

Advanced Glycation End Products in Ocular Tissue Pathologies: Mechanisms and Research Advances

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Abstract

Advanced glycation end products (AGEs) are irreversible products generated by non-enzymatic reactions of reducing sugars and biological macromolecules. Excessive accumulation of ages is closely related to a variety of eye diseases. AGEs can participate in the pathological processes of delayed corneal wound healing, cataract caused by crystallin cross-linking, glaucoma caused by trabecular meshwork matrix stiffness, retinal microvascular barrier damage, and optic nerve axonal transport disorder through non-enzymatic glycosylation, activation of RAGE receptor and NF- κ B pathway, and induction of oxidative stress. Clinical studies have shown that AGEs are significantly accumulated in the eye tissues of patients with diabetic retinopathy, glaucoma and other diseases, and are related to disease progression. Future research can focus on the development of efficient AGEs inhibitors, targeted intervention of the AGEs/RAGE pathway, combined with imaging, laboratory and other technologies to realize early lesion monitoring, and provide multi-target intervention strategies for metabolic and degenerative eye diseases.

Keywords

advanced glycation end products (AGEs); RAGE; diabetic retinopathy; cataract; glaucoma; oxidative stress

糖基化终末产物在眼部组织病变中的作用机制及研究进展

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摘要

晚期糖基化终末产物 (AGEs) 是由还原糖与生物大分子经非酶促反应生成的不可逆产物, 其过度累积与多种眼部疾病密切相关。AGEs 可通过非酶糖基化、激活 RAGE 受体及 NF- κ B 通路、诱导氧化应激等机制, 参与角膜伤口愈合延迟、晶状体蛋白交联致白内障、小梁网基质僵硬致青光眼、视网膜微血管屏障破坏及视神经轴突运输障碍等病理过程。临床研究显示, AGEs 在糖尿病视网膜病变、青光眼等患者眼组织中显著蓄积, 且与疾病进展相关。未来研究可聚焦于开发高效 AGEs 抑制剂、靶向干预 AGEs/RAGE 通路, 结合影像学、检验学等技术实现早期病变监测, 为代谢性及退行性眼病提供多靶点干预策略。

关键词

晚期糖基化终末产物 (AGEs); RAGE、糖尿病视网膜病变; 白内障; 青光眼; 氧化应激

1 引言

晚期糖基化终末产物 (advanced glycation end products, AGEs) 是一类在人体内外通过多种途径形成的化学性质多样的非均一性化合物, 通常由还原糖的羰基与核酸、蛋白质或

脂质的游离氨基经非酶促缩合反应, 再经进一步重排生成稳定不可逆的终产物^[1]。包括外源性摄入和内源性产生的 AGEs 在人体的过度累积, 不仅会影响胶原蛋白和弹性蛋白等长寿蛋白质, 还会改变循环血浆蛋白和脂质等短寿蛋白质^[2-4]。

2023 年 WHO 发布的数据表明, 每个活得足够长的人, 一生中至少会经历一种需要适当治疗的眼部疾病。导致人类视力损失的疾病众多, 其中远视力障碍或失明的主要疾病包括白内障、屈光不正、老年性黄斑变性、青光眼和糖尿病性视网膜病变^[5]。据报道, 上述几种疾病的发病过程中都有同一种致病因素 AGEs 的参与。有大量证据表明, AGEs 在人眼的不同组织中均有积累, 包括角膜、晶状体、视网膜、视

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神经等,因此与众多致使视力障碍甚至失明的眼病的发病机制有关^[6]。

本综述将详细阐述 AGEs 对眼部各组织疾病的影响与机制,并探讨未来用于眼部疾病预防与治疗的可行实验方向。

2 AGEs 对眼部的致病作用及机制

2.1 角膜

在正常衰老过程和糖尿病病程中,AGEs 均会在角膜组织中积累^[7,8]。AGEs 在后弹力层中形成可能是糖尿病患者角膜内皮细胞随着衰老和角膜内皮异常而丢失的原因^[9]。糖尿病患者的高血糖会导致蛋白质的非酶糖基化,从而导致形成在糖尿病组织中积累的 AGEs,AGEs 与其受体(RAGE)相互作用,触发细胞内信号传导,包括核因子 κ B (nuclear factor kappa-B, NF- κ B) 激活和活性氧(ROS)的形成,它们在糖尿病角膜基底膜和基质中的积累可能是临床观察到的自发荧光增加的原因^[10],同时 AGEs 以 ROS 和 RAGE 依赖性方式导致伤口愈合延迟和细胞凋亡增加^[11,12]。糖尿病与感染之间的关联多年来已得到认可^[13],而在眼部亦有相关研究表明了糖尿病患者角膜感染与 AGEs 的相关性。有实验团队在体外和离体实验证明,角膜中的 AGE 沉积增加了非液化分枝杆菌与角膜的粘附,糖尿病患者角膜中的 AGEs 沉积是发生莫拉菌角膜炎的诱发因素^[14]。此外还有动物实验研究证实,糖尿病小鼠角膜内不仅存在 AGEs 过表达,还可能同时通过调控 TLR4 信号通路来促进分泌炎症相关细胞因子从而参与到糖尿病小鼠角膜上皮损伤修复延迟愈合的过程^[15]。

2.2 晶状体

老花眼的主要病因是晶状体硬化,其致病机制涉及 α -晶状体蛋白水溶性及分子伴侣活性降低,以及氧化性谷胱甘肽等二硫化物水平升高^[16]。晶状体内变性蛋白与二硫化物的异常堆积会降低透光率,继而引发白内障。晶状体蛋白中的 AGEs 随年龄增长而累积,通过诱导蛋白交联促进白内障和老花眼发生^[17]。动物实验证实,抗坏血酸氧化产生的 AGEs 可促使晶状体核内蛋白质异常交联聚集^[18]。白内障术后常见的后囊膜混浊并发症与残留晶状体囊内 AGEs 相关,其通过诱导残留晶状体上皮细胞(LECs)衰老,触发邻近 LECs 的间充质转化,最终导致后囊混浊^[19]。而糖尿病患者年龄相关性白内障中,血浆 AGEs 水平不仅显著升高,且与白内障进展呈现明确相关性,而在非糖尿病患者中这种相关性较弱^[20]。研究显示,糖尿病患者的 AGEs 可能通过糖基化修饰导致晶状体蛋白分子伴侣功能丧失并发生异常聚集,从而引发白内障^[21]。

2.3 青光眼

青光眼的发生发展与糖基化终末产物(AGEs)密切相关,其在患者眼组织的筛板、视乳头周围血管、视网膜神经

节细胞(RGCs)细胞外基质及小梁网、Müller 细胞中异常沉积。AGEs 通过非酶糖基化使小梁网细胞外基质胶原蛋白等交联,致基质僵硬、房水外流阻力增加、眼压升高^[22]。AGEs 还可与 RGCs 表面 RAGE 受体结合,激活 NF- κ B 等炎症通路及氧化应激反应,诱导细胞凋亡,并增加筛板硬度,放大眼压所致的视神经机械损伤,加剧轴突运输障碍与视神经萎缩^[23]。

2.4 视网膜

糖尿病及其微血管并发症的发生发展与 AGEs 的异常累积存在密切关联,作为糖尿病视网膜病变(Diabetic retinopathy, DR)的核心致病因素,AGEs 通过多重机制介导视网膜微血管的病理改变^[24]。有研究表明 AGEs 的生成主要源于葡萄糖等还原糖与蛋白质类或脂质类生物大分子的非酶促反应,过程中涉及由甲基乙二醛、乙二醛等活性二羰基中间体,二羟基对细胞外蛋白质的修饰会损害细胞粘附,并产生可能与细胞表面 AGE 受体结合的配体,从而激活促炎信号通路^[25,26]。糖尿病患者由于长期高血糖状态导致该反应速率显著提升,不可逆产生羧甲基赖氨酸(CML)、戊糖苷等稳定交联结构,CML 和戊糖苷作为 AGEs 的主要组成部分在视网膜基底膜、内皮细胞及周细胞中呈现特异性蓄积特征^[27]。临床影像学分析证实这类蓄积现象与光学相干断层扫描中椭圆球体区的结构损伤存在显著相关性^[28]。

AGEs 的蓄积导致视网膜周细胞在其作用下发生凋亡,而在周围神经的周细胞则表现为在 AGEs 刺激下过度分泌纤维连接蛋白和 IV 型胶原,两种作用机制共同作用,造成基底膜增厚及血-视网膜屏障损伤,加剧 DR 和神经病变^[29]。

在分子机制上,有研究表明 AGEs 与其受体 RAGE 激活会触发级联反应。一方面通过核因子 κ B (nuclear factor kappa-B, NF- κ B) 通路促使血管内皮生长因子(vascular endothelial growth factor, VEGF)、肿瘤坏死因子 α (tumor necrosis factor α , TNF- α) 等促炎因子过量表达,导致血视网膜屏障完整性受损和血管渗漏;另一方面诱发线粒体氧化应激,引发周细胞程序性死亡和内皮功能障碍,最终加重毛细血管阻塞^[30]。此外 AGEs/RAGE 通路还能通过激活 Müller 细胞内 VEGF 的表达促进新生血管形成^[31]。有报道称,AGEs 抑制剂和 RAGE 阻断剂能够降低 DR 患者视网膜中 NF- κ B、VEGF 等因子的水平,进而抑制炎症和氧化应激反应,并使视网膜微血管渗漏显著减少,这为 AGEs/RAGE 通路未来在临床中靶向干预 DR 导致的视网膜微血管损伤提供了理论依据^[32,33]。

2.5 视神经

糖基化终末产物(AGEs)在视神经病变中的作用机制涉及多层次的病理改变。临床研究显示,AGEs 在青光眼及糖尿病患者的视神经头部显著积累,尤其在筛板及血管周围,其水平与 RAGE 受体表达增强密切相关。AGEs 通过激活 RAGE 介导的氧化应激和 NF- κ B 信号通路,导致胶原纤

维异常交联,降低筛板结构弹性,进而影响轴突的机械顺应性^[34]。分子机制上,毒性 AGEs (TAGE) 通过靶向 β -微管蛋白引发异常聚集,直接干扰轴突再生过程。动物实验证实,TAGE- β -微管蛋白的聚集会抑制神经营养因子诱导的轴突伸长。同时,AGEs 暴露上调视网膜中 tau 蛋白的磷酸化水平,提示其通过破坏微管稳定性与 tau 病理协同作用,加剧神经退行性变,这为糖尿病与阿尔茨海默病共有的视神经损伤机制提供了依据^[35]。临床影像学证据表明,AGEs 引发的微循环障碍早于结构性神经损伤。糖尿病前期患者的视神经头部整体及局部微血管密度显著下降,而视网膜神经纤维层变薄仅见于特定区域,说明微血管灌注不足可能通过损害代谢微环境,加速轴突变性。值得注意的是,这种微血管改变与血糖控制的短期波动无直接关联,提示 AGEs 的慢性累积是独立致病因素^[36]。

3 总结与展望

AGEs 通过多靶点、多途径参与眼部多组织病变,是糖尿病及年龄相关眼病的重要病理桥梁。大量数据表明,AGEs 在白内障、AMD、糖尿病视网膜病变中起着病理作用,其积累也可能涉及青光眼、糖尿病性角膜病变及视神经病变。现有靶向策略已展现治疗潜力,未来可能需要聚焦开发穿透血眼屏障的 AGEs 清除剂、联合基质交联逆转与微循环修复技术、基于糖尿病前期视神经微血管损伤建立早期干预体系等,多靶点协同干预或为代谢性及退行性眼病提供新范式。

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