糖尿病诱导认知功能障碍的分子机制及治疗策略

徐婧语[1] 蒋汀[2] 许可[1] 吴艳青[1]*

([1]温州大学, 生命与环境科学学院–生命科学研究院, 温州 325035; [2]温州医科大学, 药学院, 温州 325035)

摘要 糖尿病是一种以慢性高血糖和胰岛素抵抗为主要特征的代谢性疾病, 其患病人数日益剧增, 已引起人们的广泛关注。机体长期维持高血糖不仅会导致大血管、微血管受损, 还可引发中枢神经系统相关并发症, 显著增加认知功能障碍等神经退行性疾病的风险。该文对糖尿病诱导认知功能障碍的最新进展进行综述, 揭示自噬、内质网应激、神经炎症、血脑屏障损伤和氨基酸代谢紊乱组成的调控网络是糖尿病认知功能障碍的重要分子机制, 旨在为糖尿病认知功能障碍的治疗提供更为全面的理论基础和策略选择。

关键词 糖尿病认知功能障碍; 自噬; 内质网应激; 神经炎症; 血脑屏障; 氨基酸代谢

Molecular Mechanism and Treatment Strategy for Diabetes-Associated Cognitive Decline

XU Jingyu[1], JIANG Ting[2], XU Ke[1], WU Yanqing[1]*

([1]*The Institute of Life Sciences, College of Life and Environmental Sciences, Wenzhou University, Wenzhou 325035, China*; [2]*School of Pharmaceutical Science, Wenzhou Medical University, Wenzhou 325035, China*)

Abstract Diabetes is a kind of metabolic disease characterized by chronic hyperglycemia and insulin resistance. With the rapidly increasing characterized of diabetics, diabetes has attracted extensive attention. Chornic hyperglycemia not only leads to damage of the large vessels and microvessels, but also induces CNS (central nervous system)-related complications, significantly increases the risks of neurodegenerative diseases, such as cognitive decline. This review introduces the research progress of DACD (diabetes-associated-cognitive decline) and reveals that the regulatory network composed of autophagy, ER (endoplasmic reticulum) stress, neuroinflammation, BBB (blood brain barrier) damage and amino acid metabolism disorder are important regulatory mechanisms underlying DACD. This review is aimed to provide a more comprehensive theoretical basis and strategy choice for the treatment of DACD.

Keywords diabetes-associated cognitive decline; autophagy; endoplasmic reticulum stress; neuroinflammation; blood brain barrier; amino acid metabolism

目前, 糖尿病对中枢神经系统(central nervous system, CNS)的影响备受关注。越来越多的研究证实, 糖尿病可引起中枢神经系统损伤, 造成脑组织结构和功能改变。早在1922年, MONTE等[1]首次报道了糖尿病影响认知功能的现象。1965年, RESKE-NIELSEN[2]提出“糖尿病脑病(diabetic encephalopa-

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*通讯作者。Tel: 0577-86591683, E-mail: yqwu220946@yeah.net

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*Corresponding author. Tel: +86-577-86591683, E-mail: yqwu220946@yeah.net

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thy)”概念——由糖尿病引起的认知障碍和大脑神经生理及结构的改变, 表现为记忆功能减退, 学习能力下降, 语言、理解和判断等能力障碍, 还伴有精神性疾患等慢性脑病特征。核磁共振成像显示, 2型糖尿病(type 2 diabetes, T2D)患者有海马及杏仁核萎缩现象, 罹患阿尔茨海默病(Alzheimer’s disease, AD)风险是正常人群的2~3倍[3]。在尸检中发现, 胰岛素受体分布的脑区, 比如海马和部分大脑皮层, 可观察到β-淀粉样蛋白(β-amyloid, Aβ)沉积、Tau蛋白过度磷酸化、神经元丢失和乙酰胆碱合成障碍等与AD相似的进行性神经元退行性改变[4]。我们课题组[5]前期研究也发现, 糖尿病显著降低小鼠的空间学习和记忆能力; Aβ蛋白沉淀富集于前额皮质(prefrontal cortex, PFC)区; 脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)和微管结合蛋白2(microtubule associated protein 2, MAP2)在海马中表达水平下调; 神经元凋亡水平显著增加, 这些都是AD等神经退行性疾病的特点。糖尿病可显著诱导小鼠认知功能障碍, 但是糖尿病诱导的认知功能障碍(diabetes-associated cognitive decline, DACD)的相关机制还没有完全阐明。本文将对DACD潜在分子机制研究的最新进展进行综述, 旨在为寻找安全有效的治疗药物提供更为全面的理论基础。

1 DACD的分子调控机制

1.1 自噬

自噬是一种依赖于溶酶体功能的细胞分解代谢机制。它参与细胞器的周转, 降解在应激条件下受损的蛋白质和细胞器, 以满足细胞本身的代谢需要和某些细胞器的更新。在生理和病理条件下, 自噬可维持中枢神经系统的细胞内稳态[6]。它与许多神经退行性疾病息息有关[7], 包括AD[8]、帕金森病(Parkinson’s disease, PD)[9]、肌萎缩侧索硬化(amyotrophic lateral sclerosis, ALS)[10]和亨廷顿病[11]。越来越多的证据表明, 自噬有助于清除脑中累积的细胞毒性蛋白, 从而发挥其神经保护作用[12]。已有研究发现, 自噬体大量堆积于AD患者脑中, 而在正常人大脑中自噬体含量很低[13]。自噬参与调控细胞中Aβ蛋白的产生、清除及其向细胞外转运等过程[14-15]。自噬的缺失显著诱导细胞中Aβ蛋白的沉积[16]。另有研究发现, 大鼠被剥夺睡眠可介导自噬水平调控其所诱导的认知功能障碍[17]。我们前期的研究也发现, 成纤维细胞生长因子1(fibroblast growth factor 1, FGF1)可调控细胞自噬水平, 缓解PD的发生发展[18]。

以上研究表明, 自噬是神经退行性病变中的重要调控机制, 其在糖尿病诱导的神经系统性疾病中也发挥重要作用。CABERLOTTO课题组[19]用系统生物学方法证实, 自噬是AD和T2D的共同病理生理学机制, 并强调自噬是AD和T2D这两种高度共病疾病中的中枢障碍调节途径, 可识别、调控疾病病理生理学的特定基因, 而这些基因可能成为治疗干预DACD的新靶点。KONG课题组[20]用胰高血糖素样肽-1类似物利拉鲁肽(liraglutide)治疗DACD时发现, 利拉鲁肽可以通过AMP激活的蛋白激酶(AMP-activated protein kinase, AMPK)/哺乳动物雷帕霉素靶标(mammalian target of Rapamycin, mTOR)途径促进自噬, 对糖尿病引起的海马神经元损伤和认知损伤具有神经保护作用。本课题组[5]前期研究也发现, 糖尿病显著诱导大脑海马组织中神经元的自噬水平, 从而抑制神经元的凋亡水平, 保护神经元, 缓解认知功能障碍。此外有研究表明, 3-甲基腺嘌呤(3-methyladenine, 3-MA)抑制自噬, 会进一步促进链脲佐菌素诱导的DACD进程, 并加重其焦虑行为; 对长链非编码RNA PVT1(plasmacytoma variant translocation 1)表达的深入分析发现, 激活PVT1介导的自噬可以保护海马神经元, 改善糖尿病患者的认知障碍[21]。由上可知, 自噬是DACD疾病发生发展的重要调控机制。

1.2 内质网应激

内质网(endoplasmic reticulum, ER)是细胞内具有多种生理功能的细胞器, 它负责脂质和蛋白质的合成、折叠和加工, 以及细胞内钙的储存和运输。细胞外或细胞内因素(如钙紊乱、未折叠或错误折叠蛋白的积累或缺氧等)扰乱内质网内部稳态后可激活ER应激和未折叠蛋白反应(unfolded protein response, UPR), 从而引发下游一系列反应。UPR是维持ER稳态的一种保护机制[22], 可以激活一系列信号蛋白以恢复细胞内稳态。UPR是由3个跨膜感受蛋白介导的通路启动的, 分别是蛋白激酶样内质网激酶(protein kinase RNA like ER kinase, PERK)、肌醇需求酶1α(inositol-requiring enzyme 1α, IRE1α)和活化转录因子6(activating transcription factor 6, ATF6)。在长时间和强烈的ER应激条件下, UPR介导的适应性反应不足以恢复正常的细胞功能, 就会激活细胞凋亡信号

表1 ER应激在认知功能障碍中的作用(根据参考文献[30]修改)

Table 1 Effect of ER stress on cognitive decline (modified with reference [30])

疾病 Diseases	ER应激相关分子 Responsible molecules in ER stress	参考文献 References
Alzheimer's disease	PERK	[31]
	eIF2α	[32-34]
Traumatic brain injury	IRE1α and PERK	[35]
	CHOP	[36-37]
	PERK	[38]
	GADD34	[39]

途径。

在神经元中, ER主要集中在轴突、树突和树突棘中。研究表明, ER应激与认知功能障碍息息相关, 是神经退行性疾病发生发展的重要调控机制(表1)。有研究发现, 抑制PERK活性或者表达水平可下调真核起始因子2α(eukaryotic initiation factor 2α, eIF2α)的磷酸化水平, 从而有效缓解朊病毒疾病导致的神经退行性病变[23]。PERK也参与调节椎体神经元中的G蛋白偶联的Ca^{2+}动力学, 影响Ca^{2+}平衡, 从而影响神经元功能[24]。另一项研究发现, 脑创伤后, PERK不仅可通过环磷腺苷效应元件结合蛋白(cAMP-response element binding protein, CREB)调控BDNF的表达, 而且可以促进突触后致密蛋白95(postsynaptic dense protein 95, PSD95)磷酸化, 影响树突棘的稳定, 介导记忆能力下降, 并且该过程独立于eIF2α分子[25]。ER应激也是糖尿病及其并发症发生发展的重要分子机制[26-27]。研究表明, ER应激及其介导的凋亡途径参与调控糖尿病诱导的海马神经元丢失、突触结构改变, 从而引起认知功能下降[28]。我们当前的研究发现, 糖尿病可以协同调控PERK信号通路和磷酸肌醇3激酶/蛋白激酶B(phosphatidylinositol 3 kinase/protein kinase B, PI3K/Akt)信号通路, 从而抑制CREB活性, 下调BDNF表达, 促进认知功能降低[29]。

1.3 神经炎症

慢性炎症在CNS疾病发病过程中具有重要作用[40]。在正常的生理条件下, 神经胶质细胞的数量会随着神经损伤和修复有所变化, 并发挥其相应的生物学功能。受到外界因素刺激时, 神经胶质细胞进入激活状态并大量增殖, 这一过程被称为启动[41]。启动后的神经胶质细胞容易受到继发性外界刺激因素的影响, 触发炎症反应。炎症反应可以进一步导致神经损伤, 在慢性炎症中这种情况更为明显[42]。

T2D被认为是一种慢性炎症性疾病[43]。T2D会引发M1型巨噬细胞增加炎性细胞因子的分泌, 如肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)和白细胞介素-1β(interleukin-1β, IL-1β)等, 并激活NLRP3炎症小体[43]。在大脑中, T2D可激活M1样神经胶质细胞, 加中枢神经性炎症的易感性。一般情况下, 炎症反应可作为一种保护机制, 改善脑神经细胞中有毒物质产生的影响, 但持续的高血糖可引发核因子κB(nuclear factor kappa-B, NF-κB)通路的激活和促炎因子的释放[44], 从而导致促炎和抗炎网络之间的不平衡, 使得活性氧增加, 并无限制地形成炎症介质, 从而影响线粒体功能, 导致神经元损伤[45]。由上可知, 糖尿病可显著诱导神经炎症, 是认知功能障碍的重要机制。此外, 胰淀素也可以通过增加IL-1β合成, 进入并损伤神经细胞[46]。T2D患者脑脊液中Tau蛋白的磷酸化水平明显升高。神经炎症促进Tau的过度磷酸化以及炎性因子IL-1β的增加[47], 可以推测T2D导致的神经炎症是Tau过度磷酸化的重要分子机制。由此可见, 糖尿病相关的神经炎症会加重神经退行性疾病, 是认知功能障碍的重要调控机制。

1.4 血脑屏障损伤

血脑屏障(blood brain barrier, BBB)是由高度分化的脑微血管内皮细胞(brain microvascular endothelial cell, BMVEC)组成的, 由紧密连接(tight junction, TJ)蛋白连接, 具有吞噬活性低和独特的表达转运蛋白等特点。BMVEC的功能由包围脑内皮细胞的周细胞支持[48]。BBB是保护CNS独特的内环境, 限制有毒物质穿过的有效屏障。目前的研究证据表明, 糖尿病会引起TJ蛋白(ZO-1、occludin和claudin-5)的丢失，导致BBB的通透性增加[49]。更为重要的是, BBB完整性的破坏先于认知能力下降和神经退化[50]。因此, BBB的破坏可以作为DACD的一项早期指标。

近期在DM动物模型中发现, BBB损伤诱导的记忆缺陷和神经炎症息息相关[51]。炎症反应是介导BBB损伤的重要机制[49], TNF-α和IL-1β等炎症因子可降解TJ蛋白并调节其细胞转位, 从而抑制这些细胞因子, 保护BMVEC的紧密连接[52]。高糖会上调多种炎性细胞因子的表达, 包括TNF-α、IL-1β和白细胞介素-6(interleukin-6, IL-6)。糖尿病可诱导TNF-α和IL-6水平升高, 触发脑内TJ蛋白的降解、炎症和白细胞浸润的加剧, 促进BBB的破坏, 最终导致认知功能障碍[53]。抗炎药物普罗布考(probucol)可以有效保护BBB的完整性来预防胰岛素抵抗所导致的认知功能下降, 对脑血管内皮细胞的流式细胞术分析显示, 普罗布考的BBB保护作用主要是通过恢复TJ蛋白(occludin-1和ZO-1)的表达得以实现的[54]。

此外, 糖尿病引起的BBB功能障碍可能涉及包括基质金属蛋白酶在内的各种分子的相互作用。研究发现, 高血糖引起的BBB通透性增加与基质金属蛋白酶-9(matrix metalloproteinase-9, MMP-9)和基质金属蛋白酶组织抑制因子的表达增加有关[55]。同时, 糖尿病引起的氧化应激也会影响BBB的完整性[56]。摄入高脂饮食之后, 大脑中脂质过氧化物和蛋白质过氧化物的标志物水平都显著上升[57]。因此, 预防糖尿病引起的BBB损伤可能是降低DACD风险的一种新途径。

1.5 星形胶质细胞

星形胶质细胞是中枢神经系统中最丰富的细胞。在大脑中, 星形胶质细胞的数量超过神经元。星形胶质细胞的功能与正常的神经元活动密切相关, 参与突触前神经元的神经递质释放, 突触前神经元接收和整合来自多个相邻神经元突触的神经信号[58]。越来越多的证据表明, 星形胶质细胞在记忆和认知功能中发挥重要作用[59]。大脑需要大量的能量来维持其正常的生理功能。其中, 星形胶质细胞和神经元之间的相互作用在大脑能量代谢中发挥着核心作用[58]。因此, 神经元–星形胶质细胞之间的代谢相互作用出现紊乱时, 就会影响大脑的功能, 促进神经退行性疾病的发生。目前, ZHENG等[60]通过核磁共振(nuclear magnetic resonance, NMR)检查发现, T2D认知功能下降可能归因于神经元–星形胶质细胞之间的代谢失衡和糖异生的增加。此外, 有研究表明, 修复受损的星形胶质细胞可以改善链脲佐菌素(streptozocin, STZ)诱导的糖尿病小鼠认知障碍[61]。在糖尿病小鼠的海马组织中可以观察到星形胶质细胞的激活增强了炎症反应, 诱导神经元凋亡, 导致认知功能下调; 而且, 糖尿病相关的细胞凋亡会进一步激活海马体中的星形胶质细胞和小胶质细胞, 加重认知障碍相关的脑部疾病[62]。以上研究提示, 进一步研究星形胶质细胞在DACD中发挥的分子调控作用, 可以为临床上治疗DACD提供理论基础。

1.6 氨基酸代谢

葡萄糖代谢是机体经典的催化过程。机体中, 葡萄糖代谢、脂质代谢和氨基酸代谢三大通路相互关联, 密不可分。氨基酸在线粒体中通过谷氨酰胺(glutamine, Gln)分解途径代谢, 将Gln转变为α-酮戊二酸(α-ketoglutarate, α-KG), 其中α-KG是三羧酸循环(tricarboxylic acid cycle, TCA)的中间代谢产物[60]。谷氨酸–谷氨酰胺循环的稳态参与了神经元和星形胶质细胞的信息交流, Gln是脑部中连接神经递质代谢和TCA的重要介质。作为哺乳动物脑部的主要能量来源, 长期的高糖环境势必导致三大代谢通路发生紊乱[63], 破坏谷氨酸–谷氨酰胺循环的稳态, 影响脑部正常生理功能的发挥[64]。目前, 运用NMR技术已证实, DACD小鼠海马组织中的葡萄糖代谢和谷氨酸–谷氨酰胺循环稳态受到影响, Gln表达水平显著上调[60]。而且, Gln水平可负调控mTORC1水平, 从而促进细胞自噬[65]。

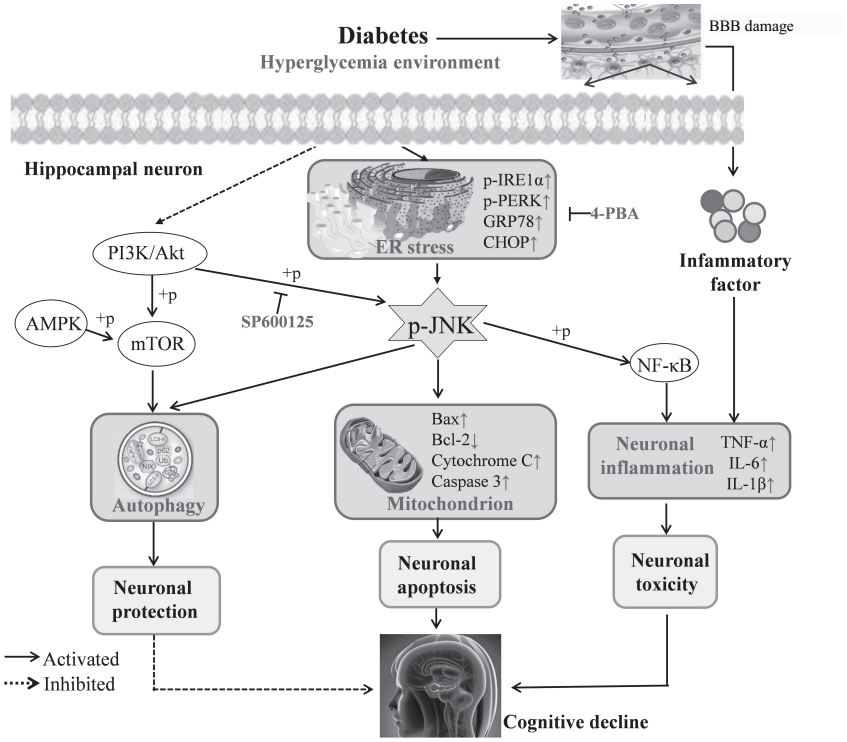
由上可知, 氨基酸代谢紊乱是DACD的重要分子机制。氨基酸代谢可以作为一种早期生物标志物, 对DACD的临床诊断提供一定帮助。SONG课题组[66]用尿液代谢组学发现, 七种代谢物可作为DACD的早期生物标志物, 包括谷胱甘肽与色氨酸的代谢。5-羟基-*L*-色氨酸已被证明可有效治疗抑郁症, 它可通过BBB从而有效增加CNS中5-羟色胺的合成[67]。研究发现, 与正常组相比, 5-羟基-*L*-色氨酸在DACD患者尿液中的含量逐渐下降[67]。焦谷氨酸是*L*-谷氨酸的环化衍生物, 它可以由谷氨酸、谷氨酰胺和γ-谷氨酰化肽在非酶作用下形成, 或者通过γ-谷氨酰环转移酶与*L*-氨基酸反应生成。研究发现, 获得性焦谷氨酸的缺乏以及谷胱甘肽耗竭在临床上通常会导致中度到重度脑病[68]。另一项研究发现, 在伴有轻度认知障碍的糖尿病患者血浆中, 同型半胱氨酸(homocysteine, Hcy)水平升高, Hcy具有神经毒性, 可诱导神经元DNA损伤和凋亡[69]。同时, Hcy升高会诱导氧化应激, 促进Tau蛋白磷酸化[70], 损害BBB的完

整性, 导致有害分子渗漏到CNS环境中, 从而导致细胞损伤和认知功能障碍[71]。因此, 将这些氨基酸作为DACD的早期潜在生物标志物可能对糖尿病患者的早期神经退行性的病理改变和分子机制提供新的认识。

2 DACD分子调控机制之间的关系

机体是一个复杂的综合体。DACD的分子机制并不是独立存在的, 而是互相影响, 互相调控, 形成一个复杂的调控网络。大量的研究证实, 胰岛素抵抗[72]、胰岛素信号传导缺陷[73]以及晚期糖基化终末产物(advanced glycation end products, AGEs)[74]等是DACD的重要因素, 可抑制PI3K/Akt信号通路, 影响自噬和炎症等生理过程。ER应激是引发炎症的重要原因[75]。ER应激诱导的神经炎症和凋亡在DACD的发生发展中起关键作用[76], 长期的高糖环境显著激活ER应激, 触发c-Jun氨基末端激酶(c-Jun N-terminal kinase, JNK)诱导的NF-κB炎症通路。进一步在脑损伤模型研究中发现, JNK信号通路激活可抑制胰岛素信号转导, 促进认知功能下降[75]。此外, ER应激也是触发自噬的重要因素, 糖尿病引发的自噬与ER应激息息相关[22]。KONG课题组[77]的研究发现, 糖尿病诱导的自噬被ER应激抑制剂4-苯基丁酸(4-phenylbutyric acid, 4-PBA)所阻断。我们前期的研究也发现, 6羟多巴胺可诱导ER应激, 抑制Tribbles同源蛋白3(Tribbles homologous protein 3, TRB3)活性, 从而调控细胞自噬, 参与调控PD的发生发展[18]。由此可见, ER应激、神经炎症和自噬等分子机制在DACD发生发展中互相影响, 协同调控(图1)。

DACD的发生发展过程中, BBB损伤与神经炎症、星型胶质细胞活化息息相关。高糖环境下, 炎症反应是介导BBB损伤的重要机制[49], TNF-α和IL-1β等炎症因子可降解TJ蛋白并调节其细胞转位, 促进BBB损伤[52]。BBB损伤反过来进一步加重炎症反应。在高糖环境下, BBB受损后, 血细胞(包括白细胞、红细胞和中性粒细胞等)、巨噬细胞和炎症因子等迅速释放进入海马组织[53], 诱导炎症反应(图2)。在妊娠期糖尿病相关的认知障碍研究中发现, 患者体

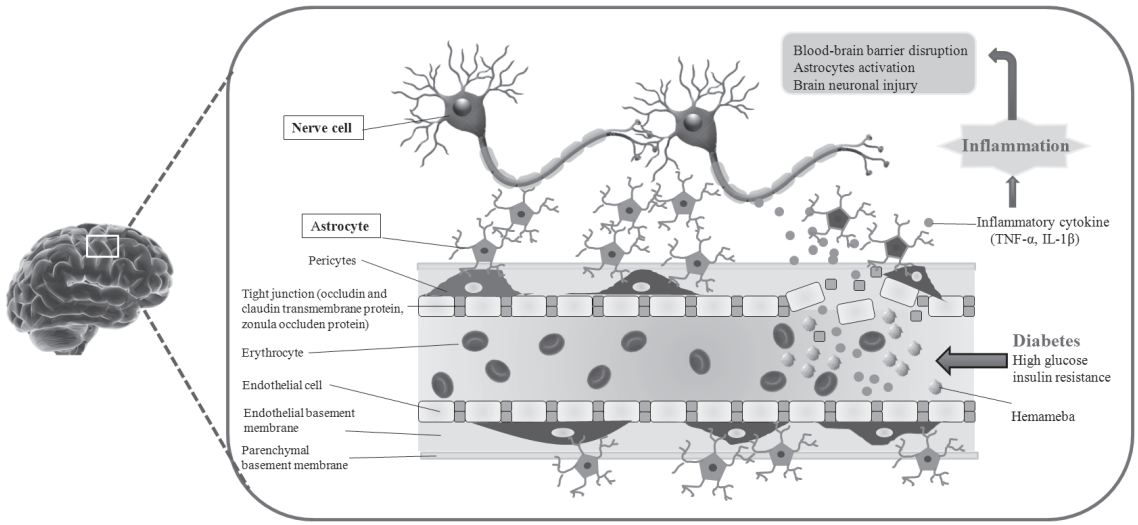


糖尿病通过调控自噬、ER应激、神经炎症和BBB损伤等分子调控机制, 最终诱导认知功能障碍。在该过程中, 自噬、ER应激、神经炎症和BBB损伤等分子机制并不是独立存在, 而是互相影响, 互相调控。PI3K: 磷酸肌醇3激酶; PKB: 蛋白激酶B; ER: 内质网; BBB: 血脑屏障。

Diabetes induces cognitive decline by regulating autophagy, ER stress, neuroinflammation and BBB damage. During this process, autophagy, ER stress, neuroinflammation and BBB damage do not exist independently. They can mutual regulate each other. PI3K: phosphoinositol 3 kinase; PKB: protein kinase B (Akt); ER: endoplasmic reticulum; BBB: blood brain barrier.

图1 糖尿病诱导认知功能障碍的分子机制调控网络

Fig.1 A network of molecular mechanisms regulating diabetes-associated cognitive decline



糖尿病诱导炎症因子增加, 炎症因子大量增加促进BBB损伤。BBB损伤后, 血细胞、巨噬细胞和炎症因子迅速释放进入组织, 加重神经炎症, 诱导神经损伤。

Diabetes induces increases of inflammatory factors, which contribute to BBB damage. Once BBB damage, it promotes the entry of blood cells, macrophages and inflammatory factors into the tissue, aggravates neuroinflammation, and subsequently induces nerve damage.

图2 神经炎症、BBB损伤和星型胶质细胞间的互相调控作用

Fig.2 The mutual regulation of neuroinflammation, BBB damage and astrocytes

内高血糖可引起抗炎细胞因子下调, 促炎细胞因子上调, 激活小胶质细胞, 引起多种神经毒性介质的改变, 诱导BBB损伤[78]。BBB损伤后, 白细胞等进入中枢神经系统, 增加炎症反应, 进一步诱导细胞凋亡和血管破裂, 促进胶质细胞损伤和神经细胞凋亡, 从而影响母体的认知功能, 并对其后代的认知功能产生更为严重的影响[79]。此外, 星形胶质细胞的末端足部与BBB相连接, BBB通透性的增加会激活星形胶质细胞[50], 造成神经损伤; 而星形胶质细胞的过度激活又会诱导并加重炎症反应[62], 就会进一步破坏BBB, 加重神经元损伤。总而言之, 炎症、BBB损伤和星形胶质细胞在DACD发生发展过程中并不是独立存在的, 而是相互影响, 协同调控DACD。

星形胶质细胞和氨基酸代谢之间也有着密不可分的联系。星形胶质细胞富含Na^+依赖的谷氨酸转运体(主要是EAA T1/GLAST和EAA T2/GLT-1), 负责将细胞外的谷氨酸迅速从突触间隙中移除, 以维持脑内稳态和避免兴奋性毒性[80]。而且, 谷氨酰胺合成酶需要在星形胶质细胞内将谷氨酸转化为谷氨酰胺, 谷氨酰胺从星形胶质细胞输出后才能被谷氨酸能神经元捕获并重新转化为谷氨酸, 然后作用于新的突触[81]。

综上所述, 自噬、ER应激、神经炎症、BBB损伤和氨基酸代谢紊乱等分子机制在DACD发生发展中都发挥重要调控作用, 并且这些分子机制并不是独立存在的, 而是形成调控网络, 在DACD发生发展中互相调控, 互相影响。

3 糖尿病认知功能障碍相关治疗药物

随着DACD分子调控机制的进一步阐明, DACD相关治疗策略的研究也有一定进展。研究发现, 成纤维细胞生长因子(fibroblast growth factors, FGFs)、丁苯酞(butylphthalide, NBP)、胰高血糖素样肽1(Glucagon like peptide 1, GLP1)类似物及其受体激动剂等都是潜在的DACD治疗药物。

FGFs家族是一类分泌蛋白, 可通过与FGF受体(FGF receptors, FGFRs)结合发挥其生理功能[82]。FGFs家族中有3个成员(FGF1、FGF15/19和FGF21)与新陈代谢调节有关[83]。肥胖或高血糖引起的代谢紊乱是导致轻度认知障碍、年龄相关性认知功能减退、血管性痴呆和AD的重要因素[84]。有研究提出, 重组人FGF21可以迅速逆转高糖诱导的代谢紊乱, 降低肥胖小鼠海马中M1极化的小胶质细胞/巨噬细胞活化, 减少促炎细胞因子表达, 并通过调节Akt/GSK-3β信号通路介导的神经炎症信号, 促进海马组织中的神经再生[85]。进一步研究发现, FGF21改善肥胖大鼠大脑线粒体功能, 降低氧化应激, 减少脑细胞凋亡和恢复海马突触可塑性, 从而预防认知功能下降[86]。SCARLETT课题组[87]发现, FGF1可以与FGFR结合并激活相关信号通路, 发挥更持久的降血糖功能。在大脑中,

FGF1是由神经元、星形胶质细胞和室管膜细胞合成的, 可增强学习和记忆功能[87]。SCARLETT课题组[87]将FGF1单次注射到侧脑室或第三脑室后发现, 糖尿病小鼠的血糖水平显著降低并趋于正常化, 并且高血糖引起的CNS回路失调也得到很好的改善。我们的研究进一步发现, FGF1可以协同调控PI3K/Akt和PERK信号通路, 保护神经元, 促进BDNF表达, 缓解DACD[29]。由以上研究可推测, 脑部FGFR可能是DACD药物研发的重要潜在靶点。

NBP(butylphthalide)是芹菜油的化学成分之一, 包括l-NBP、d-NBP和dl-NBP。NBP具有重建微循环[88]、保护线粒体功能[89]、抑制氧化应激[90]和抑制神经元凋亡[91]等一系列药理功能。NBP具有多靶点复杂性, 目前已被广泛应用于多种神经系统病变的治疗研究[92]。作为一种人工合成的神经保护药物, NBP是一种脂溶性物质, 可自由通过BBB[92]。研究发现, NBP可以激活钙/钙调蛋白依赖性蛋白激酶II(calcium/calmodulin-dependent protein kinase II, CaMKII)介导的长时程增强(long-term potentiation, LTP)[93], 增加*N*-甲基-*D*-天冬氨酸型谷氨酸受体2B亚型(*N*-methyl-*D*-aspartate-type glutamate receptor subtype 2B, NR2B)和α-氨基-3-羟基-5-甲基-4-异恶唑丙酸受体1亚型(α-amino-3-hydroxy-5-methyl-4-isoxazole-propionicaci-type glutamate receptors subtype 1, GluR1)的表达, 改善海马细胞超微结构和神经元的突触可塑性, 从而提高db/db小鼠的学习潜力和长期记忆能力, 缓解DACD。此外, NBP也可以改善氧化应激、炎症水平及凋亡的级联反应, 从而显著缓解T2D小鼠的认知功能[94]。由上可见, NBP有望成为临床上治疗DACD的新型药物。

胰高血糖素样肽-1(glucagon-like peptide-1, GLP-1)是肠上皮细胞分泌的一种内源性生长素, 通过增强胰岛素分泌来调节葡萄糖稳态。GLP-1在中枢神经系统中广泛表达, 可通过与GLP-1受体结合发挥多种生理作用[95]。目前, GLP-1类似物利拉鲁肽和艾塞那肽(exendin-4, Ex-4)是临床上用来治疗T2D的常规药物, 具有跨越BBB特性, 进入中枢神经系统发挥其相应功能[95]。有研究提出, 利拉鲁肽不仅可以缓解凋亡水平, 而且可激活大鼠海马组织中的AMPK和PI3K/Akt信号通路, 促进自噬, 从而缓解T2D诱导的学习和记忆损伤[96]。此外, 利拉鲁肽还可以改善小鼠海马突触可塑性, 抑制氧化应激, 从而改善T1D小鼠的认知功能[97]。已知, Ex-4可以介导PI3K/Akt信号通路影响海马组织中谷氨酸的摄取[98]。研究发现, Ex-4可以逆转糖尿病大鼠中谷氨酸能传递的损伤, 提高大鼠海马脑片中的谷氨酸摄取量和GluN1亚基含量, 从而在脑组织中起到保护作用[98]。进一步的研究发现, Ex-4通过上调BDNF和脑内脂素, 发挥抗炎、抗氧化、改善神经元存活和保护突触完整性的作用, 从而改善T2D大鼠的认知功能[99]。因此, GLP-1类似物及其受体激动剂也是临床上治疗糖尿病神经退行性疾病的潜在药物。

除了上述药物外, 吡格列酮、二甲双胍[100]和鸢尾素[101]等在缓解糖尿病诱导的中枢神经损伤中也有重要潜能。DACD相关的分子调控机制逐渐阐明将为DACD的新药研发提供更多的分子靶点, 从而帮助临床上治疗DACD患者。

4 结语与展望

随着糖尿病患病率的急剧上升, DACD受到了广泛的关注和探究。本文深入阐述了DACD潜在分子机制研究的最新进展, 阐明了自噬、ER应激、神经炎症、BBB损伤和氨基酸代谢紊乱等分子机制在DACD发生发展中都发挥重要调控作用, 并且这些分子机制并不独立存在, 而是形成调控网络, 在DACD发生发展中互相调控, 互相影响。目前, 随着对DACD分子机制的深入探究, 针对以上机制开展了一系列DACD治疗策略的探究。研究发现, GLP-1类似物及其受体激动剂、NBP、FGF1和FGF21都是非常有潜力的DACD治疗药物。但是, 机体是一个复杂的综合体, 当前的研究只是部分揭示了DACD的分子机制。因此, 仍需进一步深入研究DACD的分子机制, 为临床上治疗DACD提供更为全面的理论基础和分子靶点。

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