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Emerging role of advanced glycation-end products (AGEs) in the pathobiology of eye diseases

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ABSTRACT

Advanced glycation end products (AGEs) have been implicated in vision loss associated with macula degeneration, cataract formation, diabetic retinopathy and glaucoma.

This pathogenic potential is mainly attributed to their accumulation in ocular tissues where they mediate aberrant crosslinking of extracellular matrix proteins and disruption of endothelial junctional complexes that affects cell permeability, mediates angiogenesis and breakdown of the inner blood-retinal barrier. Furthermore, AGEs severely affect cellular metabolism by disrupting ATP production, enhancing oxidative stress and modulating gene expression of anti-angiogenic and anti-inflammatory genes. Elucidation of AGE-induced mechanisms of action in different eye compartments will help in the understanding of the complex cellular and molecular processes associated with eye diseases. Several pharmaceutical agents with anti-glycating and anti-oxidant properties as well as AGE crosslink 'breakers' have been currently applied to eye diseases. The role of diet and the beneficial effects of certain nutriceuticals provide an alternative way to manage chronic visual disorders that affect the quality of life of millions of people.

Contents

Abbreviations: AGEs, advanced glycation end products; ALEs, advanced lipoxidation end products; AP-1, activating protein-1; AMD, age-related macular degeneration; ARB, angiotensin II receptor blocker; BRB, Blood retinal barrier; BM, Bruch's membrane; CML, Nε-carboxymethyllysine; CEL, Nε-carboxyethyllysine; CEC, choroidal endothelial cells; DR, diabetic retinopathy; ELISA, enzyme-linked immunosorbent assay; ERK, extracellular signal regulated kinase; FFI, furoyl-furanyl imidazole; Gal-3, galectin-3; GC, gas chromatography; GA, geographic atrophy; HbA1c, glycated hemoglobin; GI, glycemic index; GO, glyoxal; GLO1, glyoxalase 1; HPLC, high performance liquid chromatography; HMGB1, high-mobility group box-1; 8-OHdG, 8-hydroxydeoxyguanosine; IHC, immunohistochemistry; iBRB, inner blood-retinal barrier; LOX, lysyl oxidase; MS, mass spectrometry; MMP-9, matrix metalloproteinase 9; MG, methylglyoxal; OCT, optimum cutting temperature; PEDF, pigment epithelium-derived factor; PDR, proliferative diabetic retinopathy; ROS, reactive oxygen species; RAGE, receptor for AGE; RGCs, retinal ganglion cells; RPE, retinal pigment epithelium; UCHL-1, ubiquitin carboxyterminal hydrolase-1; VEGF, vascular endothelial growth factor; WB, Western blot analysis; ZDF, Zucker Fatty Diabetic.

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1. Introduction

Human eye diseases contributing to visual loss encompass a wide spectrum of disorders ranging from macula degeneration, cataract, and glaucoma to various types of retinopathy. Their incidence increases with age, whereas reduced quality of life and financial burden due to visual impairment and blindness are dramatically elevated when individuals reach forty years of age. The global prevalence of diabetes has dramatically accelerated the onset of ocular diseases in younger individuals where diabetic retinopathy is the primary cause of acquired blindness (Rodriguez et al., 2002). Both environmental and genetic factors contribute to the development of these diseases. The major causes of age-related vision loss are attributed to structural and functional changes in the lens and retina, while hyperglycemia primarily affects cell metabolism and induces irreversible changes in stable macromolecules in different eye compartments (Milne and Brownstein, 2013; Nagaraj et al., 2012). A common pathogenic factor implicated in both situations is the accumulation of advanced glycation end products (AGEs) which are the toxic byproducts of the non-enzymatic reaction of lipids, proteins and nucleic acids with reducing sugars (Monnier et al., 1992).

Endogenous formation of AGEs is enhanced in situations of poor glucose utilization, insulin resistance and increased oxidative stress; these factors are associated with intracellular and extracellular changes of the vascular endothelium and disturbances in vital organ architecture (Semba et al., 2010). Furthermore, intake of AGEs from exogenous sources such as highly thermolyzed foods, beverages or cigarette smoke significantly elevates their concentration in the blood, provokes the initiation or progress of insulin resistance and accelerates tissue specific damage (de Assis et al., 2009; Cai et al., 2008a; Diamanti-Kandarakis et al., 2007a, 2007b).

Enhanced tissue deposition of AGEs, commonly observed in progressive aging, affects the function of major organs such as vascular, nervous and reproductive systems (Bengmark, 2006; Diamanti-Kandarakis et al., 2007a, 2007b). Increased circulating AGE levels in young adults have been directly linked to the risk of developing several chronic diseases that commonly affect the elderly population (Semba et al., 2010). Pathological conditions such as Diabetes mellitus, Polycystic Ovarian Syndrome, Obesity and Alzheimer's diseases have been associated with elevated AGE formation (Sensi et al., 1995; Diamanti-Kandarakis et al., 2005).

The pathogenic role of AGEs in ocular diseases has been observed principally in the retina and primarily investigated in relation to diabetic retinopathy, the leading cause of visual impairment or blindness (Rodriguez et al., 2002). However, there is significant evidence indicating that AGEs accumulate in all different compartments of the human eye, including the cornea, lens, retina, Bruch's membrane, sclera and optic nerve, thus being implicated in the pathogenesis of all major eye disorders (Stitt, 2005; Nagaraj et al., 2012; Semba et al., 2014; Zicari et al., 2014).

This review focuses primarily on the biochemical aspects of advanced glycation, providing an account of major AGE products and their methodology along with their biological effects and implication in systemic pathophysiology. Furthermore, the impact of AGEs in the pathogenesis of eye diseases is discussed, followed by a detailed account of specific AGE effects in the different eye compartments. Current interventions that reduce AGE levels with benefit to eye diseases are presented, with emphasis on the emerging role of diet restriction and nutriceuticals. Finally, a summary together with recommendations for future directions of experimental research are proposed.

2. Biochemistry of advanced glycation

2.1. Definition and products

Advanced glycation (or glycosylation) takes place in all cell types and refers to the posttranslational modification of glucose-derived dicarbonyl compounds and amino residues present in DNA, proteins, and lipids. The non enzymatic glycation reaction involves the initial Schiff base formation after the reaction of glucose with ε-amino groups (arginine or lysine) present in proteins that further rearrange to relatively stable Amadori products (Maillard reaction, Fig. 1). Additional oxidation and dehydration reactions of Amadori products result in the formation of irreversible forms of protein-bound AGEs (Thornalley et al., 1999).

Normal products of metabolism such as α-Oxoaldehydes which include methylglyoxal (MG), glyoxal (GO) and 3-deoxyglucosone (3-DG) occur at elevated levels in cells exposed to high glucose and present the most important source of intra- and extracellular