糖尿病致阿尔茨海默病的运动干预作用及机制

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摘要 流行病学研究表明, 糖尿病患者罹患阿尔茨海默病(Alzheimer's disease, AD)的机率明显增加, 说明糖尿病可能在AD发病中扮演关键角色。此外, 糖尿病所致脑胰岛素信号异常、神经炎症、氧化应激及线粒体功能障碍、血管功能障碍等致病因素, 可通过多种途径导致β-淀粉样蛋白积累和Tau磷酸化, 加速神经细胞死亡, 进而加重认知功能障碍, 促使AD发生。近年来研究发现, 多种抗糖尿病药物对AD均有不同程度的改善疗效或作用。运动亦可通过缓解神经炎症状态、抑制氧化应激及线粒体功能障碍、改善内皮功能及脑血管功能障碍、诱导神经发生等多种关键内在机制, 改善糖尿病致AD相关病理改变。为此, 该综述将对糖尿病致AD的病理机制和部分抗糖尿病药物对其防治机制进行总结, 并探讨运动改善糖尿病致AD的干预作用及机制, 以期为其治疗的多样性提供更多理论参考依据。

关键词 糖尿病; 阿尔茨海默病; 运动干预; 胰岛素抵抗

Effect and Mechanism of Exercise Intervention in Alzheimer's Disease Induced by Diabetes

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Abstract Epidemiological studies have shown that the incidence of AD (Alzheimer's disease) in patients with diabetes is significantly increased, suggesting that diabetes may play a key role in the development of AD. In addition, diabetic encephalic insulin signal abnormalities, neuroinflammation, oxidative stress, mitochondrial dysfunction, vascular dysfunction and other pathogenic factors can lead to amyloid-β accumulation and Tau phosphorylation through a variety of ways, accelerate nerve cell death, and further aggravate cognitive dysfunction and promote the occurrence of AD. In recent years, it has been found that a variety of anti-diabetes drugs can improve the efficacy or effect of AD to varying degrees. Exercise can also improve the pathological changes related to AD caused by diabetes by alleviating neuroinflammatory state, inhibiting oxidative stress and mitochondrial dysfunction, improving endothelial function and cerebrovascular dysfunction, and inducing neurogenesis. Therefore, this review will summarize the pathological mechanism of diabetes-induced AD and the prevention and treatment mechanism

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of some antidiabetic drugs, and explore the intervention effect and mechanism of exercise in improving diabetes-induced AD, in order to provide more theoretical reference for the diversity of its treatment.

Keywords diabetes; Alzheimer's disease; exercise intervention; insulin resistance

阿尔茨海默病(Alzheimer's disease, AD)是一种进行性、不可逆转的中枢神经系统退行性疾病。其病理特征主要表现为嗜银神经轴索突起包绕聚集的β-淀粉样蛋白(amyloid-β, Aβ)形成的神经炎性斑和神经元内过度磷酸化的微管Tau蛋白高度螺旋化形成的神经原纤维缠结(neurofibrillary tangle, NFT)。该特征严重时可加速神经退化, 引起记忆力丧失和认知功能障碍等症状[1]。中风、糖尿病、癫痫、骨质疏松和肾病等多种疾病均可增加AD发病的可能性, 而糖尿病则被认为是AD发生发展极为重要的危险因素[2]。荟萃分析显示, 糖尿病可使认知障碍和痴呆风险提高1.25~1.91倍, 糖尿病前期的痴呆风险亦逐步上升, 在糖尿病相关生化指标中, 空腹血糖与认知障碍呈非线性相关, 而糖尿病患者在抗阻负荷2 h后, 血糖、糖化血红蛋白及空腹血糖胰岛素水平升高, 均与痴呆风险增加密切相关[3]。另有研究报道, 在记忆、处理速度和执行能力等需要大脑参与的领域中, 老年糖尿病患者表现明显比糖耐量正常的人差, 脑葡萄糖耐受不良亦可增加其患认知障碍的风险, 且其风险率比胰岛素分泌正常的人高1%[4]。以上流行病学研究表明, 糖尿病可能是AD发病极为关键的独立风险因素。

而脑是胰岛素的重要靶器官, 胰岛素信号涉及许多脑功能。但胰岛素信号转导通路障碍可抑制磷脂酰肌醇3-激酶(phosphatidylinosi-tol 3-kinase, PI3K)/蛋白激酶B(protein kinase B, Akt)信号通路, 并诱导糖原合成激酶-3β(glycogen synthase kinase-3β, GSK-3β)过度激活, 使磷酸化Tau蛋白含量增加、神经纤维变性, 最终导致认知障碍和记忆受损[6]。TALBOT等[7]的验尸报告, 分析了海马CA1-CA3区齿状回和下丘脑胰岛素抵抗的原因和后果, 发现仅在AD晚期, 这些患者的大脑皮质才显示出Aβ沉淀等病理特征。因此, 脑胰岛素信号障碍可能导致AD病理损害。此外, 近年来研究发现, 胰岛素抵抗关联的神经炎症、氧化应激、线粒体功能障碍、血管功能障碍等均是糖尿病致AD的病理机制[8], 且证实常见抗糖尿病药物胰岛素及其类似物、二甲双胍、噻唑烷二酮类化合物、GLP-1(glucagon-like peptide-1)或其类似物等, 对AD均有不同程度的改善疗效[9], 并重点阐述运动对糖尿病致AD的良好干预效果, 可通过缓解神经炎症状态、抑制氧化应激及线粒体功能障碍、改善内皮功能及脑血管功能障碍、诱导神经发生及改善记忆力等多种内在机制, 减少糖尿病致AD相关病理改变, 降低AD患病风险[10]。为此, 本综述将在详述糖尿病致AD的相关病理机制和部分抗糖尿病药对AD疗效的基础上, 探究运动在糖尿病致AD中的积极作用和靶向分子机制, 从而为该病干预策略的多样性提供理论依据和新的见解。

1 糖尿病致AD的关键机制

1.1 胰岛素/胰岛素样生长因子-1(insulin-like growth factor-1, IGF-1)信号受损

胰岛素可调节脑葡萄糖和脂质代谢, 并在学习记忆中起重要作用。AD患者脑中存在胰岛素抵抗, 表现为脑葡萄糖代谢与胰岛素信号转导障碍, 脑胰岛素抵抗在认知相关区域表现较严重, 其与该区胰岛素/IGF-1信号受损密切相关[11]。

目前已有研究阐述了胰岛素/IGF-1功能障碍导致AD的相关病理机制。KIM等[12]发现, 高脂饮食小鼠(IR和Mets模型)脑淀粉样前体蛋白(amyloid precursor protein, APP)磷酸化增加, 在代谢应激和胰岛素抵抗条件下, PI3K/Akt途径受损, 胰岛素和IGF-1降低脑皮层神经元APP磷酸化作用受阻, 从而加重AD。在缺乏胰岛素样生长因子1受体(insulin-like growth factor 1 receptor, IGF-1R)的小鼠模型大脑中, 发现磷酸化的GSK-3β以不依赖于PI3K/Akt的形式被激活, 导致磷酸化的Tau蛋白水平升高, 进而对中枢系统稳态产生一定负面影响, 增加AD发生风险[13]。一项通过链脲佐菌素(streptozotocin, STZ)诱导糖尿病模型的研究发现, STZ诱导的胰岛素缺乏可上调小鼠大脑中β位点APP裂解酶1(β-site APP cleaving enzyme 1, BACE1)和其底物APP的表达水平, 导致脑胰岛素信号转导障碍, 进一步加速中枢神经系统中Aβ沉积[14]。同时, TAKEDA等[15]研究发现, ob/ob小鼠与*APP*转基因小鼠杂交形成的小鼠模型脑葡萄糖耐受不良, 神经元胰岛素信号受损, 导致脑血

管功能受损, 进而加重AD合并糖尿病模型的认知功能障碍。而糖尿病脑胰岛素信号功能障碍亦可增加Aβ沉积和Tau磷酸化, 导致脑神经纤维变性, 破坏记忆水平。

胰岛素抵抗和缺乏可引起胰岛素信号下调, 通过激活c-JUN-NH2-末端激酶(c-JUN-NH2-terminal kinase, JNK)/肿瘤坏死因子α(tumor necrosis factor-α, TNF-α)途径, 诱发神经炎症, 促使Tau蛋白磷酸化, 引起神经纤维变性, 从而加剧AD病理过程[17]。BPMFIM等[18]发现, 向Tg小鼠模型脑室内注射Aβ低聚物可触发海马胰岛素受体底物-1(insulin receptor substrate-1, IRS-1)丝氨酸磷酸化(IRS-1pSer)和JNK活化, 导致IRS-1信号受损, 而注射抗糖尿病药艾塞那肽(exendin-4)则可抑制海马IRS-1pSer和JNK活化, 改善大脑病理状态和认知行为。这表明脑胰岛素信号转导受损可能对认知行为产生负面效应, 从而促进AD病理进程。另外, *AβPP/ps1*双转基因小鼠与IGF-1缺陷小鼠的杂交模型, 其脑内海马IGF-1水平明显降低, 引起促炎细胞增生、活性氧(reactive oxygen species, ROS)产生量增加, 损害脑细胞功能, 导致Aβ沉积[19]。提示, IGF-1缺陷可能在AD疾病进展中发挥重要作用。

因此, 糖尿病致脑胰岛素信号转导受损可诱发或加重Aβ沉积、Tau蛋白磷酸化, 促使神经纤维发生变性, 破坏认知行为并降低记忆水平, 促进AD病理进程。

1.2 氧化应激及线粒体功能障碍

氧化应激及线粒体功能障碍与糖尿病和AD的共病机制密切相关。高水平活性氧(reactive oxygen species, ROS)或活性氮(reactive nitrogen species, RNS)累积不仅能损害细胞功能, 加速细胞死亡, 还可通过脂质过氧化作用促进线粒体损伤, 导致线粒体功能障碍, 并促进糖尿病和AD的发生发展[20]。

在糖尿病胰岛素抵抗模型中, 脑细胞衍生高水平ROS可诱导脂质过氧化产物产生, 触发小胶质细胞活化, 诱发神经炎症, 损害脑细胞功能, 导致记忆功能障碍[21]。CORREIA等[22]研究显示, STZ致糖尿病大鼠高血糖可使脑海马线粒体呼吸链受损, 脑皮层和海马匀浆中突触素蛋白水平下降及谷胱甘肽过氧化物酶(glutathione peroxidase, GPx)和超氧化物歧化酶(superoxide dismutase, SOD)活性降低, 进而导致线粒体功能障碍, 损伤脑神经元细胞, 加重认知功能损伤。RAZA等[24]研究发现, Zucker糖尿病肥胖鼠(zucker diabetic fat, ZDF)脑部分区域的ROS水平明显增加, GSH代谢降低, 导致线粒体呼吸功能受损, 氧化还原稳态失衡。高脂膳食诱导的胰岛素抵抗大鼠大脑皮层和下丘脑ROS水平显著增加, 且大脑皮层氧化损伤标志物, 如4羟基壬烯(4-hydroxynonenal, 4-HNE)、丙二醛(malonic dialdehyde, MDA)、8羟基脱氧鸟苷(8-hydroxy-2-deoxyguanosine, 8-OhdG)的水平均显著升高, 进而破坏线粒体功能, 加剧脑氧化应激, 促使神经元凋亡和记忆损伤[25]。另有研究报道, 糖尿病模型胰腺β细胞tRNA修饰失调和Aβ异常累积, 可使得电子传递链异常和线粒体功能障碍, 抑制ATP产生, 进而破坏脑认知功能[26]。此外, 糖尿病模型出现高血糖症状亦可导致皮质神经元胰岛素抵抗和线粒体功能障碍, 而靶向线粒体-AMPK信号可防治高血糖所致的神经元损害[27]。因此, 糖尿病所致脑氧化应激和线粒体功能障碍可引起认知功能损伤, 故其可能在AD发展中扮演重要角色。

线粒体质量控制(即线粒体生物发生、线粒体融合分裂循环和线粒体自噬等)在氧化应激及线粒体功能障碍介导的糖尿病和AD共病机制中亦发挥重要作用。研究表明, 糖尿病模型大脑血糖水平较高可诱导线粒体产生ROS, 降低ATP合成量, 破坏线粒体动力学平衡(即线粒体融合分裂循环失衡), 从而导致氧化应激损伤乃至脑组织损伤[28]。此外, 线粒体融合分裂失衡亦可破坏膜电位, 减少ATP产生, 使线粒体自噬功能受损, 导致线粒体功能障碍和认知功能缺陷[29]。CARVALHO等[30]研究发现, 3xTg-AD小鼠大脑皮层和海马线粒体核呼吸因子1(nuclear respiratory factor 1, NRF1)、NRF2水平降低, 自噬相关蛋白水平亦降低, 并认为糖尿病脑线粒体生物发生和自噬缺陷可诱导线粒体功能异常和ROS产生, 进而改变突触完整性, 增加记忆缺陷, 导致AD发生。另外, 随着AD的发生发展, 在糖尿病模型海马中, 参与线粒体生物发生的过氧化物酶体增殖物激活受体γ共激活因子1α(peroxisome proliferator activated receptor gamma coactivator 1 alpha, *PGC-1α*)和线粒体自噬蛋白*PINK1*等基因表达水平均显著下降[31]。这提示, 线粒体生物发生和线粒体自噬对于维持脑线粒体功能起重要作用, 而线粒体质量控制障碍可能是糖尿病致AD的潜在机制。因此, 糖尿病引起的线粒体质量控制失衡可通过氧化应激和线粒体功能障碍增加AD患病风险。

综上, 糖尿病所致脑氧化应激和线粒体功能障碍可通过多种途径影响记忆能力或认知功能水平, 最终增加AD患病风险。

1.3 神经炎症

炎症是神经退行性疾病和代谢性疾病的一个重要特征, 在许多疾病的发病机制中起关键作用, 炎症途径亦是糖尿病与AD的共病机制。糖尿病与AD相关性研究表明, 糖尿病脑胰岛素抵抗可引起一系列炎性因子如IL-6、IL-1β、IL-18、TNF-α、α1-抗糜蛋白酶(alpha-1-antichymotrypsin, α1ACT)和C-反应蛋白(C-reactive protein, CRP)等的变化[2]。

研究表明, 糖尿病和AD小鼠模型脑胰岛素抵抗可促进脑神经元、小胶质细胞和内皮细胞AGEs受体表达, 引起脑血管炎症, 刺激炎性因子IL-6、TNF-α表达增加, 并使糖尿病模型脑星形胶质细胞Aβ累积, 从而促进AD发展[32]。SHINOHARA等[33]对ob/ob小鼠*APP*基因的表达进行分析, 发现少突胶质细胞和小胶质细胞中的特异基因上调, 促炎因子IL-6和TNF-α表达水平上升, 导致Aβ积累。这提示, 脑AGEs受体上调, 以及IL-6和TNF-α表达水平升高, 可引起胶质细胞活化, 促进NFT形成, 增加AD发生风险。另有研究发现, 对高脂喂养的小鼠腹腔注射TNF-α拮抗剂XPro1595, 可改善小鼠下丘脑和前额叶皮层中枢胰岛素抵抗, 缓解神经炎, 改善异常行为[34]。提示, 神经炎症可加重脑功能障碍, 而抑制脑神经炎症状态可改善异常行为表现和认知水平。此外, 广泛分布于脑中的Toll样受体4(Toll-like receptor 4, TLR4), 可通过调节神经炎症而在中枢系统中发挥重要作用, 且TLR4慢性激活可促进胰岛素抵抗, 导致Aβ在脑中沉积[35]。以上研究均能证实神经炎症在AD发生发展中的重要作用。

为进一步印证糖尿病炎症与AD之间的关系, PIATKOWSKA-CHMIEL等[37]研究了糖尿病小鼠脑促炎因子水平升高与行为认知水平的关系, 发现了与学习记忆有关的脑区域IL-1β、IL-6、TNF-α表达水平均上升, 且小鼠认知障碍加重。因此, 认知功能受损程度可能与神经炎症指标水平增加呈正相关。另外, 糖尿病小鼠脑胰岛素抵抗和代谢紊乱可增加海马AβOs积聚, 加重神经元毒性, 促使小胶质细胞释放TNF-α, 破坏神经突触功能, 从而导致认知功能障碍[2,38]。

因此, 糖尿病所致胰岛素抵抗和代谢障碍, 可引起脑部炎性因子水平升高, 以及Aβ产生量增加, 加重神经元毒性并破坏神经突触功能, 引起记忆障碍和行为异常, 从而加剧AD发生。

1.4 血管功能障碍

脑血管内皮功能障碍亦是糖尿病和AD的共病因素。血管功能障碍包括脑血管流动减少和脑淀粉样血管病变。研究发现, 肥胖型糖尿病患者脑高血糖可导致内侧颞区微血管病变, 使大脑灌注降低, 进而损伤血管内皮细胞和神经突触, 导致神经毒性, 促使淀粉样血管病产生, 损害认知功能[39]。

TUCSEK等[40]发现, 衰老可加剧高脂喂养肥胖小鼠海马和皮层微血管密度的下降、神经血管解偶联, 并改变海马血管生成基因表达, 损伤脑微血管, 使大脑血流量降低, 引发脑血管细胞线粒体功能障碍, 促使ROS和RNS产生, 导致认知功能下降。ZULOAGA等[41]发现, 长期高脂喂养所致糖尿病小鼠, 在脑慢性低灌注时, 脑动脉血管的内皮细胞损伤, 增加脑中超氧化物和过氧亚硝酸盐产生量, 严重破坏血脑屏障, 引发血管性认知缺陷。此外, 糖尿病脑高血糖可激活小胶质细胞NLRP3炎性小体, 上调IL-1β、IL-18表达, 引起血管内皮炎症, 进而诱发血管内皮功能障碍, 导致微血管出血, 最终影响脑认知功能水平[42]。同时, 在糖尿病模型中, 脑葡萄糖供应减少, 可能引起胰岛素信号转导障碍, 破坏大脑能量平衡, 促使ROS产生和线粒体损伤, 引起脑神经元退行性形变和低代谢状态, 导致认知水平下降[43]。

因此, 糖尿病所致脑血管功能障碍是认知功能缺陷乃至AD的重要致病因素。据此对糖尿病所致脑血管功能障碍进行针对性治疗可能是防治AD的重要途径。

2 抗糖尿病药物对糖尿病致AD的治疗作用及机制

糖尿病与AD有显著相关性, 由此推测, 抗糖尿病药物或许对AD有一定的治疗作用。目前认为, 多种抗糖尿病药物, 包括胰岛素和胰岛素类似物、二甲双胍、噻唑烷二酮类化合物、GLP-1或其类似物等, 对AD均有不同程度的治疗作用[9]。

有证据表明, 在大鼠脑室注射STZ可致认知功能障碍, 注射长效胰岛素类似物到大鼠第三脑室, 可减少GSK-3β及Tau磷酸化, 进而改善STZ致糖尿病大鼠的空间记忆能力和认知功能[44]。对25名AD和轻度

认知障碍(mild cognitive impairment, MCI)受试者连续21天鼻内注射胰岛素后, 发现其注意力和言语记忆均明显得到改善[45]。而单侧鼻内注射胰岛素可能对*ApoEε4*阴性基因型AD患者认知功能的改善疗效更明显, 而对阳性AD患者效果则不甚显著[46]。因此, 胰岛素或其类似物对AD可能有良好的疗效, 但其具体治疗机制有待探究。

目前临床中最常用的抗糖尿病口服药是二甲双胍。二甲双胍治疗可改善神经元胰岛素抵抗, 降低AD患病风险, 改善记忆障碍[47]。研究发现, db/db小鼠注射二甲双胍, 可降低脑Tau磷酸化和Aβ沉积, 改善AD脑认知功能受损。二甲双胍治疗还可激活db/db小鼠脑氧化损伤诱使的神经元糖代谢中谷氨酰胺合成酶和甘油醛-3-磷酸脱氢酶的活性, 提高突触传递作用, 降低Tau蛋白磷酸化水平, 改善认知功能, 但并不能改善db/db小鼠空间学习障碍[48]。其次, 中晚期二甲双胍治疗亦可通过激活胰岛素信号通路中失活的转录因子NF-κB(nuclear factor-κB), 减少ROS生成量, 并降低脑促炎因子水平, 从而增强海马自噬能力[49]。二甲双胍亦能通过降低衰老合并糖尿病小鼠脑海马IRS1磷酸化水平, 改善海马神经发生和记忆力下降[50]。此外, 曹月盈等[51]观察到, 二甲双胍联合小檗碱给药可使db/db小鼠血清IL-6、IL-1β、TNF-α、NLRP3水平降低, 进而改善氧化应激和炎症反应, 同时, 其亦可提高海马区GSH水平、降低胆碱酯酶(cholinesterase, ChE)活性, 从而改善认知功能障碍。但长期服用二甲双胍会造成VitB12缺乏, 削弱AD患者神经系统的保护作用。因此, 二甲双胍对AD的治疗作用和机制仍需深入探讨。

噻唑烷二酮类化合物是过氧化物酶体增殖物激活受体γ(peroxisome proliferator activated receptor gamma, PPARγ)激动剂, 在糖尿病治疗中主要通过增加胰岛素增敏作用来降低血糖水平。而作为PPARγ的一种激动剂, 吡格列酮治疗可减少STZ致糖尿病小鼠脑部Aβ斑块沉积, 减弱神经炎症, 改善记忆缺陷[52]。罗格列酮是另一种PPARγ激动剂, 6个月罗格列酮治疗能降低AD患者血浆Aβ水平, 改善其延迟回忆和选择性注意, 最终改善认知能力[53], 但噻唑烷二酮类药物治疗可能导致水肿加重和充血性心力衰竭, 且二甲双胍和罗格列酮联用可导致糖尿病患者血清脂联素水平升高[54] , 因此, 噻唑烷二酮类药物对AD的治疗作用、机制及潜在风险问题仍需进一步探究。

目前证实, GLP-1或其类似物可缓解AD患者脑胰岛素抵抗, 并对突触发生、神经发生和细胞修复发挥有益作用; 最重要的是, 其还可减轻慢性炎症, 减少Aβ沉积和Tau蛋白磷酸化, 改善认知功能障碍, 故有望成为AD治疗的新策略[55]。利拉鲁肽是GLP-1长效类似药, 可透过血脑屏障, 对脑健康起神经保护作用。CHEN等[56]发现, 利拉鲁肽可改善*APP*/*PS1*/*Tau*转基因小鼠的空间学习和记忆能力, 减少Tau过度磷酸化, 抑制神经元变性, 延缓神经退行性病变。利格列汀作为DPP-4抑制剂, 亦可被用于糖尿病致AD认知功能障碍的治疗。3xTg-AD小鼠持续口服利格列汀8周, 可显著提高其大脑肠促胰素水平, 并可减少Aβ沉淀, 降低TNF-α、IL-1β水平, 维持神经元活性[57]。这说明, GLP-1或其类似药对AD具有重要治疗作用。

由此可知, 胰岛素和胰岛素类似物、二甲双胍、噻唑烷二酮类化合物、GLP-1或其类似物等抗糖尿病药物对AD治疗均有重要的应用前景, 但其治疗效用、机制及潜在风险问题仍需深入探究(表1)。

3 糖尿病致AD的运动干预作用及机制

3.1 运动减轻神经炎症状态

糖尿病脑胰岛素抵抗可使一些炎性因子, 如IL-6、IL-1β、IL-18、TNF-α和CRP等水平发生变化, 进而影响脑认知功能。中等强度训练可降低STZ致糖尿病大鼠海马中IL-1β、TNF-α水平, 缓解神经炎症, 改善脑细胞凋亡和认知功能障碍[58]。另外, 长期跑台训练可抑制db/db小鼠脑部小胶质细胞炎性反应, 降低海马等区域TNF-α、CRP等炎性指标水平, 缓解神经炎症所致海马依赖性记忆降低, 改善突触可塑性, 从而有效地保护神经元细胞[59]。而有氧和抗阻联合运动亦可抑制糖尿病模型海马IRS-1磷酸化, 下调CRP和TNF-α水平, 提高脂联素水平, 进而改善氧化应激和脑胰岛素信号障碍, 逆转神经炎症诱导的小鼠认知功能障碍[61]。这表明, 规律性运动可缓解糖尿病脑炎症状态, 降低AD发生风险。

肥胖是2型糖尿病的主要诱因, 肥胖所致炎症可加重代谢紊乱, 并对老年人认知功能有严重损害作用。高脂诱导的肥胖小鼠血浆IL-1β、IL-6、TNF-α水平均上升, 且衰老可加速其血脑屏障破坏和小胶质细胞活化, 导致海马CA3区长时程增强(long term

表1 部分抗糖尿病药物对AD的治疗作用

Table 1 The therapeutic effect of some antidiabetic drugs on AD

药物 Medicine	模型 Model	干预作用 Intervention effect	参考文献 References
Insulin analogue	Intraventricular STZ-induced Wistar rat model	Decrease Aβ expression; restore hippocampal neuron density; PI3K-Akt system signal activation; improve cognitive impairment	[44]
Intranasal insulin therapy	Intranasally administered patients with early AD, MCI, and normal subjects	Improve CNS insulin signaling disorders; regulate plasma Aβ levels; improve selective attention and information memory	[45]
Insulin	Whether the *ApoEε4* allele is homozygous in patients with AD and most intranasally administered subjects	After intranasal insulin administration, cognitive level and verbal memory of AD patients with *ApoEε4* negative gene are improved, while AD patients with *ApoEε4* positive gene have no improvement	[46]
Metformin	Male DB/DB mouse model	Decrease the level of Ser396 phosphorylated Tau protein induced by hippocampus JNK activation and improve impaired cognitive function	[48]
Metformin	Mouse model of senile diabetes	Inhibition of chronic glial cell activation and increased phosphorylation of AMPK/aPKC/IRS1 serine residues in hippocampus of middle-aged diabetic mice improve hippocampal neurogenesis and spatial memory	[50]
Pioglitazone	APP/PS1 mouse model	Decrease expression of microglia activator M1; decrease Aβ precipitation; improve cognition and memory	[52]
Lige column	3XTG-AD mice	Decrease TNF-α and IL-1β levels; decrease Aβ precipitation and Tau phosphorylation; maintain neuronal activity	[57]

potentiation, LTP)受损, 使神经炎症加重, 进而损伤认知功能[62]。而MEHTA等[63]发现, 6周跑台运动可上调高脂膳食2型糖尿病大鼠海马GSH、IL-1β、TNF-α、MCP-1等神经炎症标志物水平, 抑制糖尿病大脑炎症导致的认知水平下降。8周跑台运动可促使STZ致糖尿病大鼠海马炎症因子TNF-α水平下降, 海马CA1、CA3及DG区NGF表达能力增强, 进而改善其学习记忆能力[64]。与此同时, LI等[65]研究发现, 4周有氧运动可促使高脂联合STZ致糖尿病大鼠海马突触可塑性相关蛋白表达上调, 并抑制海马NF-κB/NLRP3/IL-1β信号转导途径, 从而改善学习记忆功能。LIN等[66]研究游泳运动对*D*-半乳糖致衰老大鼠海马炎症的影响, 发现游泳运动可刺激IGF-1R/PI3K/Akt和AMPK/SIRT1/PGC-1α信号轴, 减少衰老大鼠海马凋亡并减轻炎症, 从而改善认知功能缺陷。提示, 运动可缓解衰老合并糖尿病所致的大脑炎症状态, 降低AD发生风险。

综上, 糖尿病脑胰岛素抵抗可加重神经炎症, 抑制神经元活性, 进而损伤脑认知功能。而规律性运动可改善糖尿病模型出现的由神经炎症引起的认知功能障碍, 进而降低AD发生风险。

3.2 运动改善氧化应激及线粒体功能障碍

糖尿病脑胰岛素抵抗可诱发脑细胞氧化应激和线粒体功能障碍, 导致认知功能损伤, 增加AD患病风险。而规律性运动对于维持脑健康有重要作用, 可改善氧化应激, 增强线粒体功能和脑可塑性, 改善认知功能, 降低AD患病风险[67]。

研究发现, 规律性抗阻运动可降低糖尿病大鼠海马半胱天冬酶3(caspase-3)、B淋巴细胞瘤-2(B-cell lymphoma-2, Bcl-2)和Bax(Bcl-2-associated X protein)凋亡蛋白水平, 增强抗氧化酶活性, 从而减轻氧化应激损伤, 改善认知功能[68]。另外, 长期耐力训练联合药物干预可降低STZ致糖尿病大鼠海马MDA、AST活性, 抑制ROS产生, 提高海马抗氧化能力, 减少氧化应激对神经元的损伤, 改善糖尿病脑认知功能障碍[69]。李峰等[70]证实, 8周有氧运动可促进肥胖大鼠前额叶PPARγ表达, 激活PI3K/Akt通路, 抑制Bax/Bcl-2和caspase-9表达, 增强线粒体功能, 减少神经细胞凋亡, 增加神经可塑性, 从而改善学习记忆能力。进一步研究发现, 8周游泳运动联合白藜芦醇干预可改善糖尿病大鼠海马神经细胞形态, 并减少Bax、caspase-3表达量, 上调Bcl-2表达, 降低海马细胞凋亡

率, 改善神经元活性, 抑制学习记忆能力下降和认知功能损害, 从而降低AD的患病风险[71]。同时, 有氧间歇运动可有效上调高脂诱导小鼠海马神经元中线粒体去乙酰化酶3(Sirtuin, SIRT3)表达, 提高超氧化物歧化酶(superoxide dismutase, SOD)和过氧化氢酶(catalase, CAT)等抗氧化酶活性, 减少ROS和MDA含量, 改善学习记忆能力[72]。另外, KURBAN等[73]研究发现, 3个月有氧运动可降低2型糖尿病患者血清氧化应激水平, 并改善大脑血脑屏障通透性, 降低炎症水平, 增强脑认知功能。同时, 规律性耐力运动亦可降低糖尿病大鼠海马CAT和GPx水平, 并维持海马线粒体DNA平衡, 提高脑抗氧化能力和线粒体功能, 改善AD相关的空间学习和认知功能, 从而延缓神经退行性变[74]。

综上, 规律性运动可通过改善氧化应激和线粒体功能障碍, 增强脑可塑性, 改善认知功能, 进而对糖尿病致AD的治疗产生积极效果。

3.3 运动改善内皮功能, 提高血管舒张性, 抑制脑血管功能障碍

运动可提高血流速度, 改变与血管内皮细胞相关的层流切应力, 并刺激内皮型一氧化氮合酶(endothelial niteic oxide synthase, eNOS)表达, 从而增加内皮细胞抗炎和抗氧化作用[75]。YANG等[76]将Wista大鼠置于跑步机连续训练12周, 发现运动可通过PI3K/NOS途径增强胰岛素/IGF-1诱导的血管舒张, 并改善大脑内皮细胞功能。此外, 中等强度持续运动可提高STZ致糖尿病大鼠脑血流量, 激活PI3K/Akt通路, 并刺激eNOS表达, 减少NO受损, 增强内皮依赖性和增强胰岛素血管功能[77]。WANG等[78]发现, 8周跑台运动可减轻db/db小鼠血管周围脂肪组织炎症和氧化应激, 改善内皮功能, 减少血管壁超氧化物和内皮细胞ROS的产生, 提高NO水平, 进而改善脑神经元活性。这提示, 运动能增强eNOS/NO信号, 进而改善脑血管内皮功能。

此外, 内皮功能障碍与血管性痴呆或AD的患病风险密切相关。糖尿病模型PI3K/Akt途径异常可诱导内皮eNOS磷酸化, 引发血管相关病理变化, ZHANG等[79]发现, 16周跑台运动可改善SHRSP大鼠血压, 促进eNOS表达, 并通过IGF-1/PI3K/Akt通路减轻血管相关病理改变, 从而减少AD发生。另外, 14个月抗阻训练对2型糖尿病患者内皮依赖性血管舒张有显著作用, 可改善血管内皮功能, 降低脑高血糖对认知功能的负面影响[80]。这提示, 运动可增强糖尿病患者血管内皮功能, 改善血管舒张。另有显示, 加强生活方式干预和运动训练可强化2型糖尿病患者对其血糖的有效控制, 改善认知功能表现, 降低AD的患病风险[81]。同时, 饮食及规律性运动亦可减少脑ROS产生量, 提高内皮NO利用率, 进而改善血管稳态, 预防血管性痴呆[82]。

综上, 运动可改善内皮功能, 提高血管舒张性, 改善脑血管功能障碍, 促进脑血管健康, 进而降低糖尿病致血管性痴呆或AD的患病风险。

3.4 运动诱导神经发生, 改善记忆力

规律性运动可刺激脑营养因子表达, 进而诱导神经发生, 改善记忆力。BDNF作为脑衍生的神经营养因子, 以神经元活动依赖的方式产生, 可维持突触完整性, 抑制细胞凋亡, 维持中枢神经系统可塑性[83]。徐波等[84]发现, 8周跑台训练可增强SD大鼠学习记忆能力, 并与海马内*BDNF*基因表达量增加有关。此外, 高强度间歇训练可促进小鼠海马线粒体融合与生物发生, 抑制线粒体分裂, 进而增强线粒体功能, 并可促进海马BDNF表达, 改善认知功能障碍, 且其可能与乳酸信号增强有关[85]。提示, 运动可刺激脑营养因子BDNF表达, 进而促进神经发生, 改善记忆功能。TONOLI等[86]研究发现, 运动强度对BDNF具有剂量反应效应, 定期高强度间歇运动(high intensity interval training, HIIT)可提高糖尿病患者血清BDNF、IGF-1水平, 改善低血糖和慢性高血糖引起的认知能力下降。值得注意的是, 与久坐相比, 长期中等强度运动可改善糖尿病大鼠的空间记忆能力, 但并未使其海马BDNF水平发生变化[87]。这提示, 运动亦能以BDNF非依赖方式改善糖尿病大鼠空间记忆能力。另外, 规律性运动亦可增加脑部海马体积, 预防衰老所致的海马体退化, 维持神经元健康, 改善糖尿病致海马依赖性学习记忆功能障碍[88]。王燕军[89]发现, 8周跑台运动可激活STZ致糖尿病大鼠海马CA1、CA3区BDNF/酪氨酸受体激酶B(tyrosine kinase receptor, TrkB)信号通路并增强海马抗氧化能力, 改善STZ诱导的海马功能紊乱, 增强糖尿病大鼠学习记忆能力。此外, 跑台运动可增加STZ诱导的AD大鼠海马Bcl-2表达量, 降低casepase-3和Bax表达量, 改善空间学习能力受损, 抑制神经退行性病变所致的记忆损害[90]。

此外, 运动亦可激活糖尿病密切相关的IGF-1和血管内皮生长因子等营养因子, 进而刺激神经发生,

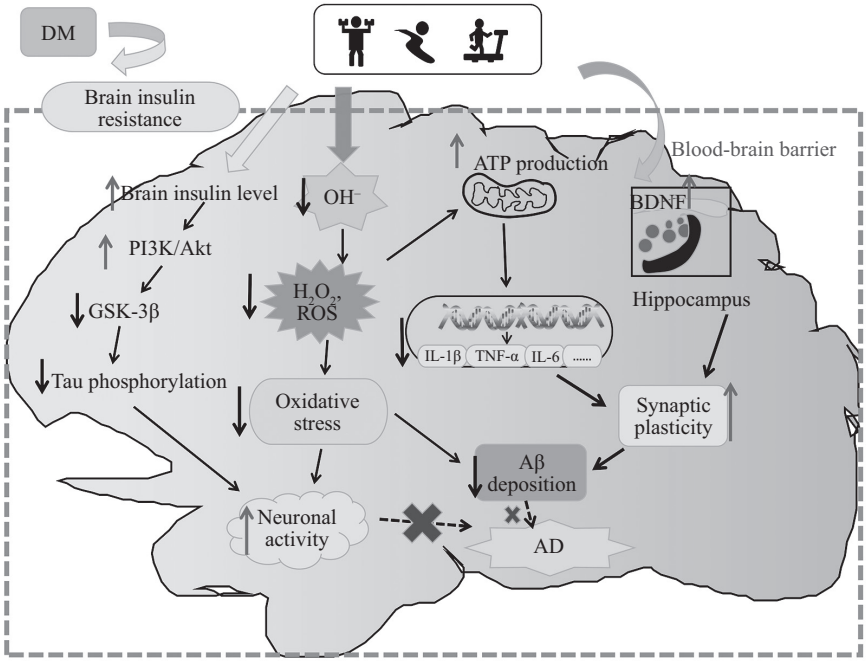

图1 运动对糖尿病致AD的干预机制示意图

Fig.1 Intervention mechanism of exercise on AD induced by diabetes

改善神经元功能, 降低AD发生风险[91]。研究发现, 有氧运动可活化糖尿病大鼠大脑胰岛素/IGF-1信号, 抑制小脑ERK1、ERK2等激酶活性, 进而上调Akt磷酸化水平, 降低Aβ沉积和Tau蛋白磷酸化水平, 改善认知功能[92]。此外, DIEGUES等[93]发现, 6周游泳运动可促进糖尿病大鼠中与胰岛素/IGF-1信号通路相关的海马蛋白IR、IGF-1R等因子表达, 降低海马Tau磷酸化和APP表达水平, 进而改善空间学习和记忆力。另有报道, 高强间歇运动可提高糖尿病患者血清BDNF和IGF-1水平, 有效改善其血糖紊乱, 进而提高认知水平, 降低AD的患病风险[94]。

因此, 运动可通过增加脑源性神经营养因子表达或促进生长因子表达, 刺激神经发生, 改善学习记忆能力, 从而降低AD的患病风险(图1)。

4 小结

流行病学研究提供了糖尿病患者AD发生风险增加的最直接证据, 因此, 找到可有效治疗或控制糖尿病致AD的方法迫在眉睫。本文通过对糖尿病致AD的病理机制及部分抗糖尿病药物对AD的改善作用进行归纳分析, 重点从以下几方面论述运动干预对糖尿病致AD的有益作用。(1) 运动干预可增强糖尿病模型大脑抗氧化酶活性, 降低ROS水平, 抑制氧化应激及线粒体功能障碍来维持神经元活性; (2) 运动干预可激活PI3K/NOS通路来促进血管舒张, 并提高内皮NO利用率, 从而维持脑血管稳态; (3) 运动亦可通过激活STZ致糖尿病大鼠海马BDNF/TrkB通路来纠正STZ诱导的海马功能紊乱, 并增加胰岛素/IGF-1信号通路相关的海马蛋白IR、IGF-1R等的表达量, 进而提高学习记忆能力, 降低AD发病风险。此外, 目前研究尚有一些亟需深入探讨的问题: (1) 多种抗糖尿病药物对AD的具体治疗作用、机制乃至潜在风险尚不明确, 运动联合药物干预能否产生叠加疗效与交互干扰作用亦未探明; (2) 内质网应激在糖尿病和AD发病中扮演重要角色。特异性降低内质网应激可抑制细胞凋亡, 改善糖尿病相关AD样病理变化, 增强学习记忆功能[95]。但运动能否通过调节内质网应激信号, 进而改善糖尿病致AD相关病理改变并未明晰; (3) 近期流行病学研究发现, 直立性低血压2型糖尿病患者具有较高的血浆神经源性外泌体Aβ42、T-Tau、P-T181-Tau水平, 且外泌体水平与从仰卧位到直立位的平均脑血流速度密切相关。据此, 外泌体能否在运动改善糖尿病致AD相关病理改变中发挥重要作用亦需明晰。总之, 深入剖析糖尿病致AD的潜在机制、抗糖尿病药物对AD的具体疗效机制及潜在风险、运动对糖尿病致AD的调节作用及机理, 可为糖尿病致AD的防治提供重要的科学指导。

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