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【文献综述】

糖尿病视网膜病变神经血管损伤发病机制的研究进展

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【摘要】　糖尿病视网膜病变（diabetic retinopathy，DR）曾被认为是糖尿病微血管病变的并发症，如今已被广泛认为是神经血管单元（neurovascular unit，NVU）损伤引起的一类神经血管性疾病。研究表明，在出现临床可检测的微血管病变之前，视网膜神经损伤已经出现，并参与了微血管病变的进展。因此，微血管病变这一观点并没有揭示视网膜神经元、神经胶质细胞和血管间相互联系及影响的重要性。以NVU作为整体研究神经血管损伤及保护机制，寻找临床新的预防和干预DR的措施必定成为未来研究的热点。
【关键词】　糖尿病视网膜病变；神经血管单元；发病机制；微血管损伤；神经损伤
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糖尿病视网膜病变（diabetic retinopathy，DR）是糖尿病眼病中最严重的并发症，已成为许多发达国家致盲的主要原因[1-2]。在2.46亿糖尿病患者中，约三分之一有DR迹象，其中三分之一可能发展至威胁视力的严重程度（增生期视网膜病变或黄斑水肿）[3-4]。越来越多的研究表明，无论是在人类，还是实验动物的早期DR中，视网膜神经元与胶质细胞结构与功能的异常发生早于视网膜微血管病变[5-7]。本文就DR中神经血管单元（neurovascular unit，NVU）损伤的发病机制研究进展进行综述。

1　NVU

NVU主要由神经元、胶质细胞和血管细胞共同耦合构成，是调控视网膜正常生理活动的基本结构与功能单元，包括神经元（神经节细胞、无长突细胞、水平和双极细胞）、神经胶质（Müller细胞和星形胶质细胞）、血管细胞（内皮细胞和周细胞）、免疫细胞（小胶质细胞和巨噬细胞）、基底膜以及细胞外基质[8-9]。在NVU中，神经元是神经系统的最终效应器，通过调控血管活动接收营养物质和消除代谢废物。胶质细胞发挥协同血管作用，以满足神经元的代谢需求，消除代谢产物，传递神经递质，维持内环境稳态以及信号转导[10-11]。小胶质细胞作为免疫细胞，监测并清除功能衰退的细胞[12]。在神经血管耦合中，视网膜血管调节发生于血管微环境，神经元通过局部代谢产物进行自身调节，如谷氨酸、一氧化氮、氧气、腺苷和花生四烯酸代谢物等，调节血管舒张或收缩，以满足神经信号转导和传输能量需求[13-15]。神经元、胶质细胞、小胶质细胞以及血管细胞的相互协同作用，对维持正常视功能至关重要[16]。

2　糖尿病引起的NVU的损伤

DR以NVU损伤作为研究对象，为临床前期患者提供了新的诊疗思路。早期DR电镜可见Müller细胞活动增强、密度增多，其附近的基底膜增厚，并伸入Müller细胞间隙[17]。暗适应[18]、对比敏感度[19]和视网膜电图[20-21]功能检测也出现相应异常。在正常生理情况下，视网膜血管通过自身调节，在闪烁光刺激时会导致视网膜血管扩张，吸入体积分数100%的氧气时会导致血管收缩，而在早期DR模型中，相应刺激对于血管的调节却减弱。多项研究表明，糖尿病患者的视网膜血管舒张或收缩功能发生障碍[22-24]。这表明，在早期DR中，视网膜神经血管复合体的正常调节机制已受损，并非单纯的血管或神经组织受损导致。

3　神经血管损伤的分子机制

NVU中各组成细胞在DR中均有损伤。在DR中，兴奋性毒性代谢产物增多、氧化应激增加、神经营养因子合成减少和神经炎症的发生，最终导致神经元凋亡[25-27]。神经应激和细胞凋亡促使胶质细胞反应性活化增生，激活的胶质细胞和小胶质细胞吞噬凋亡细胞，清除细胞碎片和毒素，并分泌神经营养因子起神经保护作用[28-29]。然而，持续的神经胶质激活对视网膜血管和神经元却是有害的[30]。过度增生的胶质细胞持续分泌炎性细胞因子、细胞毒性分子和血管生长因子，使得微血管功能障碍和神经损伤不断加重[31]。由于神经元和胶质细胞之间的影响因素繁多并交错复杂，尚不清楚这两种病理因素中的哪一种（凋亡或神经胶质激活）最先出现，并起主导作用。但两种因素互为因果，久之造成恶性循环。NVU的渐进性损害最终导致临床中血-视网膜屏障破坏的特征，即微动脉囊、出血和黄斑水

肿等。

3.1 代谢紊乱 高血糖直接诱导多元醇途径激活、细胞氧化还原状态改变、三酰甘油的生成增加以及蛋白激酶C(protein kinase C,PKC)途径激活和晚期糖基化终末产物(advanced glycation end products,AGEs)生成,致使视网膜神经组织和微血管系统的异常。

醛糖还原酶(aldose reductase,AR)是多元醇途径的限速酶,在DR的发病机制中起重要作用。高血糖激活多元醇代谢途径,AR生成增多,积累的AR造成神经节细胞损伤,参与DR的发生[32]。临床和动物实验研究表明[33-34],AR抑制剂在保护神经节细胞中起至关重要的作用,可以抑制DR的发生和发展。

视网膜是一个低流量、高代谢的组织,极易受到氧化应激的影响。而氧化应激在高血糖和糖尿病微血管并发症之间起因果关系的作用。高血糖会刺激糖酵解和三羧酸循环通路的流量增加,造成NADH和FADH2过量产生,进入电子传递链后,产生过量的超氧自由基,从而破坏自由基的稳态平衡,最终导致氧化应激。线粒体接受过多的超氧自由基,导致蛋白质和脂质膜等多种细胞结构破坏,细胞膜完整性欠缺,造成细胞凋亡,微血管损害及视网膜屏障功能的破坏,最终导致DR的发生[35]。此外,氧化应激还会介导其他途径,如多元醇和PKC途径的激活、AGEs产生,从而使损伤恶化[36],最终对视网膜内皮和周细胞造成广泛损害,从而导致DR的进展。

PKC的激活诱导下调内皮素-1受体和上调血管内皮生长因子(vascular endothelial growth factor,VEGF)[37]。内皮素-1为强有力的血管收缩剂,可导致血流动力学改变。VEGF在细胞内信号传递中起重要作用,导致血管通透性改变,并促进内皮细胞增殖迁移和血管形成[38]。PKC的激活在血管的调节异常和视网膜新生血管中起一定作用。

AGEs可以通过还原糖和二羰基修饰蛋白质氨基化而生成,高血糖状态下,AGEs产生速度增快,异常积累于视网膜。一方面直接改变蛋白质、核酸、脂质的正常结构;另一方面激活多条信号转导通路,导致视网膜周细胞凋亡、内皮细胞功能障碍,增加了VEGF的分泌,进而诱导氧化应激和炎症反应[39-40],是参与DR发生、发展的主要机制。

谷氨酸是神经元之间传递信号的兴奋性神经递质。然而,中枢神经系统突触前谷氨酸水平过高会导致兴奋性毒性,并参与神经退行性疾病的发病,如帕金森症和阿尔茨海默病等。糖尿病则通过以下3种途径调节神经胶质细胞和神经元之间谷氨酸和谷氨酰胺的平衡[41-42]。首先,Müller细胞对谷氨酸的摄取减少,致细胞外谷氨酸增多;第二,高血糖致Müller细胞中谷氨酰胺合成酶的活性降低,阻碍了谷氨酸转化为谷氨酰胺的能力;第三,谷氨酸氧化成α-酮戊二酸的能力减弱。这些均导致了神经细胞中谷氨酸在细胞外积累,N-甲基-D-天冬氨酸受体表达增加,随后神经元过度去极化和Ca^{2+}超载,激活了Caspase依赖和非依赖性凋亡级联反应,最终诱导神经细胞凋亡[43]。生长激素抑制素(somatostatin,SST)即通过抑制视网膜神经元Ca^{2+}通道和激活K^{+}通道,减少谷氨酸的释放,发挥神经保护作用[44]。SST眼液在DR中具有预防和延缓神经血管损伤的作用已得到验证[45]。

3.2 反应性胶质增生 胶质细胞位于视网膜血管系统和神经元之间,在视网膜微环境组成的精细调控中起着关键作用[46]。高血糖使视网膜处于慢性炎症状态,持续激活Müller细胞、星形胶质细胞和小胶质细胞的活化增生,分泌炎症因子以及神经毒性因子增多、神经营养因子减少而导致神经元与微血管的损伤。

小胶质细胞在启动神经炎症反应中起关键作用[47]。小胶质细胞对外界刺激非常敏感,生理情况下起监视、稳定内环境的作用。高血糖使静息状态的小胶质细胞激活并开始分泌炎性介质[48],产生神经炎症,Müller细胞和星形胶质细胞随之激活并放大炎症反应[49],最终造成视网膜损伤。Zeng等[50]研究表明,阻断胶质细胞的活化可能是一种预防DR神经退行性变的策略,抑制小胶质细胞活化的有效性研究已在最近的临床试验中得到验证。

3.3 炎性细胞因子和神经营养因子 糖尿病患者视网膜代谢与免疫调节紊乱诱导胶质细胞分泌多种炎症因子,活化的炎症介质通过级联放大效应,激活更多趋化因子直接作用于内皮细胞,既可参与白细胞募集的表达,又可作为血管生成诱导剂,如核因子-κB激活在DR的发病机制中发挥着重要作用,可诱导多种细胞因子、趋化因子、前炎症因子等合成[51]。在DR中,视网膜炎症与血管损伤相互促进,交互调控,致使血管结构破坏,基底膜溶解,最终导致血-视网膜屏障的破坏。

在临床和实验研究中,DR患者视网膜肿瘤坏死因子α(TNF-α)、白细胞介素-1β(IL-1β)、白细胞介素-6(IL-6)、细胞间黏附分子-1(ICAM-1)和血管内皮细胞黏附分子(VCAM-1)等表达上调,抑制这些炎症介质的表达有利于阻止DR的进展[52-54]。

相比之下,一些神经营养因子,如脑源性神经营养因子(brain-derived neurotrophic factor,BDNF)、神经生长因子(nerve growth factor,NGF)、色素上皮衍生因子(pigment epithelium derived factor,PEDF)等,在神经元之间的发育和调节中起重要作用。BDNF由Müller细胞和神经节细胞分泌,维持视网膜神经节和无长突细胞的正常存活。研究证明,BDNF在糖尿病视网膜中表达下调[27],补充BDNF可以通过TrkB/ERK/MAPK通路保护视网膜神经元[55]。

NGF具有抑制Müller细胞和神经元凋亡的作

用,而其前体蛋白(pro-NGF)诱导视网膜神经节细胞凋亡通路,导致神经细胞的损伤[56]。糖尿病患者视网膜的氧化环境破坏了 pro-NGF 向成熟 NGF 转化的平衡,最终导致神经节细胞凋亡、血管通透性增加和炎症反应[57]。

PEDF 是一种有效的血管生成抑制剂,在保护神经元免受光损伤和氧化应激中起重要作用[58]。DR 中 PEDF 水平的降低可能导致炎症和血管渗漏,而补充 PEDF 可减少糖尿病小鼠视网膜血管渗漏[59]。

视网膜中神经保护因子生成的失衡,促进了视网膜 NVU 的损伤,适当补充神经营养因子可以改善 DR。

4 小结

虽然目前大多数治疗仍集中于增生期 DR 和黄斑水肿,但随着研究的不断推进,基于对 DR 发病机制和神经元、胶质细胞以及血管细胞之间相互作用的不断认识,相信在不久的将来,人们能够找到更好的治疗方式,对更早期 DR 进行干预,从而延缓其进展。

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Research advances in the pathogenesis of neurovascular injury in diabetic retinopathy

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【Abstract】 Diabetic retinopathy (DR) was earlier recognized as a microvascular complication, but nowadays, it is considered as a neurovascular disorder caused by damage to neurovascular units. Study shows that changes in the neuronal damage occurs before the clinically detectable microvascular abnormalities shortly after diabetes and neuronal damage participates in the progress of microvascular disease. Therefore, microangiopathy does not reveal the importance of the connections and impact between the neurons, glial cells and microvessels. Furthermore, the neurovascular damage and its protective mechanism based on the neurovascular unit and the novel therapeutic measures for DR will be the focuses of research in future.

【Key words】 diabetic retinopathy; neurovascular unit; pathogenesis; microvascular impairment; neurodegeneration