·文献综述·

糖尿病早期视网膜神经变性研究新进展

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引用:魏凡,彭立,谢青. 糖尿病早期视网膜神经变性研究新进展. 国际眼科杂志, 2025,25(1):76-81.

基金项目:外国专家项目-海南省国际科技合作人才与交流项目(No.G20230607013E);海南省重点研发-社会发展项目(No.ZDYF2020110);海南省自然科学基金青年基金项目(No.821QN1005)

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收稿日期: 2024-03-24 修回日期: 2024-11-15

摘要

糖尿病视网膜病变(DR)是由慢性高血糖引起的晚期微神经血管并发症,可导致血-视网膜屏障受损和视网膜功能障碍。近年来研究发现,糖尿病视网膜神经变性(DN)可能是糖尿病的视网膜改变最早事件之一,主要表现包括:新诊断糖尿病患者的视网膜电图反应缺陷;发病初期,小胶质细胞和 Müller 细胞在几周内自我激活并激活相关蛋白;神经递质(如 DOPA/GABA)活性降低,损害神经节信号传递;早期线粒体功能障碍,如 Drp1-Fis1 持续裂变及 mtDNA 甲基化和碱基错配之间的潜在串扰等。探讨糖尿病早期视网膜神经变性的分子基础对于理解 DN 的发病机制及早期治疗至关重要。文章总结糖尿病早期视网膜感光功能及神经胶质细胞、神经递质、线粒体和其他因子的病理变化及机制,旨在为研究 DN 早期机制及靶向治疗提供理论依据。

关键词:糖尿病视网膜病变;糖尿病视网膜神经变性;视网膜电图;线粒体自噬;神经胶质细胞;多巴胺
DOI:10.3980/j.issn.1672-5123.2025.1.14

Advances in early diabetic neuroretinopathy

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Foundation items: Foreign Experts Project - Hainan Province International Science and Technology Cooperation Talent and Exchange Project (No. G20230607013E); Key Research and Development Project of Hainan Province (No. ZDYF2020110); Natural Science Foundation of Hainan Province (No.821QN1005)
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Received: 2024-03-24 Accepted: 2024-11-15

Abstract

• Diabetic retinopathy (DR) is a late-stage peripheral micro-neurovascular complication of chronic hyperglycemia, leading to blood-retinal barrier impairment and retinal dysfunction. Recent studies have found that diabetic neuroretinopathy (DN) may be one of the earliest events in diabetic retinal alterations. The main features include defective electroretinographic responses in newly diagnosed patients, early self-activation of microglia and Müller cells, reduced activity of neurotransmitters (*e. g.*, DOPA/GABA), and early mitochondrial dysfunction, such as persistent Drp1-Fis1 fission and mtDNA methylation mismatches. Understanding the molecular basis of DN is essential for elucidating its pathogenesis and developing early treatments. This review summarizes pathological changes and mechanisms of retinal function, glial cells, neurotransmitters, mitochondria, and other factors in early diabetes mellitus, in order to provide a theoretical foundation for investigating early DN mechanisms and developing targeted therapies.

• KEYWORDS: diabetic retinopathy; diabetic neuroretinopathy; electroretinography; mitophagy; glial cells; dopamine

Citation: Wei F, Peng L, Xie Q. Advances in early diabetic neuroretinopathy. Guoji Yanke Zazhi (Int Eye Sci), 2025,25(1):76-81.

0 引言

糖尿病视网膜病变(diabetic retinopathy, DR),是一类由慢性高血糖环境诱发的周围微神经血管并发症。至 2020 年,全球 DR 患病率估计为 1.03 亿,成为导致全球 50 岁以上人群失明的第 5 大类疾病[1];预计到 2045 年将增加到 1.605 亿[2]。视网膜的稳定基于复杂的视觉网络,包括多种神经元亚型、血管内皮细胞及胞间释放的介质传递和信号传导[3]。当视网膜受到高血糖刺激的几个月内,电镜下微神经血管结构即可发生改变[4]。近年来研究表明,糖尿病视网膜神经变性(diabetic neuroretinopathy, DN)的发生或先于病理学可定义的血管病变[5],其最典型特征是神经细胞的凋亡及胶质细胞的活化:如在糖尿病发病仅 4 wk可出现视网膜神经节细胞(retinal ganglion cell, RGC)

凋亡[6-7];几个月内即可出现神经元轴突断裂,致使轴突运输受阻[8-9];这些病理生理过程可能独立于血管病变,并且与糖化血红蛋白(HbA1C)无关[10]。视网膜神经的早期变性可能归因于神经胶质细胞、神经递质、相关因子的激活及各组分相互间的信号传递。最终可引起视网膜代谢失衡,出现视网膜神经纤维层(retinal nerve fiber layer, RNFL)变薄[11]、感光功能障碍等改变。因此,本文将重点关注近年来针对糖尿病早期视网膜感光功能变化以及早期糖尿病视网膜神经变性的相关因子变化的研究进展。

1 视网膜电图

最近的研究揭示了新诊断的 1 型和 2 型糖尿病患者的视网膜电图(electroretinogram, ERG)反应缺陷,这些患者没有临床上明显的视网膜病变。2 型糖尿病中 RGC 的电生理缺陷先于视网膜微血管变化[12]。纯合型肥胖小鼠(ob^-/ob^-小鼠)较野生型而言,在 6 周龄时出现 a 波及 b 波振幅降低[13]。a 波、b 波隐式时间及振荡电位(oscillatory potential, OP)隐式时间的延迟提示了光感受器及 ON 双极细胞功能缺陷,这一异常远早于可见的视网膜微血管病变[14],OP 延迟还可确定糖尿病视网膜病变的最早功能缺陷,是糖尿病视网膜中唯一发生持续变化的 ERG 参数[15]。

多参数多焦视网膜电图(multifocal electroretinogram, mfERG)可在早期识别无临床症状的糖尿病患者的视网膜病变(识别率约 60%),从而提高诊断效果。mfERG 可能是衡量视网膜神经变性程度的指标[16],其变异程度与糖尿病程度密切相关,但不能用于检测 DR 分期[17]。P1 隐式时间(P1 implicit time, P1IT)因变异性较低,是治疗中广泛使用的 mfERG 参数;然而,另一项横断面研究发现,视网膜中央到周边的 P1 振幅(P1 amplitude, P1A)差异可能才是神经退行性过程的有效监测指标,与 SD-OCT 结构损伤对应,这种关系随早期 DR 的出现而加剧[18]。

未出现显著 DR 的糖尿病患者的 ERG 检查结果显示:PERG-N95、phNR 波幅、隐式潜伏期较对照组有显着降低和延迟。这些变化反映了视网膜神经元尤其是 RGC 功能的损伤[19]。无论有无 DR 的糖尿病人群,均出现暗适应隐式时间的延长,即视杆细胞通路的损伤。相反,无 DR 的早期糖尿病患者视锥通路传导未出现明显异常[15,20-21]。

以上研究证据均表示,糖尿病早期的视网膜损伤主要发生在感光细胞及各类神经元中,并在初期就已经发生视杆通路的损伤。

2 神经胶质细胞

2.1 小胶质细胞 小胶质细胞(microglia, MG)是视网膜中最主要的免疫细胞类型(>90%)[22],在糖尿病发病 1 wk 内即可发生激活[23]。小胶质细胞在中枢神经系统参与神经元凋亡,突触形成,及细胞因子信号传导等活动[24],稳态下形态表现为分枝状,以监视、修剪突触[25]。糖尿病初期,大鼠的视网膜内小胶质细胞密度显著增高,在 GCL、IPL、RPE 均被探测到,以 GCL 分布密度最高[26],并随病程推移呈现形态学上激活态的肥大细胞体、边缘粗糙突起及变形虫样[23]。早期糖尿病小胶质细胞的活化由独特的坏死性凋亡程序引发[27],受体相互作用蛋白激酶 3(receptor-interacting protein kinase 1, RIP3)是这一程序的关键介导因子[28];抑制性无长突细胞群的突触功能性失调可能也部分参与活化程序[26]。激活态的小胶质细胞展现出表达大量 TNF-α 的促炎表型[29]。在早期,RPE 层可探测到 IL-6 mRNA 增高及大量募集的小胶质细胞,这可能通过 IL-6 上调 VEGFA mRNA 及小胶质细胞的趋化因子实现[30]。随后,活化的小胶质细胞可减少 RPE 细胞闭合小带、破坏紧密连接,最终造成外层 BRB 的破坏[31]。

在糖尿病状态的视网膜中,小胶质细胞可分泌大量的脂质载运蛋白-2(Lcn2)[32],通过抑制光感受器间视黄醇结合蛋白(IRBP)并影响糖酵解,导致早期光感受器功能受损[33]。此外,它们也表达趋化因子(C-X3-C 基序)配体 1(CX3CL1),通过特异性受体 Cx3cr1 信号通路监测和调节血管与神经元突触的活动[34],参与调节视网膜毛细血管的血流速度和口径[35]。实验表明,在拥有 CX3CR1 信号轴的动物模型中诱导小胶质细胞的耗竭可以保护早期糖尿病小鼠免受神经变性。此外,小胶质细胞还表达血管紧张素-醛固酮系统(RAS)成分,在糖尿病早期可能与 Ang Ⅱ产生正反馈循环反应,进一步激活小胶质细胞[36]。

2.2 Müller 细胞 视网膜 Müller 细胞(retinal müller cell, RMC)是一类神经大胶质细胞,占全部神经胶质细胞的 90%。高血糖环境下 RMC 的一连串改变及表达可促早期神经变性[37]。短期暴露在高糖状态中,视网膜总谷氨酰胺水平不变,谷氨酸总体释放增加;但 RMC 末足中可出现谷氨酰胺水平的局部降低及谷氨酸的积累。这可能与谷氨酸的关键代谢酶——谷氨酰胺合成酶的下调相关[38]。长期处于正常血糖环境中的 RMC 在暂时的血糖震荡中能够激活更多胶质细胞以保护神经元,表现为无 DR 的糖尿病患者视网膜内核层厚度与血糖浓度成正相关;而持续处于高血糖状态下的 RMC 对正常葡萄糖状态异常敏感,并抑制与神经保护相关的 ERK1/2 信号通路,诱导神经变性[39]。

高糖状态下,IL-17A 可通过激活型 RMC 表达的 IL-17R来诱导 RMC 对 RGC 的毒性作用,以介导糖尿病鼠早期 RGC 凋亡[40-41]。分拣蛋白/p75 神经营养蛋白受体(p75 NTR)复合体是神经营养蛋白信号传导的重要调节剂[42]。在早期糖尿病的人及小鼠视网膜研究中,分布在 RGC 周围的 RMC 中的分拣蛋白表达明显增高,可致视网膜神经营养蛋白信号传导紊乱。其抗体可保护视网膜内层结构完整,并避免早期视网膜神经变性[43]。神经胶质成熟因子(glia maturation factor-β, GMF-β)可影响多种神经因子的凋亡和代谢[44]。糖尿病初始期,RMC 可大量释放 GMF-β,并在玻璃体内迅速直接性上调[45]。GMF-β 诱导的溶酶体酸化和自噬通量的增加可致 RPE 细胞铁死亡(调节性死亡途径,受到自噬调控)[46-47]。在未来可深入研究 GMF-β 降解或 GMF-β 抗体对治疗早期 DN 的可能性。

种种证据表明,在糖尿病早期,小胶质细胞、Müller 细胞能够通过自身活化并释放各类活性趋化因子以介导

RGC 凋亡并抑制神经信号传导,促使神经变性的发生及发展。

3 神经递质

各类神经递质在视网膜中可调控神经元信号传递的兴奋或抑制,直接参与微环境平衡[48]。当机体处于高血糖状态时,神经递质可能发生异常改变,导致视网膜稳态失衡。

3.1 多巴胺 多巴胺(dopamine)由内核层中的多巴胺能无长突细胞群产生并释放至视网膜,调节正常视网膜的光适应功能[49]。在早期糖尿病的小鼠中,视网膜多巴胺水平下降,导致多巴胺能受体长期低活化,进而减弱神经节细胞的信号传导效率[50]。研究发现,患糖尿病 6 wk 后,尽管未发现视网膜神经细胞及 GABA、DOPA 神经元的损失,但暗适应下自发性抑制性突触后电流(IPSC)的峰值幅度显著降低,损害了 ON 持续神经节信号传递[51]。GK 大鼠作为多基因 2 型糖尿病模型,其视网膜表达高含量的内源性多巴胺及其代谢物 DOPAC[14]。最新研究表明,GK 大鼠早在 1 月龄时视网膜功能就出现缺陷,表现为闪烁和振荡电位隐含时间(OPIT)显著延迟。因此,内源性高表达的多巴胺可能有助于阻止早期视网膜功能变化[52]。而当 OPIT 出现显著的延迟后,补充外源性多巴胺能够治疗视杆通路暗视的电生理应答,将隐式时间恢复至正常水平[53]。

3.2 γ-氨基丁酸 γ-氨基丁酸(Gamma-aminobutyric acid, GABA)介导抑制性神经突触传递[54-56],在视网膜中可由不同类别的无长突细胞分泌。早期研究表明,在糖尿病初期状态下,视网膜 GABA 的制造酶 GAD 可出现表达水平下降[57-58]。高糖环境下,视杆通路中无长突细胞内部的 Ca^{2+} 动员机制发生故障,引起抑制性信号的传导障碍,导致了激活态的 GABA 能无长突细胞释放 GABA 的功能出现缺陷[59]。多重因素影响下,视网膜 GABA 受体含量可显著下降,并导致视杆双极细胞光诱发的抑制减少而兴奋输出增加,即“兴奋-抑制”信号不平衡,这可能引起早期对比敏感度下降[20]。最新研究确定了共定位在 RGC 树突的“混合 GABA-甘氨酸能突触电路”,在糖尿病中可能充当某种调节作用,期待未来进一步研究的阐述[60]。

以上研究证据表明,神经元信号传导和调控功能的异常而非神经元细胞的破坏可能是 DR 最早可检测到的变化之一。

4 线粒体损害

线粒体功能障碍在早期糖尿病视网膜神经变性中被认为是最关键环节之一[5,61]。良好的线粒体质量控制(mitochondrial quality control, MQC)是维持视网膜稳态的重要原因,并取决于线粒体“自噬-生物发生”间的平衡。糖尿病早期,外层视网膜线粒体可探测到过度的自噬[62]。当裂变的碎片持续沉积,则会增加 ROS 生成并发生氧化应激事件[63]。动力相关蛋白(dynamin-related protein 1, Drp1)是启动线粒体裂变程序的关键因子[64],其聚集由裂变蛋白 1(fission protein 1, Fis1)介导。短暂高血糖环境下,Drp1 水平显著升高;即使血糖环境恢复正常,Drp1-Fis1 裂变程序仍然进行,从而带来持续的线粒体 Drp1 碎片积累及 ROS 上调[65]。除裂变事件外,早期糖尿病的视网膜 mtDNA 甲基化和碱基错配之间存在潜在的串扰。在高血糖终止后,DNA 甲基化和碱基错配之间的这种串扰也仍在继续[66]。即使高血糖环境被终止、血糖控制良好后,视网膜线粒体动力学和 mtDNA 仍会持续受损、受损的线粒体将持续积累[67-68];受损线粒体的清除率也依旧低于正常值[69]。糖尿病早期的感光细胞功能障碍也与线粒体的破坏密切相关。研究发现,短期(48 h)高血糖条件培育的感光细胞系可出现线粒体碎片化及细胞色素 C 异位的增加,这表明早期感光细胞功能障碍及凋亡与线粒体破坏密切相关[61]。

其他因子也参与早期线粒体的破坏及功能障碍。糖原合成酶激酶 3β(GAK3β)是一类参与能量代谢与神经元发育的酶。早期糖尿病中, GSK3β 异常激活,可减少线粒体能量产生,破坏突触作用,并且引发高度磷酸化的微管相关蛋白 tau 损害微管,抑制局部突触蛋白合成;从而引起 RGC 突触缺失和功能障碍[12]。而 RGC 的突触变性远早于 RGC 出现明显凋亡迹象,被认为是糖尿病视网膜病变发病机制的最早事件。最新研究发现, 糖尿病初期,视网膜内局部甲状腺激素(thyroid hormones, TH)分泌调控产生变化,而循环 TH 并无显著变化。db/db 小鼠出现视网膜局部低 T3 含量状态(low T3 state, LT3S),并可引起线粒体相关基因的明显下调(如 PGC-1α、CPT2 和 MFN2)[70]。这表明视网膜局部 LT3S 的调控在糖尿病初期阶段可以实现抑制线粒体过度活跃的补偿反应,起到保护作用。

5 其他因子

E2fs 是一类转录因子,在细胞分化、凋亡中发挥重要作用。其中,E2f1 是糖尿病早期诱导视网膜神经元如 RGC、双极细胞异位分裂及死亡的重要介质,而 E2f1 敲除可挽救高糖诱导的视网膜神经元死亡[71]。值得注意的是,$E2f1^{-/-}$ 并不能挽救 Müller 细胞异位分裂。这可能说明在糖尿病初期,神经元、神经胶质细胞与血管内皮细胞的周期调控及异位分裂相互独立,随后逐渐通过细胞信号的传递相互交织。

硫美特寡肽酶 (THOP1),与大脑中积累的 β 淀粉样蛋白(Aβ)清除有关,其中 Aβ 病理与糖尿病视网膜病变高度正相关[72]。非糖尿病视网膜已鉴定出 THOP1 通路的存在,而糖尿病患者视网膜 THOP1 通路缺失[8]。这些证据表明视网膜内的保护性 THOP1 可能具有清除蛋白、神经支持作用,但在糖尿病早期即失活,成为介导早期视网膜神经变性的众多诱因之一。

铁离子失衡被认为在早期糖尿病视网膜神经变性中扮演重要角色。一般情况下,铁调节蛋白(iron-regulatory-protein, IRP)通过增加铁蛋白的表达来储存铁[73]。在糖尿病早期, 由于血-视网膜屏障(blood-retina-barrier, BRB)完整,铁离子难以进入视网膜,导致视网膜内增加的是铁蛋白而非铁。此时,转铁蛋白受体 mRNA 不稳定,无法结合 IRP,导致 IRP 耗竭。这表明在糖尿病早期,视网

膜可能通过监测全身铁超载并激活铁蛋白合成来做出补偿反应,为下一步 BRB 破坏和全身铁进入视网膜做准备[45,74]。一旦 BRB 分解,大量铁离子将涌入视网膜。例如,12 周龄的铁调节蛋白敲除的糖尿病小鼠即可出现视网膜 RGC 凋亡[75]。

6 小结

本文主要着眼于早期糖尿病的视网膜神经变性相关的感光功能改变、神经胶质细胞、神经递质及线粒体、各类因子改变的研究新进展。近年来,已有类似综述侧重于探讨 DR 在不同阶段的血管神经变化及神经损伤的始动因素[76-78]。然而,本文首次系统总结了糖尿病初期视网膜神经变性的起始过程及各组成成份在此期间的病理变化。本文还总结了糖尿病初期视网膜神经变性的时间框架,并提出了新兴的神经变性预测指标,这些发现对于早期干预和病程阻断具有重要意义。然而近年的研究证实,视网膜的内部稳态依赖于神经-血管单元(neovascular unit, NVU)的整体协调[79]。视网膜微血管与神经共同在糖尿病视网膜病变病程中发挥作用,而神经血管耦合的不足可能成为关键因素之一[80]。本综述的局限在于尚未探讨视网膜神经元与微血管在早期糖尿病中的信号传导及相互调控,需要进一步深入研究神经血管耦合系统的内部联系。目前,针对糖尿病早期视网膜改变的一线治疗仅局限于全身降糖控制。若能够针对神经变性的异常环节进行靶向治疗,如调节或扭转各类因子及细胞间的异常信息传导,将推动早期 DR 疗法的发展。但这仍需要更进一步的研究及探讨。

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作者贡献声明:魏凡论文选题、文献检索与初稿撰写;彭立、谢青选题指导,论文修改。所有作者阅读并同意最终的文本。

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