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运动调节星形胶质细胞改善阿尔茨海默病机制研究*

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摘要 阿尔茨海默病(Alzheimer's disease，AD)是老年人中最常见的中枢神经系统退行性疾病之一，AD的病理性改变与星形胶质细胞（astrocytes）密切相关。星形胶质细胞是血脑屏障和三方突触的重要组成部分。越来越多的证据表明，在AD早期阶段星形胶质细胞已出现分子和细胞水平的改变。星形胶质细胞的功能会影响AD的发生发展。多项研究表明，运动可以通过调节星形胶质细胞的激活、营养因子的释放、能量代谢、炎症及氧化应激反应，延缓AD的病理变化及改善AD认知功能障碍。本文对运动通过星形胶质细胞改善AD认知功能障碍的作用及机制进行综述和展望，旨在为AD的预防和治疗提供新策略。

关键词 阿尔茨海默病，星形胶质细胞，运动，认知功能障碍
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阿尔茨海默病（Alzheimer's disease，AD）是老年人最常见的中枢神经系统退行性疾病之一。根据国际阿尔茨海默病协会最新发布的统计数据，预计到2030年全球痴呆症患病率将增加到7 500万[1]。目前，中国AD患者已超过1 000万，居全球之首，预计到2050年将突破4 000万[2]。AD不仅严重降低了患者的生活质量，也加重了家庭和社会的负担，目前全球AD成本年均超过8 000亿美元，约占总GDP的1%[1]。尽管随着老龄化社会的加剧，研究者们对AD的关注程度不断增加，但由于神经系统的复杂性等原因，迄今为止，临床上应用于AD的药物都未能从根本上治愈，多数只起到改善延缓症状的作用[3]。AD病理是个渐进发展的过程，目前普遍认为有效的治疗应该从AD早期开始[4]。因此，对AD的早期预警及非药物干预的重要性和迫切性日益突出。

AD的发生与遗传、环境、年龄、代谢等多因素相关，良好的生活方式已被证明可以降低AD发生风险或缓解AD发展进程，其中包括适量运动[5]、健康饮食[6]、社会参与[7]以及高等教育[8]等。多项研究表明，运动可以降低AD发生的潜在风险，显著改善健康老年人和AD患者的精神健康状况、提高认知能力[9-16]，本文总结了近3年运动干预改善认知功能障碍患者病理特征的临床实验数据（表1）。星形胶质细胞（astrocytes）作为中枢神经系统中分布最广泛、数量最多的一类神经胶质细胞，其对维持神经生理功能起关键作用：a. 星形

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Table 1　Physical activity affects the pathological characteristics of cognition impairment group in clinical trial

表1　临床实验中运动影响认知功能障碍患者的病理特征

干预对象	运动强度	运动周期	样本量/例	年龄	检测与评估方式	病理改变
携带AD风险基因的老年人	中等强度跑步	26周	23	64.9±5	VO_{2peak}、MMSE、CVLT、血样检验	运动后患者心肺功能改善、认知功能改善[9]
轻度MCI患者	中等强度舞蹈	12周	36	72.9±5.6	WMS-III、RBANS、BNT、MMSE、HADS、BBS	运动后患者语言识别记忆、平衡能力和步态表现均改善，认知功能改善[10]
轻度MCI患者	中等强度快走上坡	12个月	30	66±7	MRI、ADAS-Cog、WAIS-III、COWAT	运动增加海马区血流量，改善患者记忆功能[11]
轻度MCI患者	中高强度快走	12个月	70	64±6.6	VO_{2peak}、CBFV、CVLT-II、D-KEFS	运动提高患者VO_{2peak}，改善脑血流量，提高认知能力[12]
轻度MCI和AD患者	中等强度自行车	6个月	87	79±9	MMSE、TMT、6MWT、ADAS-Cog、BMI、血样检验	运动改善患者心血管功能，减缓认知能力下降[13]
轻度AD患者	有氧运动	4年	376	80±7	ADAS-Cog、CDR-SOB	运动后患者认知功能、语言流畅性和情景记忆能力均得到改善[14]
AD患者	高强度抗阻训练	6个月	101	69.5±6.6	ADAS-Cog、WAIS-III、MRI	运动改善患者认知功能[15]
AD患者	有氧运动	6个月	96	77.4±6.8	ADAS-Cog	运动减轻患者认知功能障碍[16]

VO_{2peak}：摄氧量峰值；MMSE：简易精神状态检查；CVLT：加州语言学习测试；WAIS-III：韦氏成人智力量表第三版；RBANS：可重复成套神经心理状态评定量表；BNT：波士顿命名测试；HADS：医院焦虑和抑郁量表；BBS：伯格平衡量表；MRI：磁共振成像；ADAS-Cog：阿尔茨海默病评估量表-认知分量表；COWAT：受控口语单词联想测试；CBFV：平均血流速度；D-KEFS：Delis-Kaplan执行功能系统测试；TMT：连线测试；6MWT：六分钟步行测试；BMI：体重指数；CDR-SOB：临床痴呆评分总和量表。

胶质细胞末端接触血管，并与内皮细胞和周细胞一起形成血脑屏障（blood brain barrier，BBB）参与调控循环系统和神经组织之间的物质交换[17]；b. 星形胶质细胞可以分泌递质或调质，如谷氨酸（glutamate）、d-丝氨酸（d-serine）、三磷酸腺苷（adenosine triphosphate，ATP）等调控神经元的活动[18]；c. 星形胶质细胞作为“三方突触”（tripartite synapse）神经传递模型的一个重要组成部分，围绕在神经元的突触前和突触后，感知和调控突触输出，在大脑的功能整合中发挥重要作用[17, 19]。星形胶质细胞的病理性改变会导致AD认知能力下降甚至记忆丧失[15]。在AD早期，星形胶质细胞的形态与功能改变，引起脑内神经炎症水平上升，能量代谢障碍以及氧化应激损伤，进而影响神经血管单元功能，引起AD认知功能障碍[20-24]。研究发现，运动可以通过调节星形胶质细胞的形态及功能，改善AD的病理特征，缓解认知功能障碍[25]。运动对AD的改善作用及潜在的机制是神经生物学领域的研究热点之一。本文将从运动抑制星形胶质细胞的激活，减轻脑内炎症反应、增加脑内营养因子和改善大脑能量代谢等方面进行综述，旨在阐明运动对星形胶质细胞的调控及其改善AD的病理机制（图1）。

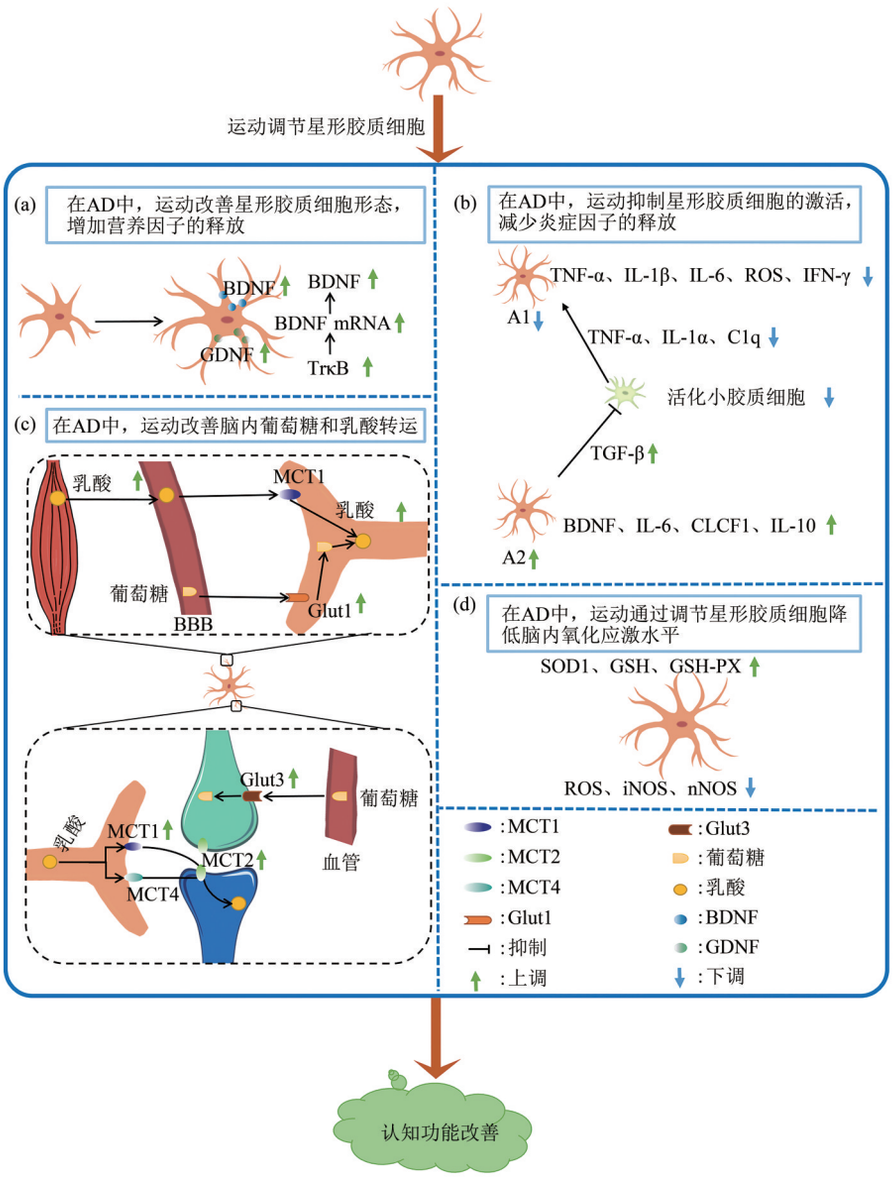

Fig. 1　Mechanism of improved function of astrocytes in Alzheimer's disease mediated by physical activity

图1　运动调节星形胶质细胞改善阿尔茨海默病机制

BDNF：脑源性神经营养因子；GDNF：胶质细胞源性神经营养因子；TrkB：原肌球蛋白受体激酶B；Glut：葡萄糖转运蛋白；BBB：血脑屏障；MCT：单羧酸转运蛋白；TNF-α：肿瘤坏死因子α；IL：白介素；CLCF1：心肌营养素样细胞因子1；TGF-β：转化生长因子β；IFN-γ：干扰素γ；C1q：补体1q；ROS：活性氧；iNOS：诱导型一氧化氮合酶；nNOS：神经元型一氧化氮合酶；SOD1：超氧化物歧化酶1；GSH：谷胱甘肽；SGH-PX：谷胱甘肽过氧化物酶。

1　运动调节AD脑内星形胶质细胞的形态

在AD中星形胶质细胞的形态改变表现为体积减小、突起变薄，这导致大脑连接和突触传递损伤[26]。研究发现，来源于AD患者的诱导多能干细胞（iPSC）诱导的星形胶质细胞与对照组细胞相比表现出明显的分支减少和细胞关键功能标志物S100β、EAAT1和GS的异常定位[27]。在1月龄3×Tg-AD小鼠中可观察到内嗅皮质（entorhinal cortex，EC）中出现形态改变的星形胶质细胞，表现为初级分支、次级分支以及远端分支的减少，且这种现象在AD发生发展过程中持续[28]。在5×FAD、PDAPP-J20和Swiss3等小鼠中同样也观察到星形胶质细胞突起减少[29-31]。经过4周跑步干

预后，C57BL/6小鼠、Wistar大鼠海马区星形胶质细胞的密度、表面积、分支及突起长度增加[32-33]。6个月的自主跑步干预没有改变5×FAD小鼠海马的神经发生和神经元存活，但显著增加了星形胶质细胞的胞体面积、增多了突起和分支的数目与长度，改善了5×FAD小鼠的空间记忆损伤和认知功能障碍[34]。以上研究表明，运动调节星形胶质细胞的形态，增加星形胶质细胞的突起及分支，进而改善认知能力。

2　运动调节AD脑内星形胶质细胞的激活及其介导的炎症反应

持续且广泛的星形胶质细胞激活是AD早期的一种现象[35]，在AD患者和AD动物模型的大脑中均发现星形胶质细胞标记物GFAP水平升高[36]。激活的星形胶质细胞即反应性星形胶质细胞（reactive astrocytes），包括具有促炎功能的A1亚型和具有保护作用的A2亚型[22]。在AD中，激活的小胶质细胞分泌白介素-1α（interleukin-1α，IL-1α）、肿瘤坏死因子α（tumor necrosis factor alpha，TNF-α）、补体1q（complement 1q，C1q）等促炎因子，可诱导产生A1型星形胶质细胞[37-38]，A1型星形胶质细胞的增多会释放细胞因子（TNF-α、转化生长因子（transforming growth factor-β，TGF-β）、IL-1β、IL-6和干扰素γ（interferon-γ，IFN-γ））、趋化因子（C-X-C motif chemokine 10，C-C motif chemokine 5）、补体（C3、C5-C9）和活性氧等[21，39]，进一步诱导小胶质细胞和星形胶质细胞的相互激活，加剧炎症反应[40]。A2型星形胶质细胞可以释放TGF-β减弱小胶质细胞的活化[41]，还可通过上调神经营养因子和抗炎因子，如脑源性神经营养因子（brain derived neurotrophic factor，BDNF）、心肌营养素样细胞因子1（cardiotrophin like cytokine factor 1，CLCF1）、IL-6、IL-10、白血病抑制因子（leukemia inhibitory factor，LIF）等发挥保护作用[42]。运动通过调节星形胶质细胞的激活及其介导的炎症反应可改善AD的病理过程。对APP/ PS1小鼠进行5个月的跑步干预后发现，运动减弱了星形胶质细胞的激活，减少了Aβ斑块数量和大小，增加了神经元密度，这显示长期跑步运动可以通过抑制星形胶质细胞激活发挥神经保护作用[43]。对衰老加速小鼠8（senescence accelerated mouse/ prone 8，SAMP8）的海马检测发现，反应性星形胶质细胞的数量随着年龄的增长而显著增加，对其进行10周低强度旋转运动干预后发现，小鼠海马中A1型星形胶质细胞的标志物C3蛋白水平显著下降[38]。在5×FAD小鼠海马区检测到反应性星形胶质细胞增加，6个月的跑步干预降低7月龄的5×FAD小鼠海马区A1型星形胶质细胞标记物Serping1、Srgn含量，增加A2型星形胶质细胞标记物S100A10含量，同时降低AD脑内炎症水平，改善小鼠的认知功能损伤[34]。综上所述，运动可以通过调节反应性星形胶质细胞亚型，减轻脑内神经炎症，改善认知功能。

3　运动通过星形胶质细胞改善AD脑内能量代谢异常

AD病理严重程度及AD认知损伤与脑内葡萄糖代谢下降显著相关。对AD患者功能性脑成像检测发现脑内葡萄糖代谢进行性降低，对AD患者大脑蛋白质组学检测可以发现，AD患者大脑中存在星形胶质细胞的代谢异常[44]。星形胶质细胞作为血脑屏障重要组成部分，其末端通过葡萄糖转运蛋白1（glucose transporter 1，Glut1）选择性地从血液中摄取葡萄糖，从而平衡大脑中葡萄糖代谢[45]。在AD小鼠、老年大鼠以及AD患者脑部的尸检中，均显示Glut1蛋白水平下降[46-48]。对转基因AD模型小鼠进行16周跑步干预后，在小鼠脑内检测到Glut1和Glut3蛋白表达升高，同时脑内葡萄糖代谢水平和认知功能障碍均得到改善[49-50]。相似的结果也出现在进行了4周游泳干预的APP/PS1小鼠中，运动增加了海马和皮质中的Glut1、Glut3含量，改善了脑内葡萄糖代谢和认知功能障碍[51]。运动除了调节Glut1、Glut3的表达改善AD脑内能量代谢外，还有可能通过星形胶质细胞调控外周乳酸往脑内的转运以及乳酸在星形胶质细胞和神经元之间穿梭。运动导致肌肉组织糖酵解产生乳酸，并积聚在血液中。单羧酸转运蛋白（monocarboxylate transporters，MCTs）是乳酸转运蛋白，其中MCT1和MCT4主要在星形胶质细胞上表达，MCT2主要在神经元上表达[52]。星形胶质细胞中糖酵解或糖原分解产生的乳酸也可通过MCT1和MCT4转移到细胞外，并通过MCT2进入神经元[53]。当外周乳酸增多时，MCT1也随之增加。在老年脑与AD脑内，MCT1含量下降[54]。运动可使MCT1及MCT4上调，进而增加乳酸转运至脑内，缓解脑内能量代谢障碍[45]。对小鼠进行30 d跑步运动可在海马中检测到大脑中乳酸的累积增多，且认知能力得到提

升，这进一步证明运动产生的乳酸对认知功能的积极作用[55]。综上所述，运动可以增加星形胶质细胞葡萄和乳酸的转运，改善脑内能量代谢异常。

4 运动调控星形胶质细胞释放神经营养因子改善AD认知功能

神经营养因子（neurotrophic factors，NTF）是指机体产生的能够促进神经细胞存活、生长、分化的一类蛋白质因子。胶质细胞源性神经营养因子（glial cell derived neurotrophie factor，GDNF）是神经胶质细胞系衍生的细胞因子，其可促进中脑多巴胺能神经元内多巴胺的摄取[51]。BDNF是神经元存活、活动、神经发生以及影响突触可塑性的关键神经营养因子[56-57]。大量证据表明，BDNF参与轴突和树突的分支和重塑，增强突触传递[58]。星形胶质细胞可以分泌营养因子，如GDNF[59-60]、BDNF[61-62]等从而发挥神经保护作用。在3×Tg-AD小鼠脑内检测到GDNF表达降低，进行6个月的自愿运动后，小鼠脑内GDNF水平上升，认知功能障碍也得到改善[23]。对成年C57BL/6J雄性小鼠进行6周自愿跑步干预发现，运动增加了小鼠海马中GDNF、BDNF的表达，提高了脑内线粒体活性，且增强了小鼠的神经可塑性，改善了抑郁样情绪[63]。运动干预后，星形胶质细胞能够通过表达原肌球蛋白受体激酶B（tyrosine kinase receptor B，TrkB）受体对BDNF作出应答[64]。对小鼠进行一次性或长期跑步干预均可检测到小鼠星形胶质细胞BDNF mRNA水平升高[65-66]。脑内BDNF表达的增加有可能是运动产生的乳酸穿过BBB，并激活氧化物酶体增殖物激活受体γ辅激活因子1α/纤维连结蛋白III型域包含蛋白5（PGC1α/FNDC5）信号通路引起的[67-68]。使用特异性免疫黏附嵌合体阻断BDNF，将消除运动对大鼠学习和记忆能力的积极影响，同时也消除运动干预后BDNF增加介导的突触可塑性增强[69]。因此，运动可能调控星形胶质细胞GDNF、BDNF等神经营养因子的合成和释放改善AD认知功能障碍。

5 运动抑制AD星形胶质细胞氧化应激反应

在AD病理情况下，脑内抗氧化系统发生紊乱，产生氧化应激损伤，导致ROS水平增加[24]。不仅如此，AD脑内糖代谢水平的下降进一步导致氧化应激[70]。星形胶质细胞是大脑抗氧化的主要参与者。研究发现，通过阻断AD小鼠大脑中反应性星形胶质细胞氧化应激，可减少小鼠炎症反应和Aβ斑块沉积，从而改善小鼠记忆并延缓病程进展。在一次运动后即可观察到，ROS水平瞬时升高，并调节氧化还原的适应性，增加内源性抗氧化能力。随着运动的持续，大脑对氧化应激的耐受水平随之提高[71]。连续16周的中强度跑步运动可降低成年大鼠海马体中的ROS水平和蛋白质羰基数目，并增加超氧化物歧化酶1（superoxide dismutase 1，SOD1）和谷胱甘肽过氧化物酶（glutathione peroxidase，GSH-PX）[51]。对AD模型小鼠进行5周的跑步运动改善了其空间记忆损伤，且增加了CA1区海马内星形胶质细胞中谷胱甘肽（glutathione，GSH）的含量[72]。对SAMP8进行10周低强度旋转运动发现，抑制AD进展早期海马中的神经元型一氧化氮合酶（neuronal nitric oxide synthase，nNOS）和诱导型一氧化氮合酶（inducible nitric oxide synthase，iNOS）活性，改善了衰老带来的认知功能障碍[38]。因此，运动通过星形胶质细胞调节AD中异常的氧化应激水平，改善AD病理状况，缓解认知障碍。

6 总结与展望

作为一种对全身具有广泛影响的干预方式，动物和临床研究均表明，运动能够改善AD的认知功能障碍。星形胶质细胞作为血脑屏障和三方突触的重要组成部分，其激活状态与AD发生发展阶段密切相关。星形胶质细胞是运动改善AD的重要效应细胞，运动可以通过调节星形胶质细胞激活、营养因子的释放、能量代谢、炎症及氧化应激反应，延缓AD的病理变化及改善AD认知功能障碍。但是星形胶质细胞在运动调节改善AD的作用及机制研究中仍有些问题等待进一步探究：a. 目前缺乏能用于筛选反应星形胶质细胞不同激活状态及功能，而且适用于临床检测与诊断的特异性标志物；b. 运动调节星形胶质细胞激活状态和剂量效应等问题也有待进一步研究；c. 运动预防和治疗AD认知功能的有效时间窗值得进一步的研究，在可逆性认知衰弱（轻度认知功能障碍前阶段）、潜在可逆性认知衰弱（轻度认知功能阶段）以及AD早期，运动是否会有更好预防和治疗效果；d. 不同患者疾病进展和身体机能等方面有较大差异性，运动能力和运动方式喜好也不同，如何为每位患者制定安全有效的个性化运动方案。

综上所述，本文总结了运动调节星形胶质细胞

在干预和改善AD发生发展过程中的作用及机制，为AD患者的运动治疗提供了更多理论支撑。但AD是一种多因素导致的复杂疾病，未来“联合-多靶点”策略的治疗可能是新的发展趋势[73]，需要从多个角度出发，联合运动干预、营养手段、认知干预、物理刺激等的多模态干预也是未来的研究方向。相信随着研究的不断深入必将更好地预防和治疗AD在内的神经退行性疾病。

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Mechanism of Improved Function of Astrocytes in Alzheimer's Disease Mediated by Physical Activity*

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Abstract Alzheimer's disease (AD) is an unremitting neurodegenerative disorder. Astrocytes play a fundamental role in maintaining the health and function of the central nervous system and memory. The pathological changes in brain of AD are closely related to astrocytes. Increasing evidence indicates that astrocytes undergo both cellular and molecular changes at an early stage in AD. Physical activity can effectively relieve cognitive impairment by regulating astrocytes in AD. In this review, we have summarized the multiple improvement effects on AD by physical activity through the regulation of astrocytes, including improving cell morphology and regulating astrocytes activation, increasing the release of trophic factors, regulating astrocytes phenotype and reducing neuroinflammation, improving glucose and lactate transportation in the brain as well as degrading oxidative stress. The knowledge of this review will pave the way for the prevent and treatment of AD through understanding the mechanisms of the beneficial effects mediated by physical activity through regulating astrocytes in AD.

Key words Alzheimer's disease, astrocytes, physical activity, cognitive impairment
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