调控神经递质释放以及支持神经元轴突和树突生长[15]。相比之下，pro-BDNF主要与肿瘤坏死因子TNF受体家族成员p75神经营养因子受体（p75 neurotrophin receptor，p75NTR）结合，诱导神经元凋亡和突触修剪[16]。此外，BDNF不仅作用于中枢神经系统，还参与调节外周多个生理过程。BDNF可表达于单核细胞和T细胞，调节免疫和炎症反应。在骨骼肌中，BDNF通过激活腺苷酸活化蛋白激酶（adenosine activated protein kinase，AMPK）通路调节能量代谢，从而对代谢过程和心血管功能产生影响。需要注意的是，在脑发育的不同阶段，两者比例有所变化。研究表明，个体出生后早期pro-BDNF浓度较高，而成年期则以mBDNF为主[17]。总之，BDNF不仅在神经系统中发挥作用，还参与调节免疫、代谢等生理过程。pro-BDNF和mBDNF在不同的生理阶段和过程中各自具有不同功能，维持两者平衡对神经发育、学习记忆等至关重要（图1）。

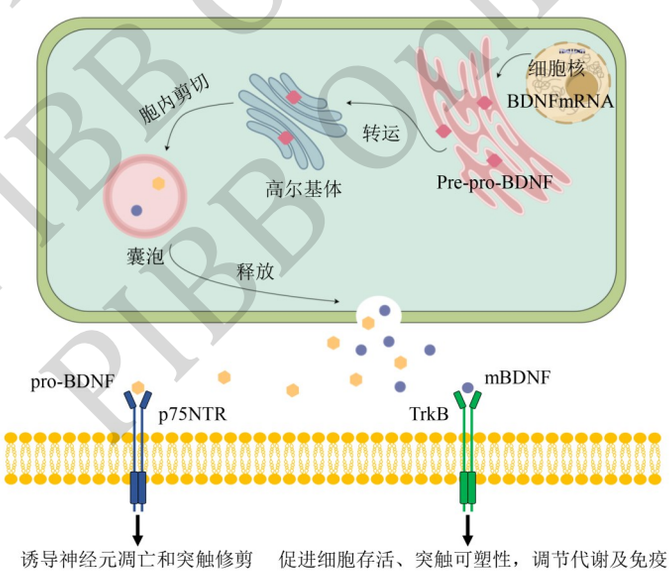

Fig. 1　Structure and function of BDNF

图1　BDNF的结构与功能

BDNF：脑源性神经营养因子（brain-derived neurotrophic factor）；pre-pro-BDNF：前体原脑源性神经营养因子；pro-BDNF：脑源性神经营养因子前体蛋白；mBDNF：成熟脑源性神经营养因子；p75NTR：肿瘤坏死因子TNF受体家族成员p75神经营养因子受体（p75 neurotrophin receptor）；TrkB：酪氨酸激酶受体B（tropomyosin receptor kinase B）。本图采用Figdraw绘制（IDTYPPPcbbbf）。

2　BDNF与代谢性炎症的关联

BDNF通过多种机制调节全身代谢性炎症。在中枢神经系统中，BDNF可调控下丘脑、海马体、前额叶皮质和脑干的炎症反应，从而改善能量代谢和认知功能；在外周组织中，则通过作用于肝脏、脂肪组织、肠道和骨骼肌，发挥免疫调节、维持代谢稳态并促进组织修复。BDNF主要通过调控NF-κB、TrkB、PI3K/Akt等信号通路，发挥抗炎作用并促进细胞功能恢复，从而在系统水平上改善代谢健康（图2）。

2.1　BDNF调节中枢代谢性炎症

2.1.1　BDNF调节下丘脑炎症

下丘脑是调节能量代谢及食欲的重要脑区，可通过感知激素和神经递质水平调节食欲和能量消耗。肥胖与高脂膳食（high food diet，HFD）不仅导致下丘脑功能障碍，还促进炎症反应扰乱机体代谢稳态与能量平衡[18-19]。BDNF作为能量平衡调节因子，可抑制下丘脑炎症改善胰岛素和瘦素的信号传导，调节与摄食相关的神经肽表达，恢复下丘脑-垂体-肾上腺轴功能，以维持能量代谢稳态及神经内分泌平衡[20-21]。有研究表明，HFD诱导*TRIM67*基因敲除肥胖小鼠的下丘脑刺鼠关联肽（agouti-related peptide，AgRP）神经元激活，BDNF mRNA表达下降，并进一步加剧下丘脑炎症和脂肪累积[22]；电针治疗后，下丘脑BDNF水平升高，抑制弓状核小胶质细胞过度激活，减少Toll样受体4（Toll-like receptor 4，TLR4）和白介素-6（interleukin-6，IL-6）表达，恢复了原阿片黑素皮质素（proopiomelanocortin，POMC）神经元活性，进而延缓小鼠体重增长[23]。进一步研究显示，趋化因子1（CX3C chemokine ligand 1，CX3CL1）与其受体（C-X3-C motif chemokine receptor 1，CX3CR1）结合后可激活BDNF-TrkB信号通路，抑制肿瘤坏死因子α（tumor necrosis factor-α，TNF-α）和IL-6 mRNA表达，减轻HFD诱导的下丘脑炎症，并调控肥胖小鼠的厌食行为[24]。Queen等[25]利用腺相关病毒BDNF基因疗法，逆转了表现为食欲过盛并伴有肥胖的普拉德-威利综合征（prader-willi syndrome）小鼠下丘脑小胶质细胞过度激活，并下调TNF、髓样分化初始反应基因88（myeloid differentiation primary response 88，Myd88）和C-X-C基序趋化因子受体3（C-X-C motif chemokine receptor 3，Cxcr3）等炎症相关标志物的基因表达，进而改善小鼠的过度进食行为。综上，BDNF可通过多种生理途径抑制下丘脑炎症，促进机体代谢及内分泌稳态平衡恢复。

2.1.2　BDNF调节海马体炎症

海马体作为调控学习、记忆及认知功能的关键脑区，其功能高度依赖BDNF水平[26]。长期HFD不仅诱发肥胖，同时亦可损害认知功能[27-29]。一方面，HFD可上调海马区环氧化酶2（cyclooxygenase-2，COX-2）和前列腺素E2（prostaglandin E2，PGE2）水平，促进TNF-α、白介素-1β（interleukin-1 beta，IL-1β）及IL-6释放，抑制BDNF表达[30]；另一方面，HFD诱导海马CA1区、CA3区及齿状回（dentate gyrus，DG）小胶质细胞激活，促进IL-1β及其受体（interleukin-1 receptor，IL-1R）表达，加剧炎症反应，损害小鼠的空间学习记忆能力[31-32]。针对上述问题，研究人员试图通过物理或药物等途径升高BDNF水平，逆转上述病理过程，如电针治疗可上调小胶质细胞内BDNF表达，减轻HFD诱导的炎症反应，改善小鼠认知功能[31]；药物干预，如氟西汀（10 mg·kg^{-1}·d^{-1}）可激活环磷腺苷反应元件结合蛋白（cAMP-response element binding protein，CREB）-BDNF信号通路，促进其下游分子丝裂原活化蛋白激酶1（mitogen-activated protein kinase 1，*MAPK1*）基因表达减轻海马体炎症，逆转HFD诱导的小鼠认知缺陷[33]；此外，益生元或益生菌饮食干预可增加海马体BDNF水平，改善炎症状态，减少淀粉样斑块累积，提高小鼠空间学习和记忆能力，减少焦虑样行为[34-35]。综上，BDNF可抑制HFD诱导的海马体炎症，促进学习和记忆功能恢复。

2.1.3　BDNF调节前额叶皮质炎症

前额叶皮质是大脑额叶的重要组成部分，在调节高级认知功能（如执行功能）、情绪（如决策与奖赏评估）以及社会行为（如心理理论和共情）中发挥重要作用。临床研究表明，肥胖成人循环系统中BDNF水平显著降低，且与其认知能力下降有关[36]。动物研究进一步揭示，高脂高糖饮食会显著抑制前额叶皮质中BDNF表达，诱导大鼠出现快感缺失、社交互动行为减少、新物体识别能力下降及社交记忆受损[37-38]。究其原因，一方面是HFD通过降低BDNF与TrkB受体结合，抑制下游CREB的磷酸化，影响PFC的调节功能[39]；另一方面是HFD还激活了TLR4-MyD88信号通路，促进NF-

κB、TNF-α、IL-1β等促炎因子水平升高，并引发腹内侧前额叶皮质COX-2上调，诱导小鼠产生焦虑和抑郁样行为[40]。通过给予益生元治疗可促进BDNF与TrkB受体结合，激活Akt/PI3K-CREB通路，增加内源性BDNF合成缓解炎症，进而改善认知、焦虑及抑郁样行为[40-41]。因此，BDNF可通过TrKB信号通路抑制HFD诱导的PFC炎症并恢复其调节功能。

2.1.4 BDNF调节脑干炎症

脑干位于大脑和脊髓之间，由中脑、脑桥及延髓组成。其中，中脑腹侧被盖区和孤束核是研究奖赏[42]、摄食[43]和“肠-脑”轴[43]互作机制中学界较为关注的两个脑区。一方面，HFD诱导的炎症反应可通过影响多巴胺能神经元活性，破坏奖赏信号传递，导致奖赏功能异常，改变机体对食物奖赏的反应[44]；另一方面，HFD诱导肠道炎症，并通过“肠-脑”轴调节迷走神经活性进而调节摄食行为[45]。虽然已有研究证实，腹侧被盖区和孤束核中的BDNF能够有效调节奖赏及摄食功能[46-47]，但其是否通过介导炎症途径来调节这些功能鲜有研究报道。然而，抑郁症和其他动物模型研究为这一可能的机制提供了有力证据。抑郁小鼠腹侧被盖区中小胶质细胞激活，TNF-α、IL-1β及IL-6水平升高，BDNF表达减少；通过注射小胶质细胞抑制剂（米诺环素或PLX3397）能显著改善小鼠抑郁样行为，且腹侧被盖区BDNF mRNA表达水平有上升趋势[48-49]。此外，暴露于香烟环境中的小鼠孤束核BDNF水平下降，但未观察到明显的炎症反应[50]；相反，暴露于柴油机尾气的大鼠孤束核中小胶质细胞和星形胶质细胞激活，炎症反应增强；孤束核神经元胞体内发生内质网扩张、核糖体丢失及线粒体空泡化等超微结构损伤，但未发现BDNF水平的变化差异[51]。这两项研究结果不同的原因可能是动物模型之间存在差异，以及暴露因素和暴露剂量不同导致最终结果各异。尽管没有直接证据表明BDNF可调节HFD诱导的腹侧被盖区和孤束核炎症反应来改善奖赏及摄食功能，但综上所述提示，BDNF可能发挥一定作用，仍需进一步研究证实。

2.2 BDNF调节外周代谢性炎症

2.2.1 BDNF调节肝脏炎症

HFD可诱导肝脏巨噬细胞浸润、氧化应激及IL-1β和TNF-α等促炎因子水平升高[52-53]，BDNF在肝脏代谢及免疫调节中发挥重要作用。动物研究表明，*BDNF*基因敲除大鼠的肝脏重量增加，BDNF-TrkB信号传导减弱，肝脏脂代谢能力下降，并进一步促进肝脏脂肪变性和肥胖形成[54]。临床研究显示，非酒精性脂肪肝病（non-alcoholic fatty liver disease，NAFLD）患者的血清BDNF水平高于正常人，且与疾病严重程度呈显著正相关，提示NAFLD导致患者血清BDNF代偿性增加[55]。推测其机制可能与BDNF介导的炎症反应有关。因为随着疾病的进展，部分患者可发展为非酒精性脂肪性肝炎（non-alcoholic steatohepatitis，NASH），其特征包括肝细胞损伤、炎症反应以及不同程度的肝纤维化。2023年Ichimura-Shimizu等[56]首次报道BDNF在NASH动物模型中的调节作用。该研究发现，*BDNF*基因敲除小鼠肝脏增大，颜色苍白，肝小叶中性粒细胞浸润，肝细胞脂肪变性，并发生气球样变和纤维化，该病理性改变与NASH患者的病理特征十分相似；随后该团队于2024年发表相关综述，系统阐述了外周BDNF在NAFLD和NASH中的调节作用，这为BDNF调节肝脏炎症提供了较为直接的参考[57]。尽管现有证据表明，BDNF在肝脏疾病的不同阶段和不同实验动物模型下均能发挥作用，但BDNF调节肝脏代谢性炎症反应的潜在机制尚未完全阐明，仍缺乏动物或细胞模式研究对其深入探讨。

2.2.2 BDNF调节脂肪组织炎症

脂肪组织不仅是能量储存器官，还具有内分泌和免疫调节功能。巨噬细胞及其前体单核细胞是脂肪组织免疫细胞的主要组成部分。在肥胖发展过程中，白色脂肪组织（white adipose tissue，WAT）中M1型促炎巨噬细胞数量显著高于M2型抗炎巨噬细胞；BDNF在WAT中广泛表达，参与调节脂肪代谢及炎症反应[58-59]。一项模拟人类*BDNF* Val66Met基因突变的动物研究显示，与野生型小鼠相比，*BDNF* Val66Met基因突变小鼠附睾WAT形态发生改变，并伴有较强的炎症反应[60]。接受*BDNF*基因转移治疗小鼠的脂肪细胞面积减小，腹股沟、性腺以及肾脏周围的WAT中IL-1β和IL-6 mRNA表达水平显著下降[61]。体外研究进一步显示，给予外源性BDNF刺激可促进M1型巨噬细胞向M2型巨噬细胞转化，并抑制IL-1β和IL-6促炎因子分泌[62]。总之，上述研究为BDNF介导脂肪组织炎症反应供了证据支持，但仍缺乏对BDNF在该过程中自分泌与旁分泌作用贡献的深入研究。

2.2.3 BDNF调节肠道炎症

肠道稳态与代谢性疾病的发生和发展存在密切

联系[63]。HFD和肥胖会破坏肠道稳态平衡，引发肠道炎症，加剧焦虑和抑郁[64]、阿尔茨海默病[65]、帕金森病[66]以及代谢性肝病[67]等疾病的发生。本课题组前期研究[68]显示，12周HFD诱导大鼠结肠隐窝结构受损，结肠黏膜间隙浮肿，杯状细胞减少，并伴有明显的炎性浸润现象，推测其机制可能与BDNF调节肠道炎症反应有关。有证据显示，BDNF可通过与肠道免疫系统和神经系统的相互作用调控炎症反应[69-70]。一方面，BDNF介导NF-κB通路，降低促炎因子IL-6水平，抑制结肠炎症[64]；另一方面，BDNF可直接与TrKB受体结合，减少结肠组织中TNF-α、IL-1β蛋白表达，促进与肠道屏障功能相关蛋白表达，如紧密黏连蛋白1（zonula occludens-1，ZO-1）和闭合蛋白（occludin），进而恢复肠道屏障完整性减轻肠道炎症[71-73]。总之，已有大量证据表明，BDNF通过免疫调节和肠道屏障修复发挥抗炎作用，未来需深入解析其在“肠-脑”轴中的动态调控机制，为代谢性疾病的防治提供新策略。

2.2.4　BDNF调节骨骼肌炎症

骨骼肌是分泌外周BDNF的重要器官，在代谢和炎症反应调节中发挥关键作用。一项涉及17 646名患者的回顾性研究表明，肥胖性肌少症的实际患病率可能显著高于临床确诊率，提示肥胖人群中有更多潜在的肌少症患者[74]，其病理机制可能与肥胖诱导循环系统中促炎因子水平升高有关。全身性炎症导致骨骼肌中蛋白质分解速率增加，合成速率降低，这种失衡导致肌肉质量显著下降[75]。动物研究进一步揭示，HFD诱导肥胖小鼠腓肠肌平均横截面积减小，氧化应激和炎症反应增强，以及与肌肉降解相关的蛋白表达升高，BDNF蛋白表达下降[76]；特异性敲除骨骼肌中*BDNF*基因后，小鼠胫骨前肌组织中与肌肉再生相关的分子标志物mRNA表达水平下降，且再生的肌纤维与野生型小鼠相比5 d内减少了40%，同时还观察到单核细胞数量增加约25%[77]。上述研究表明，BDNF可介导炎症反应促进骨骼肌损伤后的修复；与此同时，炎症反应增强也进一步促进免疫细胞分泌

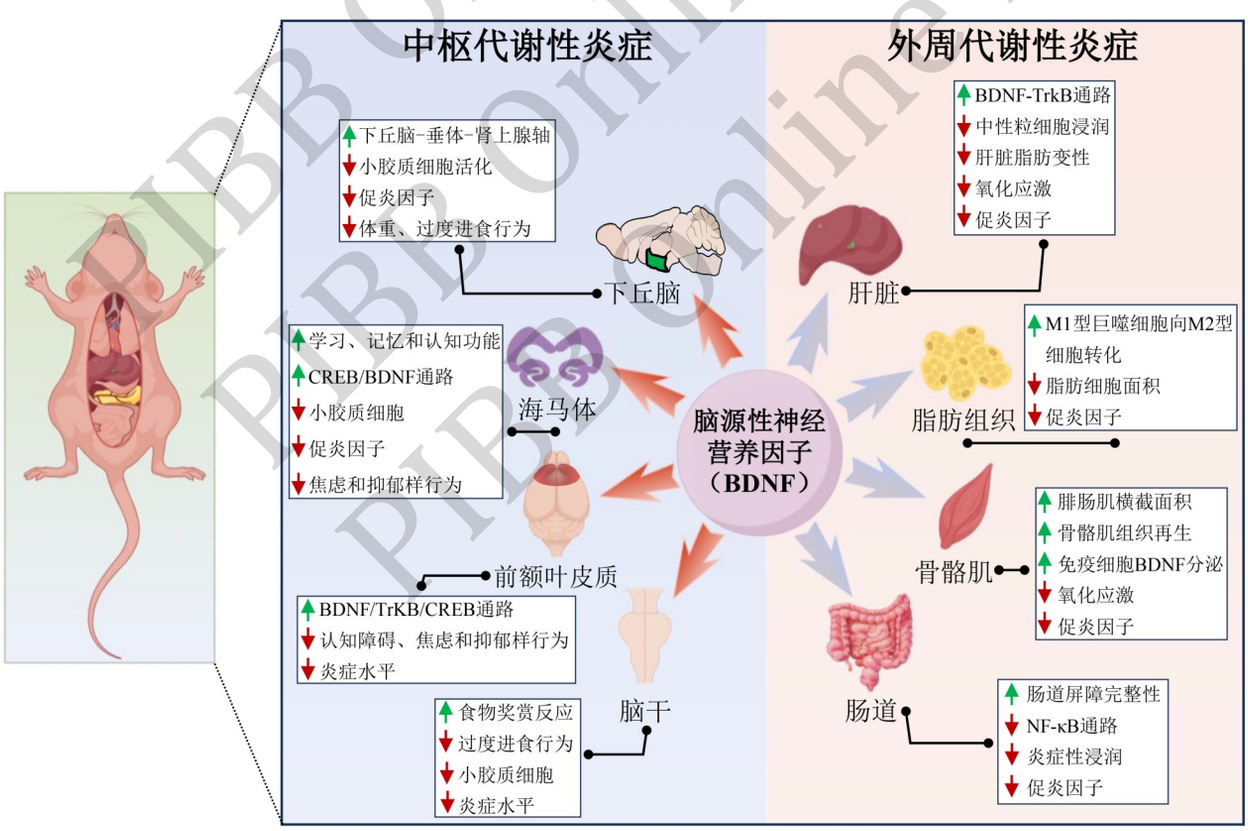

Fig. 2　BDNF mediated regulation of central and peripheral metaflammation

图2　BDNF调节中枢和外周代谢性炎症

BDNF：脑源性神经营养因子（brain-derived neurotrophic factor）；TrKB：酪氨酸激酶受体B（tropomyosin receptor kinase B）；CREB：环磷腺苷反应元件结合蛋白（cAMP-response element binding protein）；NF-κB：核因子κB（nuclear factor kappa-B）。本图采用Figdraw绘制（IDOARRU37b31）。

BDNF，形成良性循环[78]。

3 运动对代谢性疾病相关人群BDNF分泌的影响

代谢性疾病相关人群（metabolic disease-related population，MDRP）包括临床已经确诊为肥胖、糖尿病、高血压、高脂血症、NAFLD等疾病患者和未确诊但伴有超重/肥胖、代谢指标异常等亚健康人群。大量研究表明，此类人群BDNF水平显著下降。运动作为促进人类全生命周期健康发展的重要方式，其多维价值已在临床与实践中得到充分证实[79]。运动涉及全身多系统之间的协同互作，不同运动处方对人体的影响各异，且不同个体对同一处方的运动反应和适应不尽相同，故遵循运动个体化原则对运动处方的制定尤为重要。运动处方主要包括运动类型、运动强度、运动时间、运动频率、运动周期等[80]，深入总结并探讨运动各要素对代谢性疾病相关人群BDNF分泌的影响，对运动精准化防控代谢性疾病具有重要意义（表1）。

表1 运动对代谢性疾病相关人群BDNF分泌的影响

Table 1 Effects of exercise on BDNF secretion in individuals with metabolic disorders

作 者	疾病类型	总样本量/人	年龄/岁	运动类型	运动强度	运动时间	运动频率	运动周期	BDNF/pro-BDNF水平变化	发表年份/年
Walsh等[81]	肥胖	男（*n*=66）女（*n*=136）	15.4±1.4	有氧运动和/或抗阻力量练习	a. 有氧运动强度65%~85% HR_{max} b. 抗阻力量练习为8RM c. 联合组在每次训练中均进行完整的有氧训练计划，并附加抗阻力量练习[82]	20~45 min[82]	4次/周	6个月	BDNF↑	2018
Alizadeh等[83]	肥胖	女（*n*=25）	26.3±4.7	功能训练	Borg量表评分6~7级	60 min/次	3次/周	8周	BDNF↑	2022
De Lima等[84]	超重	男（*n*=25）	40.0±5.5	MICT/HIIT	a. MICT：第1~2周以60%最大速度持续跑3 500~4 000 m；第3~4周提升至65%最大速度，距离增加到4 000~4 500 m；第5~6周保持65%最大速度，距离4 500~5 000 m；第7周提升至70%最大速度，距离5 000 m；第8周达到75%最大速度，距离5 000 m b. HIIT：第1~2周进行7~8次200 m冲刺，速度为85%最大速度，每次冲刺间隔1 min被动恢复；第3~6周冲刺次数增加到8~9次，速度提升至90%最大速度；第7周冲刺10次，95%最大速度；第8周冲刺10次，100%最大速度	a. MICT：每次训练持续时间根据不同阶段的跑步距离和速度而定，整体为持续跑步，如第1周以60%最大速度跑3 500 m b. HIIT：每次训练由多次200 m冲刺和间隔1 min被动恢复组成，总时长因冲刺次数和速度变化而不同，例如第1周7次200 m冲刺，加间隔休息时间	3次/周	8周	BDNF↑	2022

续表

作　者	疾病类型	总样本量/人	年龄/岁	运动类型	运动强度	运动时间	运动频率	运动周期	BDNF/pro-BDNF水平变化	发表年份/年
Inoue等[85]	肥胖	男（*n*=20）	30.0±5.4	MICT/HIIT	MICT：65% MAV的持续步行/跑步 HIIT：100% MAV间歇跑（1 min快跑，1 min被动恢复），共10组	约40 min/次	3次/周	6周	BDNF↑ pro-BDNF无显著变化	2020
Silveira-Rodrigues等[86]	T2DM	男（*n*=2） 女（*n*=9）	63.8±7.1	有氧运动/抗阻力量练习	a. 有氧运动：以6 min步行测试获得的最大速度的90%~95%在跑步机上行走 b. 阻力运动：进行8个上肢和下肢力量练习，每个练习3组，每组10次，强度为70% 10RM	40 min/次	实验在非连续日分别进行两种运动测试	两种运动各进行1次	1.有氧运动：BDNF↑ 2.抗阻力量练习：BDNF↓	2023
Ploydang等[87]	T2DM	男（*n*=7） 女（*n*=10）	69.2±5.3	水中健步走	40%~50% HRR（1~6周），50%~60% HRR（7~12周）	60 min/次	3次/周	12周	BDNF↑	2023
Bang等[88]	肥胖	女（*n*=31）	59.9±2.8	抗阻力量练习	70%~80% 1RM	60 min/次	5 d/周	12周	BDNF↑	2023
Malin等[89]	T2DM前期	男（*n*=3） 女（*n*=18）	60.0±8.6	持续/间歇性功率车训练	连续训练强度：70%HR_{peak}；间歇训练以90%HR_{peak}和50%HR_{peak}交替进行，每次3min	60 min/次	1次/d	13 d（第7天休息，共12次训练）	pro-BDNF↓	2025
Donyaei等[90]	T2DM	女（*n*=34）	60.6±6.3	有氧结合抗阻力量练习	a. 有氧运动强度：50%~70%HRR b.抗阻运动强度：50%~70% 1RM	60 min/次	3次/周	12周	BDNF↑	2024
Ceylan等[91]	肥胖	男（*n*=20）	40.1±4.2	中等强度有氧运动（AE）、高强度间歇运动（HIIE）	AE：运动时HRR保持在40%~59% HIIE：运动时保持75%~90% HRR持续1 min，共10次，中间穿插1 min以上30% HRR进行的主动休息	1.AE：总时长约50 min 2.HIIE：总时长约35 min。	单次	单次	BDNF↑ HIIE升高幅度优于AE	2023

续表

作 者	疾病类型	总样本量/人	年龄/岁	运动类型	运动强度	运动时间	运动频率	运动周期	BDNF/pro-BDNF水平变化	发表年份/年
Li等[92]	超重/肥胖	男（*n*=18）女（*n*=11）	64.8±3.9	HIIT/VICT	a. HIIT：4个3 min高强度骑行，强度为90%$\dot{V}O_{2max}$，期间穿插3个3 min低强度骑行，强度为60%$\dot{V}O_{2max}$ b. VICT：70%$\dot{V}O_{2max}$持续骑行25 min	45 min/次	3次/周	12周	BDNF↑	2021
Garneau等[93]	T2DM	男（*n*=11）女（*n*=11）	49.1±7.6	有氧运动	1~4周为50%~70% $\dot{V}O_{2max}$；5~8周同1~4周强度，时间延长至45 min；9~10周强度为75%$\dot{V}O_{2max}$	1~4周每次至少20 min；5~10周为45 min。	4次/周	10周	BDNF无显著变化	2024
Ghodrati等[94]	T2DM	女（*n*=21）	57.5±5.1	有氧、抗阻及平衡相结合的运动训练	a. 有氧运动：1~6周，强度为55% HRR；7~12周，强度提升至75% HRR b. 抗阻运动：强度为65%~75% 1RM（1~4周）；5~8周，强度逐渐增加到75%~80% 1RM；9~12周，强度为80%~85% 1RM	65 min/次	3次/周	12周	BDNF无显著变化	2023
Rodriguez-Ayllon等[95]	超重/肥胖	*n*=81（女孩占41%）	10.1±1.1	有氧运动结合抗阻力量练习	儿童在运动过程中平均每次有38 min高于其80% HR_{max}	90 min/次	5次/周	20周	BDNF无显著变化	2023
Cokar等[96]	T2DM	女（*n*=16）	57.5±7.4	有氧运动	50%~70% HR_{max}	60 min/次	3天/周	单次有氧运动/12周有氧运动	BDNF无显著变化	2022
Zlibinaite等[97]	超重/肥胖	女（*n*=33）	46.8±6.2	有氧骑行	50%~60%$\dot{V}O_{2peak}$（后4周强度增加15 W）	60 min/次	5次/周	8周	BDNF无显著变化	2021

T2DM：2型糖尿病；HR_{max}：最大心率；RM：最大重复重量；MICT：中等强度持续训练；HIIT：高强度间歇训练；MAV：最大有氧速度；VICT：剧烈强度持续训练；HRR：储备心率；HR_{peak}：峰值心率；$\dot{V}O_{2max}$：最大摄氧量；HR_{max}：最大心率；$\dot{V}O_{2peak}$：峰值摄氧量；不同组别年龄平均值±标准差合并参考Deeks等[98]计算。

3.1 运动类型对代谢性疾病相关人群BDNF分泌的影响

有氧和无氧运动、抗阻力量练习、灵活性及平衡性训练是超重/肥胖、2型糖尿病及NAFLD等人群较为常见的运动形式。已有研究探讨了MDRP不同年龄段，包括儿童/青少年、青中年及老年人运动对BDNF水平的影响。如Plaza-Florido等[99]针对101名超重/肥胖儿童的随机对照研究显示，携带高反应性基因型（含rs6265 BDNF等6个脑健康相关位点）儿童在有氧运动与抗阻力量练习的联合干预方案中，相较于低反应性基因型个体，前者在认知灵活性方面表现出更显著的改善效应，且这两种运动类型的联合干预亦可诱导肥胖青少年血清BDNF水平升高，降低糖尿病发生风险[81]。部分针对青年或中老年MDRP的研究表明，功能性训练（核心稳定性训练、运动协调和平衡训练）[83]、

跑步[84-85]、步行[86]、水中健步走[87]、抗阻力量练习（胸部推举、背部下拉、腿部伸展等）[88]、持续或间歇性功率车[89]等运动均能不同程度的调节循环系统中BDNF和/或pro-BDNF水平，进而改善认知功能和胰岛素敏感性。总之，运动种类繁多，包括单独或联合的多种运动形式，MDRP可根据主观偏好，选择依从性高且运动体验好的运动项目健身促进健康。

3.2　运动强度对代谢性疾病相关人群BDNF分泌的影响

运动负荷是运动处方的核心，运动强度是运动负荷的重要组成成分，决定了运动能否发挥预期的康体效果，同时也是评价运动安全性和依从性的关键因素。通常适宜运动强度的选择有赖于实验室测试（如运动耐量实验及心肺运动实验等）以及相关公式推算。常用指标如心率（储备心率（heart rate reserve，HRR），最大心率（maximum heart rate，HR_{max}）或峰值心率（peak heart rate，HR_{peak}））、摄氧量（最大摄氧量（maximal oxygen uptake，$\dot{V}O_{2max}$）或峰值摄氧量（peak oxygen uptake，$\dot{V}O_{2peak}$））、主观用力感觉量表（rating of perceived exertion，RPE）及一次最大重复重量（one repetition maximum，1RM）等[80]。既往研究报道了不同强度运动对代谢性疾病相关人群BDNF分泌的影响，研究显示，40%~85% HRR[87，90-91]、6~7级RPE[83]、60%最大有氧速度（maximal aerobic velocity，MAV）[85]以及70% HR_{peak}[89]的中等或高强度运动；70%~80% 1RM或70% 10RM抗阻力量练习[88]；100% MAV间歇跑或90%V̇O2max配合60%V̇O2max的高强度间歇踏车[92]可显著调节循环系统中BDNF水平，进而改善体重、血糖、认知功能等与脑健康或代谢性相关结局指标。然而，亦有部分研究显示，50%~70% $\dot{V}O_{2peak}$有氧运动[93]；55%~75% HRR的有氧运动联合65%~80% 1RM的抗阻力量练习及平衡训练[94]；80% HR_{max}有氧联合抗阻运动[95]；50%~70% HR_{max}有氧运动[96]对血清BDNF水平无显著影响。产生矛盾结果的原因存在多种情况。首先，无论运动效果显著与否，上述研究均存在样本量偏小、运动强度评价方式各异的共性问题，且缺乏大样本双盲随机对照试验；其次，部分研究纳入受试者仅为男性或女性，加之纳入人群年龄跨度较大[96-97]，可能导致结果波动幅度较大；最后，受个体差异如激素水平、经期[100]等因素影响导致研究结果不同。综上研究提示，仅从单一维度无法作出定性判断，还需结合其他运动变量综合考量，但上述运动强度参数可为后续相关研究提供参考。

3.3　运动频率和时间对代谢性疾病相关人群BDNF分泌的影响

运动是“双刃剑”，将运动控制在合理的频率和时间范围内可最大限度降低运动损伤风险、增加运动总量，促进身体全面适应与健康提升。现有不同国家及组织推出MDRP运动指南，其中包含了具体的运动频率和时间建议，如美国糖尿病协会（Americn Diabetos Association，ADA）于2023年12月发布的《糖尿病护理标准》（Standards of Care in Diabetes）[101]，建议1型或2型糖尿病青少年每天进行60 min或更长时间的中等至高强度有氧运动，每周至少3 d进行高强度的肌肉和骨骼强化活动；成年患者，每周应进行至少3 d累计150 min或更长时间的中等至高强度有氧运动（连续不活动天数不超过2 d），且每周还应在非连续日进行2~3次抗阻力量练习。同年，欧洲心脏病学会（European Society of Cardiology，ESC）发布《2023欧洲心脏病学会糖尿病患者心血管疾病管理指南》（2023 ESC Guidelines for the Management of Cardiovascular Disease in Patients with Diabetes）[102]，建议2型糖尿病患者每周应进行150 min中等强度运动或75 min高强度耐力运动，对于合并心血管疾病患者应在专业指导下进行有氧健身操练习，以及每周至少2次的抗阻力量练习。中国国家卫生健康委员会于2024年发布高血压等慢性病营养和运动指导原则[103]，建议高血压、高尿酸血症患者每周应进行5~7次累计150~300 min中等强度有氧运动；高血糖患者每周应进行3~7 d，每次30 min以上中等强度运动；高血脂患者每周大于5 d，每天50~60 min或更长时间的有氧运动；此外，所有患者在上述运动基础上再结合每周2~3次的抗阻力量练习和柔韧训练。综上，部分研究显示[87，89]，将运动频率和时间设定为60 min/d，每周进行3~5次有氧或高强度间歇运动能够显著调节BDNF水平，改善代谢相关结局指标，提升认知功能。

3.4　运动周期对代谢性疾病相关人群BDNF分泌的影响

若将运动比作“药物”，运动周期则是药物处方中的“服药”疗程[104]。运动周期可分为急性运动（单次）和持续性运动（以周为单位或维持数

月），科学的运动周期有利于机体长期处于健康状态。一项系统评价和荟萃分析结果显示，急性运动可显著提高肥胖人群循环BDNF水平，而规律运动虽无显著提升，但也有一定的积极影响，说明两者均有调节BDNF水平的潜力；进一步亚组分析结果显示，约8~12周高强度有氧运动更易使循环BDNF水平升高，且效果优于抗阻力量练习[105]；Alizadeh等[83]研究证实，8周中等强度运动能够显著升高肥胖女性血清BDNF水平，改善执行功能。亦有研究表明，急性有氧运动和抗阻力量练习可显著调节2型糖尿病中老年患者血浆BDNF水平，但对血浆BDNF浓度影响相反，有氧运动使其升高，抗阻力量练习使其降低[86]，这可能与该研究未设置安静对照组和样本量较小有关。Donyaei等[90]报道，12周有氧运动联合抗阻力量练习可显著升高2型糖尿病女性患者的BDNF水平，且停训8周后BDNF在运动改善患者抑郁症状过程中仍发挥部分作用。然而亦有部分研究显示，持续2个月遵循全球身体活动建议（300 min/周）进行中等强度有氧运动未对超重/肥胖中年女性血清BDNF水平产生显著影响[97]。同样，Rodriguez-Ayllon等[95]报道，持续20周的有氧运动联合抗阻力量练习对超重/肥胖儿童血浆中BDNF水平无显著影响。分析上述研究结果差异的原因可能与运动强度不足以及采用BDNF检测方法的灵敏度不同有关，后续可进行相关系统评价与荟萃分析以进一步补充证据。总之，运动周期对结局指标影响较大，若想制定科学的运动周期首要任务仍需结合其他运动变量综合判断。

综上所述，运动对MDRP全生命周期均产生健康效益，并在多数情况下通过促进BDNF分泌，促进身体健康。然而运动是双刃剑，运动与健康的量效关系非线性正向关系，运动不足无效果，运动过量会造成健康损害，因此科学制定运动处方，明确适宜运动负荷，将健康效益最大化对调节机体代谢格外重要。2024年上海体育大学王茹教授团队在《*Nature Protocols*》发文报道[106]，已开发出一种新型体内、体外乳酸荧光传感器（FiLa），该传感器具有高精度、简便快捷的特点，可在短时间内检测出乳酸水平，从而实现运动强度的精准评估和标准化控制，为人体及分子层面的相关实验研究统一运动强度提供技术支持，并为科学制定个性化运动处方提供有力保障。

4 BDNF介导运动改善代谢性炎症的潜在机制

BDNF在运动中通过多种机制改善代谢性炎症（图3）。首先，BDNF通过调节神经和免疫细胞的双向信号传递，抑制促炎因子并促进抗炎因子的释放，从而减轻炎症反应[107-112]。其次，运动通过BDNF激活PI3K/Akt、AMPK等信号通路，改善胰岛素敏感性、减轻脂毒性，促进线粒体生物合成，进一步改善机体代谢状态[113-115]。此外，运动诱导的BDNF还通过与多器官的协同作用，改善肝脏抗氧化能力、调节免疫反应及“肠-脑”轴功能，帮助减轻全身性炎症反应[116-118]。这些潜在机制支持了运动作为非药物干预手段在抗炎和促进代谢健康中的应用潜力。

4.1 BDNF介导运动抗炎与免疫调节

运动通过多种途径调节免疫系统和神经可塑性。动物研究表明，BDNF表达在运动过程中显著增加，其可通过调节神经和免疫细胞之间的双向信号传递，抑制促炎因子分泌同时促进抗炎因子释放，减轻炎症反应[107, 110]。一方面，运动通过BDNF-TrkB信号通路和毒蕈碱型胆碱能受体M1（muscarinic acetylcholine receptor M1，CHRM1）依赖的乙酰胆碱能活动，增强抗炎效果[107]；另一方面，运动过程中产生的乳酸通过激活沉默信息调节因子1（silent information regulator 1，SIRT1）依赖的途径促进BDNF表达，改善学习及记忆功能[119]。在免疫调节方面，运动可通过BDNF抑制NF-κB的核转位和信号转导及转录激活蛋白3（signal transducer and activator of transcription 3，STAT3）磷酸化水平，降低促炎因子表达[108]；诱导巨噬细胞向M2型极化，并分泌抗炎因子如白介素-10（interleukin 10，IL-10）抑制炎症反应，而这种极化过程也可能通过抑制NF-κB信号通路实现[109-110]。此外，BDNF介导运动对调节性T细胞（Treg）的功能也有一定积极影响，其可能通过间接途径介导运动增强T细胞功能，进而抑制辅助性T细胞17（T helper 17 cell，Th17）调控免疫反应[111-112]。综上，BDNF可介导运动调节NF-κB、STAT3、巨噬细胞极化及调节性T细胞功能等多个机制抑制炎症。

4.2 BDNF介导运动代谢调控及线粒体功能修复

PI3K/Akt-AMPK信号通路是细胞内重要的信号转导途径之一，参与调节细胞的生长、增殖和代谢过程[120]。BDNF可通过激活PI3K/Akt信号通路，

增强胰岛素信号传导，促进葡萄糖摄取和利用，改善胰岛素抵抗[113-115]。AMPK作为细胞能量状态的感应器，能够在能量缺乏时被激活，进而促进脂肪酸氧化和葡萄糖摄取，抑制脂肪合成[121-122]。动物及细胞实验表明，BDNF通过激活AMPK，不仅能够改善胰岛素敏感性，还能够减轻脂毒性，保护肝脏和骨骼肌免受脂质沉积的损害[4, 123]。在促进线粒体生物合成方面，BDNF通过激活过氧化物酶体增殖物激活受体γ辅激活因子1α（peroxisome proliferator-activated receptor γ coactivator-l alpha，PGC-1α）-核呼吸因子1（nuclear respiratory factor 1，NRF1）信号通路发挥作用。PGC-1α是线粒体生物合成的关键调节因子，能够促进线粒体生成和功能增强[124]。NRF1作为PGC-1α的下游靶点，参与调控线粒体基因表达[125]。BDNF通过增强PGC-1α和NRF1的活性，促进线粒体生物合成，提高细胞能量代谢，进而改善整体代谢状态[126-127]。综上，BDNF通过激活PI3K/Akt-AMPK通路和PGC-1α/NRF1信号通路，改善胰岛素敏感性和脂毒性，减轻炎症反应，促进线粒体生物合成，进而促进机体代谢健康。

4.3　BDNF介导运动多器官互作抗炎与菌群–肠脑轴调控

运动诱导的BDNF可与多器官协同作用，逆转全身代谢性炎症[116-118]。例如，下丘脑中的BDNF通过交感神经β肾上腺素能信号上调脂肪细胞中白介素-15（interleukin-15，IL-15）表达，从而调控免疫反应[128]；自主跑轮运动可促进BDNF表达，减少海马体中神经型一氧化氮合酶（neuronal nitric oxide synthasen，NOS）表达，改善肝脏纤维化和小鼠的焦虑行为[129]；亦有报道显示，运动显著上调大鼠肝脏核因子红细胞2相关因子2（nuclear factor erythroid 2-related factor 2，Nrf2）和血红素加氧酶1（heme oxygenase-1，HO-1）的基因表达，提示肝脏抗氧化能力得到增强，其机制可能与骨骼肌源性BDNF介导肝脏Nrf2/HO-1/谷胱甘肽过氧化物酶4（glutathione peroxidase 4，GPX4）通路有关[130-131]。此外，外源性补充益生菌（如乳酸菌、双歧杆菌和嗜黏蛋白阿克曼菌等）不仅能激活BDNF-TrkB-磷脂酰肌醇磷脂酶C（phospholipase C，PLC）/三磷酸肌醇（inositol trisphosphate，IP3）信号通路，修复肠神经系统-肠道间质细胞-平滑肌细胞网络，改善肠道屏障，增强肠道通透性，调节免疫反应[132]；还可通过调节“肠-肝-脑”轴中的BDNF通路，促进脑BDNF的合成分泌，减轻中枢神经系统炎症反应，改善人类及啮齿动物的认知功能[133-135]。综上所述，运动可促进BDNF释放，并通过“肝-脑”轴、“肠-脑”轴以及“肝-肠-脑”轴等多器官协同相互作用，减轻全身性炎症反应促进代谢。

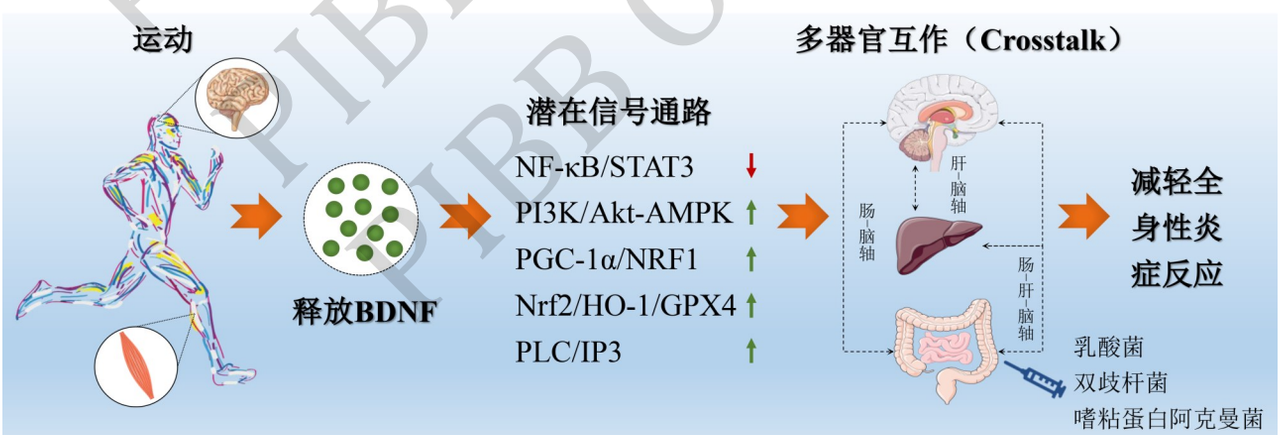

Fig. 3　Potential mechanisms by which BDNF mediates the improvement of metaflammation through exercise

图3　BDNF介导运动改善代谢性炎症的潜在机制

NF-κB：核因子κB（nuclear factor kappa-B）；STAT3：信号转导及转录激活蛋白3（signal transducer and activator of transcription 3）；PI3K：磷脂酰肌醇3激酶（phosphoinositide 3-kinase）Akt：蛋白激酶B（protein kinase B）；AMPK：腺苷酸活化蛋白激酶（adenosine activated protein kinase）；PGC-1α：过氧化物酶体增殖物激活受体γ辅激活因子1α（peroxisome proliferators-activated receptor γ coactivator-l alpha）；NRF1：核呼吸因子1（nuclear respiratory factor 1）；Nrf2：核因子红细胞2相关因子2（nuclear factor erythroid 2-related factor 2）；HO-1：血红素加氧酶1（heme oxygenase-1）；GPX4：谷胱甘肽过氧化物酶4（glutathione peroxidase 4）；PLC：磷脂酰肌醇磷脂酶C（phospholipase C）；IP3：三磷酸肌醇（inositol trisphosphate）。

5　总结与展望

代谢性炎症已被广泛认为是肥胖、2型糖尿病及NAFLD病等代谢相关疾病发生和发展的前驱机制之一。该类炎症不仅局限于免疫系统，更可通过侵袭中枢神经系统（如下丘脑、海马体）以及外周代谢相关组织器官（如肝脏、脂肪组织及骨骼肌等），破坏其代谢调控功能，最终导致机体代谢稳态失衡。近年来的研究逐渐揭示BDNF在代谢调控和抗炎机制中的关键作用。BDNF通过下调促炎因子、增强线粒体功能、改善胰岛素敏感性等多种路径，部分逆转系统性炎症状态，进而在改善体重状态、身体成分以及认知功能等方面发挥积极作用，成为联结神经健康与代谢健康的重要媒介。运动被认为是激活内源性BDNF表达的最有效非药物干预手段之一，适量、规律的运动能够显著提升中枢和外周BDNF水平，从而对代谢性炎症状态产生调节作用。合理的运动处方不仅能提升机体应对炎症反应的能力，还可通过BDNF通路优化代谢环境。然而，因运动处方主要构成要素之间存在复杂的交互作用，不同运动模式所产生的生理效应差异显著。因此，运动干预的最佳方案尚未达成明确共识，仍需深入研究以明确不同运动参数对BDNF表达及其对代谢性炎症调控作用的具体影响。

尽管已有大量实验证据支持运动在抑制炎症、提升BDNF水平方面的有效性，但当前研究仍存在诸多局限。首先，大多数研究集中在分子生物学层面，缺乏直接验证BDNF是否为运动调控代谢性炎症的关键中介的因果性实验证据。其次，现有的分子研究结果在实际临床中的可转化性不足，尚未建立清晰的“运动-BDNF-代谢性炎症”调控路径。此外，目前以动物模型或小样本人体为主的研究设计，也限制了研究结果的广泛推广。未来研究应逐步从割裂、局部的机制探索，向整合系统生物学与运动生理学的多层次、多维度研究框架转变。在实践层面，亟需结合多组学技术（如转录组、蛋白组及代谢组）开展大样本双盲随机对照的全生命周期人体研究，深入挖掘BDNF介导代谢性炎症的关键信号通路，并在分子水平进一步明确其因果关系与作用链条。通过构建更加完善的科学证据体系，有望为运动在代谢相关疾病防治中的机制阐释、临床应用、药物研发提供更为坚实的理论基础与实践指导。

参 考 文 献

[1] Hotamisligil G S. Inflammation and metabolic disorders. Nature, 2006, **444**(7121): 860-867

[2] Li Y, Li F, Qin D, *et al*. The role of brain derived neurotrophic factor in central nervous system. Front Aging Neurosci, 2022, **14**: 986443

[3] Iu E C Y, Chan C B. Is brain-derived neurotrophic factor a metabolic hormone in peripheral tissues? Biology (Basel), 2022, **11**(7): 1063

[4] Chan W S, Ng C F, Pang B P S, *et al*. Exercise-induced BDNF promotes PPARδ-dependent reprogramming of lipid metabolism in skeletal muscle during exercise recovery. Sci Signal, 2024, **17**(828): eadh2783

[5] Bianchi A, Marchetti L, Hall Z, *et al*. Moderate exercise inhibits age-related inflammation, liver steatosis, senescence, and tumorigenesis. J Immunol, 2021, **206**(4): 904-916

[6] Papathanassoglou E D E, Miltiadous P, Karanikola M N. May BDNF be implicated in the exercise-mediated regulation of inflammation? Critical review and synthesis of evidence. Biol Res Nurs, 2015, **17**(5): 521-539

[7] 段锐, 李跃程. 我国运动人体科学学科发展的问题反思与展望. 上海体育大学学报, 2025, **49**(4): 1-8, 29
Duan R, Li Y C. J Shanghai Univ Sport, 2025, **49**(4): 1-8, 29

[8] Barde Y A, Edgar D, Thoenen H. Purification of a new neurotrophic factor from mammalian brain. EMBO J, 1982, **1**(5): 549-553

[9] Barde Y A, Lindsay R M, Monard D, *et al*. New factor released by cultured glioma cells supporting survival and growth of sensory neurones. Nature, 1978, **274**(5673): 818

[10] Ge X, Zheng M, Hu M, *et al*. Butyrate ameliorates quinolinic acid-induced cognitive decline in obesity models. J Clin Invest, 2023, **133**(4): e154612

[11] Niu C, Yue X, An J J, *et al*. Genetic dissection of BDNF and TrkB expression in glial cells. Biomolecules, 2024, **14**(1): 91

[12] Pedersen B K. Physical activity and muscle-brain crosstalk. Nat Rev Endocrinol, 2019, **15**(7): 383-392

[13] Matsuda N, Lu H, Fukata Y, *et al*. Differential activity-dependent secretion of brain-derived neurotrophic factor from axon and dendrite. J Neurosci, 2009, **29**(45): 14185-14198

[14] Pang P T, Teng H K, Zaitsev E, *et al*. Cleavage of proBDNF by tPA/plasmin is essential for long-term hippocampal plasticity. Science, 2004, **306**(5695): 487-491

[15] Zeng J, Xie Z, Chen L, *et al*. Rosmarinic acid alleviate CORT-induced depressive-like behavior by promoting neurogenesis and regulating BDNF/TrkB/PI3K signaling axis. Biomed Pharmacother, 2024, **170**: 115994

[16] Colucci-D'Amato L, Speranza L, Volpicelli F. Neurotrophic factor BDNF, physiological functions and therapeutic potential in depression, neurodegeneration and brain cancer. Int J Mol Sci, 2020, **21**(20): 7777

[17] Yang J, Siao C J, Nagappan G, *et al*. Neuronal release of proBDNF. Nat Neurosci, 2009, **12** (2): 113-115

[18] Seong J, Kang J Y, Sun J S, *et al*. Hypothalamic inflammation and obesity: a mechanistic review. Arch Pharm Res, 2019, **42**(5): 383-392

[19] Eroglu B, Isales C, Eroglu A. Age and duration of obesity modulate the inflammatory response and expression of neuroprotective factors in mammalian female brain. Aging Cell, 2024, **23**(12): e14313

[20] Eyileten C, Kaplon-Cieslicka A, Mirowska-Guzel D, *et al*. Antidiabetic effect of brain-derived neurotrophic factor and its association with inflammation in type 2 diabetes mellitus. J Diabetes Res, 2017, **2017**: 2823671

[21] Javed S, Chang Y T, Cho Y, *et al*. Smith-Magenis syndrome protein RAI1 regulates body weight homeostasis through hypothalamic BDNF-producing neurons and neurotrophin downstream signalling. eLife, 2023, **12**: RP90333

[22] Jia L, Chen Z, Pan T, *et al*. TRIM67 deficiency exacerbates hypothalamic inflammation and fat accumulation in obese mice. Int J Mol Sci, 2022, **23**(16): 9438

[23] He Y, Yang K, Zhang L, *et al*. Electroacupuncture for weight loss by regulating microglial polarization in the arcuate nucleus of the hypothalamus. Life Sci, 2023, **330**: 121981

[24] Kawamura N, Katsuura G, Yamada-Goto N, *et al*. Brain fractalkine-CX3CR1 signalling is anti-obesity system as anorexigenic and anti-inflammatory actions in diet-induced obese mice. Sci Rep, 2022, **12**(1): 12604

[25] Queen N J, Huang W, Zou X, *et al*. AAV-BDNF gene therapy ameliorates a hypothalamic neuroinflammatory signature in the *Magel2*-null model of Prader-Willi syndrome. Mol Ther Methods Clin Dev, 2023, **31**: 101108

[26] Zhu X Y, Luo J, Wei X J, *et al*. PPARα is involved in high-fat diet-induced risk avoidance impairment *via* the regulation of hippocampal BDNF. Food Funct, 2023, **14**(14): 6541-6553

[27] Guo D H, Yamamoto M, Hernandez C M, *et al*. Visceral adipose NLRP3 impairs cognition in obesity *via* IL-1R1 on CX3CR1+ cells. J Clin Invest, 2020, **130**(4): 1961-1976

[28] Liang Z, Gong X, Ye R, *et al*. Long-term high-fat diet consumption induces cognitive decline accompanied by tau hyper-phosphorylation and microglial activation in aging. Nutrients, 2023, **15**(1): 250

[29] Li J, Wu D, Mu Y, *et al*. The combined damage of bisphenol A and high fat diet to learning and memory in young male mice: the regulatory effect of BDNF/TrkB/PI3K/AKT pathway on autophagy. Environ Res, 2025, **276**: 121538

[30] Treviño S, Díaz A, González-López G, *et al*. Differential biochemical-inflammatory patterns in the astrocyte-neuron axis of the hippocampus and frontal cortex in Wistar rats with metabolic syndrome induced by high fat or carbohydrate diets. J Chem Neuroanat, 2022, **126**: 102186

[31] Yang X, Yu Z, An L, *et al*. Electroacupuncture stimulation ameliorates cognitive impairment induced by long-term high-fat diet by regulating microglial BDNF. Brain Res, 2024, **1825**: 148710

[32] Zhang W, Wang J, Wang L, *et al*. Alternate-day fasting prevents non-alcoholic fatty liver disease and working memory impairment in diet-induced obese mice. J Nutr Biochem, 2022, **110**: 109146

[33] Zuo X, Zhu Z, Liu M, *et al*. Fluoxetine ameliorates cognitive deficits in high-fat diet mice by regulating BDNF expression. ACS Chem Neurosci, 2024, **15**(22): 4229-4240

[34] Teng C Y, Kao N J, Nguyen N T K, *et al*. Effects of xylo-oligosaccharide on gut microbiota, brain protein expression, and lipid profile induced by high-fat diet. J Nutr Biochem, 2024, **129**: 109640

[35] Schmidt N P, Molz P, Fraga B S, *et al*. Effect of probiotic *Lacticaseibacillus rhamnosus* LB1.5 on anxiety-like behavior, neuroprotection and neuroinflammation markers of male mice fed a high-fat diet. Nutrients, 2024, **16**(6): 879

[36] Katuri R B, Gaur G S, Sahoo J P, *et al*. Association of circulating brain-derived neurotrophic factor with cognition among adult obese population. J Obes Metab Syndr, 2021, **30**(2): 163-172

[37] Reichelt A C, Loughman A, Bernard A, *et al*. An intermittent hypercaloric diet alters gut microbiota, prefrontal cortical gene expression and social behaviours in rats. Nutr Neurosci, 2020, **23**(8): 613-627

[38] Hu X, Zhao H L, Kurban N, *et al*. Reduction of BDNF levels and biphasic changes in glutamate release in the prefrontal cortex correlate with susceptibility to chronic stress-induced anhedonia. eNeuro, 2023, **10**(11): ENEURO.0406-23.2023

[39] Baranowski B J, MacPherson R E K. Acute exercise induced BDNF-TrkB signalling is intact in the prefrontal cortex of obese, glucose-intolerant male mice. Appl Physiol Nutr Metab, 2018, **43**(10): 1083-1089

[40] Paiva I H R, Maciel L M, Silva R S D, *et al*. Prebiotics modulate the microbiota-gut-brain axis and ameliorate anxiety and depression-like behavior in HFD-fed mice. Food Res Int, 2024, **182**: 114153

[41] Pan W, Jiang P, Zhao J, *et al*. β-Glucan from *Lentinula edodes* prevents cognitive impairments in high-fat diet-induced obese mice: involvement of colon-brain axis. J Transl Med, 2021, **19**(1): 54

[42] Merkel R, Hernandez N S, Weir V, *et al*. An endogenous GLP-1 circuit engages VTA GABA neurons to regulate mesolimbic dopamine neurons and attenuate cocaine seeking. Sci Adv, 2025, **11**(9): eadr5051

[43] Alhadeff A L, Rupprecht L E, Hayes M R. GLP-1 neurons in the nucleus of the solitary tract project directly to the ventral tegmental area and nucleus accumbens to control for food intake. Endocrinology, 2012, **153**(2): 647-658

[44] 代玉玺, 何玉秀, 陈巍. 肥胖成因的新视角: 代谢性炎症诱导食物奖赏异常. 生物化学与生物物理进展, 2024, **51**(6): 1327-1340
Dai Y X, He Y X, Chen W. Prog Biochem Biophys, 2024, **51**(6): 1327-1340

[45] Chen J, Cheng M, Wang L, *et al*. A vagal-NTS neural pathway that stimulates feeding. Curr Biol, 2020, **30**(20): 3986-3998.e5

[46] Li W Q, Liu S N, Yang S C, *et al*. Nitrous oxide exerts rewarding

effect *via* regulating D1 receptor and BDNF pathway in ventral tegmental area-nucleus accumbens dopamine circuit. Transl Psychiatry, 2025, **15**(1): 34

[47] Spaeth A M, Kanoski S E, Hayes M R, *et al*. TrkB receptor signaling in the nucleus tractus solitarius mediates the food intake-suppressive effects of hindbrain BDNF and leptin. Am J Physiol Endocrinol Metab, 2012, **302**(10): E1252-E1260

[48] Wang J, Jia Y, Li G, *et al*. The dopamine receptor D3 regulates lipopolysaccharide-induced depressive-like behavior in mice. Int J Neuropsychopharmacol, 2018, **21**(5): 448-460

[49] Wang J, Lai S, Li G, *et al*. Microglial activation contributes to depressive-like behavior in dopamine D3 receptor knockout mice. Brain Behav Immun, 2020, 83: 226-238

[50] Machaalani R, Thawley M, Huang J, *et al*. Effects of prenatal cigarette smoke exposure on BDNF, PACAP, microglia and gliosis expression in the young male mouse brainstem. Neurotoxicology, 2019, 74: 40-46

[51] Chen Z, Chen F, Fang Z, *et al*. Glial activation and inflammation in the NTS in a rat model after exposure to diesel exhaust particles. Environ Toxicol Pharmacol, 2021, **83**: 103584

[52] Irisarri A, Corral A, Perez-Salvador N, *et al*. FTO inhibition mitigates high-fat diet-induced metabolic disturbances and cognitive decline in SAMP8 mice. Mol Med, 2025, **31**(1): 73

[53] Singh T, Kwatra M, Kushwah P, *et al*. Binge alcohol consumption exacerbates high-fat diet-induced neurobehavioral anomalies: possible underlying mechanisms. Chem Biol Interact, 2022, **364**: 110039

[54] Grzelak N, Kaczmarek D, Mrówczyński W. Comparison of the effects of BDNF/TRKB signalling on metabolic biomarkers in the liver of sedentary and trained rats with normal and knockout BDNF genotypes. Front Physiol, 2023, **14**: 1268648

[55] Hattori Y, Yamada H, Munetsuna E, *et al*. Increased brain-derived neurotrophic factor in the serum of persons with nonalcoholic fatty liver disease. Endocr J, 2022, **69**(8): 999-1006

[56] Ichimura-Shimizu M, Kojima M, Suzuki S, *et al*. Brain-derived neurotrophic factor knock-out mice develop non-alcoholic steatohepatitis. J Pathol, 2023, **261**(4): 465-476

[57] Ichimura-Shimizu M, Kurrey K, Miyata M, *et al*. Emerging insights into the role of BDNF on health and disease in periphery. Biomolecules, 2024, **14**(4): 444

[58] Sakata K, Fukuchi M. Accelerated BDNF expression in visceral white adipose tissues following high-fat diet feeding in mice. Genes Cells, 2024, **29**(11): 1077-1084

[59] Blaszkiewicz M, Wood E, Koizar S, *et al*. The involvement of neuroimmune cells in adipose innervation. Mol Med, 2020, **26** (1): 126

[60] Sandrini L, Ieraci A, Amadio P, *et al*. Physical exercise affects adipose tissue profile and prevents arterial thrombosis in *BDNF* Val66Met mice. Cells, 2019, **8**(8): 875

[61] McMurphy T, Huang W, Liu X, *et al*. Hypothalamic gene transfer of BDNF promotes healthy aging in mice. Aging Cell, 2019, **18**(2): e12846

[62] Yu H C, Huang H B, Huang Tseng H Y, *et al*. Brain-derived neurotrophic factor suppressed proinflammatory cytokines secretion and enhanced microRNA (miR) -3168 expression in macrophages. Int J Mol Sci, 2022, **23**(1): 570

[63] Ochoa-Repáraz J, Kasper L H. The second brain: is the gut microbiota a link between obesity and central nervous system disorders. Curr Obes Rep, 2016, **5**(1): 51-64

[64] Han S K, Kim J K, Park H S, *et al*. Chaihu-Shugan-San (*Shihosogansan*) alleviates restraint stress-generated anxiety and depression in mice by regulating NF- κB-mediated BDNF expression through the modulation of gut microbiota. Chin Med, 2021, **16**(1): 77

[65] Donaldson A I C, Fyfe C L, Martin J C, *et al*. Aging gut-brain interactions: pro-inflammatory gut bacteria are elevated in fecal samples from individuals living with Alzheimer's dementia. Geriatrics, 2025, **10**(2): 37

[66] Guo T T, Zhang Z, Sun Y, *et al*. Neuroprotective effects of sodium butyrate by restoring gut microbiota and inhibiting TLR4 signaling in mice with MPTP-induced Parkinson's disease. Nutrients, 2023, **15**(4): 930

[67] Sharma S, Tiwari N, Tanwar S S. The current findings on the gut-liver axis and the molecular basis of NAFLD/NASH associated with gut microbiome dysbiosis. Naunyn Schmiedebergs Arch Pharmacol, 2025

[68] 王伟欢, 代玉玺, 吴卫东, 等. 中等强度持续运动与高强度间歇运动对高脂膳食大鼠肠道炎症及 α7 型烟碱乙酰胆碱受体、核转录因子 κBp65 的影响. 中华物理医学与康复杂志, 2024, **46**(12): 1072-1078
Wang W H, Dai Y X, Wu W D, *et al*. Chin J Phys Med Rehabil, 2024, **46**(12): 1072-1078

[69] Bose D, Saha P, Mondal A, *et al*. Obesity worsens gulf war illness symptom persistence pathology by linking altered gut microbiome species to long-term gastrointestinal, hepatic, and neuronal inflammation in a mouse model. Nutrients, 2020, **12**(9): 2764

[70] Yun S W, Park H S, Shin Y J, *et al*. *Lactobacillus gasseri* NK109 and its supplement alleviate cognitive impairment in mice by modulating NF- κB activation, BDNF expression, and gut microbiota composition. Nutrients, 2023, **15**(3): 790

[71] 杨敏, 辛欢, 邹燃, 等. 针灸通过阻断 BDNF/TrkB 信号通路改善肠易激综合征大鼠的肠道屏障功能和内脏疼痛. 中国免疫学杂志, 2024, **40**(6): 1234-1239
Yang M, Xin H, Zou R, *et al*. Chin J Immunol, 2024, **40**(6): 1234-1239

[72] Chang L, Wang C, Peng J, *et al*. Rattan pepper polysaccharide regulates DSS-induced intestinal inflammation and depressive behavior through microbiota-gut-brain axis. J Agric Food Chem, 2024, **72**(1): 437-448

[73] Mo L, Li J, Lu H, *et al*. Aloe polysaccharides ameliorate obesity-associated cognitive dysfunction in high-fat diet-fed mice by targeting the gut microbiota and intestinal barrier integrity. Food Funct, 2024, **15**(15): 8070-8086

[74] Zambrano Chaves J M, Hom J, Lenchik L, *et al*. Sarcopenia,

obesity, and sarcopenic obesity: retrospective audit of electronic health record documentation versus automated CT analysis in 17 646 patients. Radiology, 2025, **315**(1): e243525

[75] Deger S M, Hung A M, Gamboa J L, *et al*. Systemic inflammation is associated with exaggerated skeletal muscle protein catabolism in maintenance hemodialysis patients. JCI Insight, 2017, **2**(22): e95185

[76] Lee H, Kim S Y, Lim Y. Solanum melongena extract supplementation protected skeletal muscle and brain damage by regulation of BDNF/PGC1α/irisin pathway *via* brain function-related myokines in high-fat diet induced obese mice. J Nutr Biochem, 2024, **124**: 109537

[77] Clow C, Jasmin B J. Brain-derived neurotrophic factor regulates satellite cell differentiation and skeltal muscle regeneration. Mol Biol Cell, 2010, **21**(13): 2182-2190

[78] Waldemer-Streyer R J, Kim D, Chen J. Muscle cell-derived cytokines in skeletal muscle regeneration. FEBS J, 2022, **289**(21): 6463-6483

[79] Garcia M B, Schadler K L, Chandra J, *et al*. Translating energy balance research from the bench to the clinic to the community: parallel animal-human studies in cancer. CA Cancer J Clin, 2023, **73**(4): 425-442

[80] 王帝之, 李省天, 李鑫铭, 等. 健康中国战略下运动处方的临床实践. 体育科学, 2023, **43**(11): 89-97
Wang D Z, Li X T, Li X M, *et al*. China Sport Sci, 2023, **43**(11): 89-97

[81] Walsh J J, D'Angiulli A, Cameron J D, *et al*. Changes in the brain-derived neurotrophic factor are associated with improvements in diabetes risk factors after exercise training in adolescents with obesity: the HEARTY randomized controlled trial. Neural Plast, 2018, **2018**: 7169583

[82] Sigal R J, Alberga A S, Goldfield G S, *et al*. Effects of aerobic training, resistance training, or both on percentage body fat and cardiometabolic risk markers in obese adolescents: the healthy eating aerobic and resistance training in youth randomized clinical trial. JAMA Pediatr, 2014, **168**(11): 1006-1014

[83] Alizadeh M, Dehghanizade J. The effect of functional training on level of brain-derived neurotrophic factor and functional performance in women with obesity. Physiol Behav, 2022, **251**: 113798

[84] de Lima N S, De Sousa R A L, Amorim F T, *et al*. Moderate-intensity continuous training and high-intensity interval training improve cognition, and BDNF levels of middle-aged overweight men. Metab Brain Dis, 2022, **37**(2): 463-471

[85] Inoue D S, Monteiro P A, Gerosa-Neto J, *et al*. Acute increases in brain-derived neurotrophic factor following high or moderate-intensity exercise is accompanied with better cognition performance in obese adults. Sci Rep, 2020, **10**(1): 13493

[86] Silveira-Rodrigues J G, Campos B T, de Lima A T, *et al*. Acute bouts of aerobic and resistance exercise similarly alter inhibitory control and response time while inversely modifying plasma BDNF concentrations in middle-aged and older adults with type 2 diabetes. Exp Brain Res, 2023, **241**(4): 1173-1183

[87] Ploydang T, Khovidhunkit W, Tanaka H, *et al*. Nordic walking in water on cerebrovascular reactivity and cognitive function in elderly patients with type 2 diabetes. Med Sci Sports Exerc, 2023, **55**(10): 1803-1811

[88] Bang H S. Effect of resistance training with different set structures on neurotrophic factors and obesity-related biomarkers in middle-aged Korean women with obesity. J Clin Med, 2023, **12**(9): 3135

[89] Malin S K, Battillo D J, Beeri M S, *et al*. Two weeks of exercise alters neuronal extracellular vesicle insulin signaling proteins and pro-BDNF in older adults with prediabetes. Aging Cell, 2025, **24**(1): e14369

[90] Donyaei A, Kiani E, Bahrololoum H, *et al*. Effect of combined aerobic-resistance training and subsequent detraining on brain-derived neurotrophic factor (BDNF) and depression in women with type 2 diabetes mellitus: a randomized controlled trial. Diabet Med, 2024, **41**(3): e15188

[91] Ceylan H İ, Öztürk M E, Öztürk D, *et al*. Acute effect of moderate and high-intensity interval exercises on asprosin and BDNF levels in inactive normal weight and obese individuals. Sci Rep, 2023, **13**(1): 7040

[92] Li X, Han T, Zou X, *et al*. Long-term high-intensity interval training increases serum neurotrophic factors in elderly overweight and obese Chinese adults. Eur J Appl Physiol, 2021, **121**(10): 2773-2785

[93] Garneau L, Mulvihill E E, Smith S R, *et al*. Myokine secretion following an aerobic exercise intervention in individuals with type 2 diabetes with or without exercise resistance. Int J Mol Sci, 2024, **25**(9): 4889

[94] Ghodrati N, Haghighi A H, Hosseini Kakhak S A, *et al*. Effect of combined exercise training on physical and cognitive function in women with type 2 diabetes. Can J Diabetes, 2023, **47**(2): 162-170

[95] Rodriguez-Ayllon M, Plaza-Florido A, Mendez-Gutierrez A, *et al*. The effects of a 20-week exercise program on blood-circulating biomarkers related to brain health in overweight or obese children: the ActiveBrains project. J Sport Health Sci, 2023, **12**(2): 175-185

[96] Cokar D, Polat M G, Timurtas E, *et al*. Neuroprotective and metabotropic effect of aerobic exercise training in female patients with type 2 diabetes mellitus. Turk J Biochem, 2022, **47**(6): 741-748

[97] Zlibinaite L, Skurvydas A, Kilikeviciene S, *et al*. Two months of using global recommendations for physical activity had no impact on cognitive or motor functions in overweight and obese middle-aged women. J Phys Act Health, 2021, **18**(1): 52-60

[98] Deeks J J, Higgins J P T, Altman D G. Analysing data and undertaking meta-analyses. Cochrane Handb Syst Rev Interv, 2019: 241-284

[99] Plaza-Florido A, Esteban-Cornejo I, Mora-Gonzalez J, *et al*. Gene-exercise interaction on brain health in children with overweight/obesity: the ActiveBrains randomized controlled trial. J Appl Physiol (1985), 2023, **135**(4): 775-785

[100] Luine V N. Estradiol and cognitive function: past, present and

future. Horm Behav, 2014, **66**(4): 602-618

[101] American Diabetes Association Professional Practice Committee. 5. facilitating positive health behaviors and well-being to improve health outcomes: standards of care in diabetes-2024. Diabetes Care, 2024, **47**(Suppl 1): S77-S110

[102] Marx N, Federici M, Schütt K, *et al*. 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes: developed by the task force on the management of cardiovascular disease in patients with diabetes of the European Society of Cardiology (ESC). Free Eur Heart J, 2023, **44**(39): 4043-4140

[103] 国家卫生健康委办公厅. 国家卫生健康委办公厅关于印发高血压等慢性病营养和运动指导原则(2024年版)的通知[EB/OL]. 北京: 国家卫生健康委, 2024[2025-4-23]. https://www.gov.cn/zhengce/zhengceku/202407/content_6960475.htm
National Health Commission of the People's Republic of China, General Office. Notice of the general office of the national health commission on issuing the nutritional and exercise guidelines for chronic diseases such as hypertension (**2024**) [EB/OL]. Beijing: National Health Commission of the People's Republic of China, 2024 [2025-04-23]. https://www. gov. cn/zhengce/zhengceku/202407/content_6960475.htm

[104] 王正珍. 运动处方的研究与应用进展. 体育学研究, 2021, **35**(3): 40-49 Wang Z Z. J Phys Res, 2021, **35**(3): 40-49

[105] Ceylan H İ, Silva A F, Ramirez-Campillo R, *et al*. Exploring the effect of acute and regular physical exercise on circulating brain-derived neurotrophic factor levels in individuals with obesity: a comprehensive systematic review and meta-analysis. Biology (Basel), 2024, **13**(5): 323

[106] Wang A, Zou Y, Liu S, *et al*. Comprehensive multiscale analysis of lactate metabolic dynamics *in vitro* and *in vivo* using highly responsive biosensors. Nat Protoc, 2024, **19**(5): 1311-1347

[107] Lu X, Xiong W, Chen Z, *et al*. Exercise-conditioned plasma ameliorates postoperative cognitive dysfunction by activating hippocampal cholinergic circuit and enhancing BDNF/TrkB signaling. Cell Commun Signal, 2024, **22**(1): 551

[108] Gao L, Zhang Y, Sterling K, *et al*. Brain-derived neurotrophic factor in Alzheimer's disease and its pharmaceutical potential. Transl Neurodegener, 2022, **11**(1): 4

[109] Tian H, Chen A, Gao P, *et al*. Human umbilical cord mesenchymal stem cell-derived exosomes induce macrophage M2 polarization by antagonizing LPS-mediated stimulation of the NF-κB and STAT3 pathways. Comb Chem High Throughput Screen, 2024. DOI: 10.2174/0113862073314685240514050119

[110] Ji X C, Dang Y Y, Gao H Y, *et al*. Local injection of lenti-BDNF at the lesion site promotes M2 macrophage polarization and inhibits inflammatory response after spinal cord injury in mice. Cell Mol Neurobiol, 2015, **35**(6): 881-890

[111] Yang Y, Li S, Xu H. BPIFA1 alleviates allergic rhinitis by regulating the NF-κB signaling pathway and Treg/Th17 balance. Int J Rheum Dis, 2024, **27**(10): e15372

[112] Blank M, Israeli D, Shoenfeld Y. Exercise, autoimmune diseases and T-regulatory cells. J Autoimmun, 2024, **149**: 103317

[113] Chen A, Xiong L J, Tong Y, *et al*. Neuroprotective effect of brain-derived neurotrophic factor mediated by autophagy through the PI3K/Akt/mTOR pathway. Mol Med Rep, 2013, **8**(4): 1011-1016

[114] Zhang H, Liang J L, Wu Q Y, *et al*. Swimming suppresses cognitive decline of HFD-induced obese mice through reversing hippocampal inflammation, insulin resistance, and BDNF level. Nutrients, 2022, **14**(12): 2432

[115] Harvey T, Rios M. The role of BDNF and TrkB in the central control of energy and glucose balance: an update. Biomolecules, 2024, **14**(4): 424

[116] 陈演, 邱俊强, 于涛, 等. 肌肉-器官交互作用: 运动诱导的肌肉因子研究进展. 中国运动医学杂志, 2022, **41**(11): 887-895
Chen Y, Qiu J Q, Yu T, *et al*. Chin J Phys Med, 2022, **41**(11): 887-895

[117] Kirk B, Feehan J, Lombardi G, *et al*. Muscle, bone, and fat crosstalk: the biological role of myokines, osteokines, and adipokines. Curr Osteoporos Rep, 2020, **18**(4): 388-400

[118] Cutuli D, Decandia D, Giacovazzo G, *et al*. Physical exercise as disease-modifying alternative against Alzheimer's disease: a gut-muscle-brain partnership. Int J Mol Sci, 2023, **24**(19): 14686

[119] El Hayek L, Khalifeh M, Zibara V, *et al*. Lactate mediates the effects of exercise on learning and memory through SIRT1-dependent activation of hippocampal brain-derived neurotrophic factor (BDNF). J Neurosci, 2019, **39**(13): 2369-2382

[120] Alzahrani A S. PI3K/Akt/mTOR inhibitors in cancer: at the bench and bedside. Semin Cancer Biol, 2019, 59: 125-132

[121] Ren Y, Wang K, Wu Y, *et al*. *Lycium barbarum* polysaccharide mitigates high-fat-diet-induced skeletal muscle atrophy by promoting AMPK/PINK1/Parkin-mediated mitophagy. Int J Biol Macromol, 2025, **301**: 140488

[122] Zhang Q, Wang J, Hu X, *et al*. GLP-1RAs regulate lipid metabolism and induce autophagy through AMPK/SIRT1 pathway to improve NAFLD. Prostaglandins Other Lipid Mediat, 2025, **178**: 106987

[123] Genzer Y, Chapnik N, Froy O. Effect of brain-derived neurotrophic factor (BDNF) on hepatocyte metabolism. Int J Biochem Cell Biol, 2017, 88: 69-74

[124] Wu Z, Puigserver P, Andersson U, *et al*. Mechanisms controlling mitochondrial biogenesis and respiration through the thermogenic coactivator PGC-1. Cell, 1999, **98**(1): 115-124

[125] Scarpulla R C. Transcriptional paradigms in mammalian mitochondrial biogenesis and function. Physiol Rev, 2008, **88**(2): 611-638

[126] Matsumoto J, Takada S, Furihata T, *et al*. Brain-derived neurotrophic factor improves impaired fatty acid oxidation *via* the activation of adenosine monophosphate-activated protein kinase-α - proliferator-activated receptor-r coactivator-1α signaling in skeletal muscle of mice with heart failure. Circ Heart Fail, 2021, **14**(1): e005890

[127] U-Pathi J, Yeh Y C, Chen C W, *et al*. Relationship between aspartame-induced cerebral cortex injury and oxidative stress, inflammation, mitochondrial dysfunction, and apoptosis in

sprague dawley rats. Antioxidants (Basel), 2023, **13**(1): 2

[128] Bergin S M, Xiao R, Huang W, *et al*. Environmental activation of a hypothalamic BDNF-adipocyte IL-15 axis regulates adipose-natural killer cells. Brain Behav Immun, 2021, 95: 477-488

[129] Tomiga Y, Tanaka K, Kusuyama J, *et al*. Exercise training ameliorates carbon tetrachloride-induced liver fibrosis and anxiety-like behaviors. Am J Physiol Gastrointest Liver Physiol, 2024, **327**(6): G850-G860

[130] Fathi R, Nasiri K, Akbari A, *et al*. Exercise protects against ethanol-induced damage in rat heart and liver through the inhibition of apoptosis and activation of Nrf2/Keap-1/HO-1 pathway. Life Sci, 2020, **256**: 117958

[131] Bucarey J L, Trujillo-González I, Paules E M, *et al*. Myokines and their potential protective role against oxidative stress in metabolic dysfunction-associated steatotic liver disease (MASLD). Antioxidants (Basel), 2024, **13**(11): 1363

[132] Zhu S, Yu Q, Xue Y, *et al*. *Bifidobacterium bifidum* CCFM1163 alleviates cathartic colon by activating the BDNF-TrkB-PLC/IP_3 pathway to reconstruct the intestinal nerve and barrier. Food Funct, 2025, **16**(5): 2057-2072

[133] Ge Y, Cao Y, Zhang J, *et al*. GOS enhances BDNF-mediated mammary gland development in pubertal mice *via* the gut-brain axis. NPJ Biofilms Microbiomes, 2024, **10**(1): 130

[134] Orlando A, Chimienti G, Lezza A M S, *et al*. *Lactobacillus rhamnosus* GG affects the BDNF system in brain samples of wistar rats with pepsin-trypsin-digested gliadin (PTG) -induced enteropathy. Nutrients, 2020, **12**(3): 629

[135] Kang E J, Cha M G, Kwon G H, *et al*. Akkermansia muciniphila improve cognitive dysfunction by regulating BDNF and serotonin pathway in gut-liver-brain axis. Microbiome, 2024, **12**(1): 181

Exercise Improves Metaflammation: The Potential Regulatory Role of BDNF*

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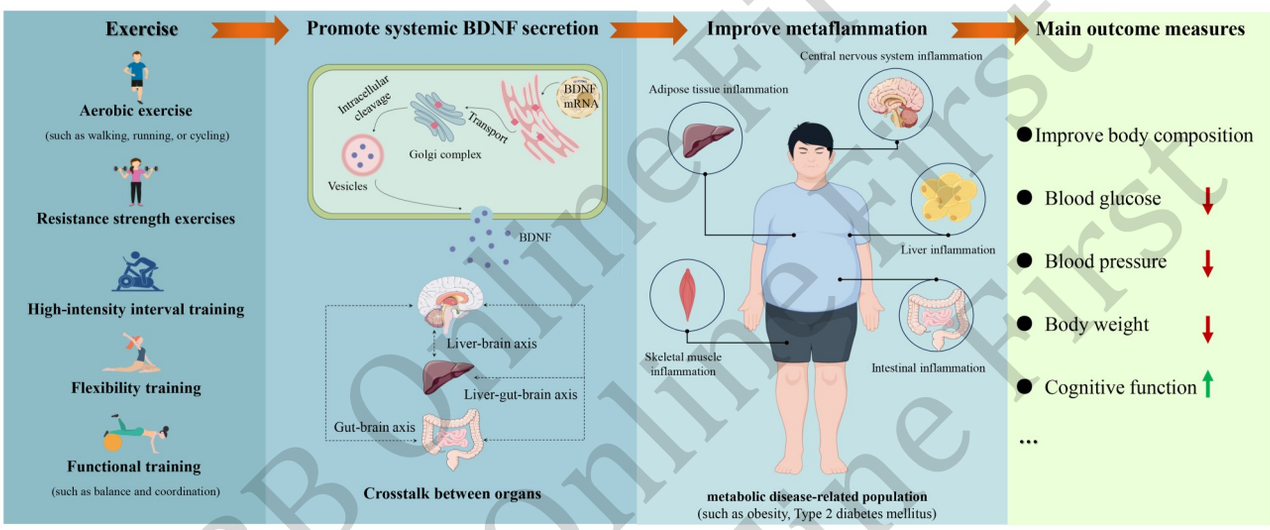
Graphical abstract



Abstract　Metaflammation is a crucial mechanism in the onset and advancement of metabolic disorders, primarily defined by the activation of immune cells and increased concentrations of pro-inflammatory substances. The function of brain-derived neurotrophic factor (BDNF) in modulating immune and metabolic processes has garnered heightened interest, as BDNF suppresses glial cell activation and orchestrates inflammatory responses in the central nervous system *via* its receptor tyrosine kinase receptor B (TrkB), while also diminishing local inflammation in peripheral tissues by influencing macrophage polarization. Exercise, as a non-pharmacological intervention, is extensively employed to enhance metabolic disorders. A crucial mechanism underlying its efficacy is the significant induction of BDNF expression in central (hypothalamus, hippocampus, prefrontal cortex, and brainstem) and peripheral (liver, adipose tissue, intestines, and skeletal muscle) tissues and organs. This induction subsequently regulates inflammatory responses, ameliorates metabolic conditions, and decelerates disease progression. Consequently, BDNF is considered a pivotal molecule in the motor-metabolic regulation axis. Despite prior suggestions that BDNF may have a role in the regulation of exercise-induced inflammation, systematic data remains inadequate. Since that time, the field continues to lack structured descriptions and conversations pertinent to it. As exercise physiology research has advanced, the academic community has increasingly recognized that exercise is a multifaceted activity regulated by various systems, with its effects contingent upon the interplay of elements such as type, intensity, and frequency of exercise. Consequently, it is imperative to transcend the prior study paradigm that concentrated solely on localized effects and singular mechanisms and transition towards a comprehensive understanding of the systemic advantages of exercise. A multitude of investigations has validated that exercise confers health advantages for individuals with metabolic

disorders, encompassing youngsters, adolescents, middle-aged individuals, and older persons, and typically enhances health *via* BDNF secretion. However, exercise is a double-edged sword; the relationship between exercise and health is not linearly positive. Insufficient exercise is ineffective, while excessive exercise can be detrimental to health. Consequently, it is crucial to scientifically develop exercise prescriptions, define appropriate exercise loads, and optimize health benefits to regulate bodily metabolism. BDNF mitigates metaflammation *via* many pathways during exercise. Initially, BDNF suppresses pro-inflammatory factors and facilitates the production of anti-inflammatory factors by modulating bidirectional transmission between neural and immune cells, therefore diminishing the inflammatory response. Secondly, exercise stimulates the PI3K/Akt, AMPK, and other signaling pathways *via* BDNF, enhancing insulin sensitivity, reducing lipotoxicity, and fostering mitochondrial production, so further optimizing the body's metabolic condition. Moreover, exercise-induced BDNF contributes to the attenuation of systemic inflammation by collaborating with several organs, enhancing hepatic antioxidant capacity, regulating immunological response, and optimizing "gut-brain" axis functionality. These processes underscore the efficacy of exercise as a non-pharmacological intervention for enhancing anti-inflammatory and metabolic health. Despite substantial experimental evidence demonstrating the efficacy of exercise in mitigating inflammation and enhancing BDNF levels, numerous limitations persist in the existing studies. Primarily, the majority of studies have concentrated on molecular biology and lack causal experimental evidence that explicitly confirms BDNF as a crucial mediator in the exercise regulation of metaflammation. Furthermore, the outcomes of current molecular investigations are inadequately applicable to clinical practice, and a definitive pathway of "exercise-BDNF-metaflammation" remains unestablished. Moreover, the existing research methodology, reliant on animal models or limited human subject samples, constrains the broad dissemination of the findings. Future research should progressively transition from investigating isolated and localized pathways to a comprehensive multilevel and multidimensional framework that incorporates systems biology and exercise physiology. Practically, there is an immediate necessity to undertake extensive, double-blind, randomized controlled longitudinal human studies utilizing multi-omics technologies (*e.g.*, transcriptomics, proteomics, and metabolomics) to investigate the principal signaling pathways of BDNF-mediated metaflammation and to elucidate the causal relationships and molecular mechanisms involved. Establishing a more comprehensive scientific evidence system aims to furnish a robust theoretical framework and practical guidance for the mechanistic interpretation, clinical application, and pharmaceutical development of exercise in the prevention and treatment of metabolic diseases.

Key words　exercise, metaflammation, brain-derived neurotrophic factor, pro-BDNF
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