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REVIEW ARTICLE

The pathogenic role of Maillard reaction in the aging eye

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Abstract The proteins of the human eye are highly susceptible to the formation of advanced glycation end products (AGEs) from the reaction of sugars and carbonyl compounds. AGEs progressively accumulate in the aging lens and retina and accumulate at a higher rate in diseases that adversely affect vision such as, cataract, diabetic retinopathy and age-related macular degeneration. In the lens AGEs induce irreversible changes in structural proteins, which lead to lens protein aggregation and formation of high-molecular-weight aggregates that scatter light and impede vision. In the retina AGEs modify intra- and extracellular proteins that lead to an increase in oxidative stress and formation of pro-inflammatory cytokines, which promote vascular dysfunction. This review outlines recent advances in AGE research focusing on the mechanisms of their formation and their role in cataract and pathologies of the retina. The therapeutic action and pharmacological strategies of anti-AGE agents that can inhibit or prevent AGE formation in the eye are also discussed.

Keywords Lens · Retina · Aging · Diabetes · Cataract · Diabetic retinopathy · Age-related macular degeneration

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Background

The formation of advanced glycation end products (AGEs) is now accepted as an important pathogenic event in a number of human age-related disorders. AGEs that form from a range of precursors through many different pathways have been implicated in the initiation and progression of inflammatory disorders (Calfee et al. 2007), Alzheimer's disease (Munch et al. 2003), decreased skin elasticity (Ohshima et al. 2009), male erectile dysfunction (Jiaan et al. 1995), diabetic microvasculopathy (Yamagishi et al. 2003) and atherosclerosis (Basta et al. 2004; Cooper 2004).

Many of the cells and tissues that form the visual system are also profoundly influenced by aging and it is appropriate that advanced glycation is now receiving more attention as a key pathogenic step in many age-related disorders of the eye. AGEs accumulate at sites of known age-related ocular pathology. Studies have also demonstrated how such AGE adducts inflict considerable damage to proteins through cross-linking, changing tertiary structure, conferring resistance to digestion, altering enzymatic activity or impairing receptor recognition. This review outlines some of the important effects that advanced glycation has on ocular tissues during the aging process with particular emphasis placed on the lens and retina. Diabetic retinopathy is not covered in this review since it is dealt with elsewhere (Stitt 2010). A perspective is provided on how AGEs initiate and progress sight-threatening disorders such as cataract, glaucoma and age-related macular degeneration (AMD). The review also considers pharmacologic strategies to prevent or neutralize the effects of AGEs and the recent development of potential therapies for age-related diseases that impair vision.

AGEs and aging

Aging is associated with increased modification of free amino groups on proteins, lipids and DNA. An important source for these modifications is non-enzymatic glycation reactions by aldehyde groups on sugars and carbonyls. The so-called Maillard reaction is a natural process and, as a consequence, nearly all body proteins carry some "burden" of chemically attached carbohydrate (Monnier et al. 1992). The Maillard reaction begins with the reaction of carbohydrates (with reactive carbonyl groups) with amino groups on proteins. In the case of sugars, the first reaction site is usually the epsilon amino group of lysine residues of proteins. This leads to the formation of an initial Schiff's base, which undergoes a spontaneous rearrangement to form a more stable product, known as the Amadori product. An example of the Amadori product is glycated hemoglobin (HbA1c), which is a long-term indicator of blood glucose control. With time, the Amadori compound undergoes a series of reactions to form a heterogeneous group of compounds that are collectively called AGEs (Monnier et al. 1996). These adducts have many unique characteristics; they often exhibit autofluorescence and their formation coincides with protein structural changes and cross-linking (Linetsky et al. 2008; Prabhakaram et al. 1996; Swamy and Abraham 1987). All of these are similar to changes that occur as we get older (Bron et al. 2000); thus, the Maillard reaction has been considered as a major contributor to age-related eye disease. In this context, such chemical modifications have been especially well studied in the ocular lens.

AGEs in lens aging and cataract formation

Introduction to the lens

The lens focuses the light entering the eye onto the retina. To perform this function, the lens must retain its elasticity and remain completely transparent; this is maintained by the highly ordered configuration of proteins. The mature lens lacks blood supply and derives its nutrients mostly from the aqueous humor present on its anterior side. It is surrounded by an extracellular matrix, the lens capsule, which provides mechanical support and acts as a substrate for the lens epithelium. The lens consists of two types of cells: a single layer of cuboidal epithelial cells on the anterior side and long terminally differentiated, epithelium-derived fiber cells that run from the anterior to the posterior side of the lens. As the lens develops, these cells lose organelles during differentiation to minimize the diffraction of light and accumulate significant quantities of proteins. Indeed, the overall protein concentration in the lens is ~400 mg/ml, which is among the highest in the body (Delaye and Tardieu 1983). Crystallins are the major proteins of the lens and are designated α, β and γ, in order of their abundance. These crystallins are highly water soluble and linked to the chaperone function of α-crystallin (Horwitz 2009). Protein synthesis in the lens continues throughout life; new proteins are added on to the existing protein layers (Jaenicke 1994). This feature gives the lens an "inverted onion"-like structure where the oldest proteins are at the center of the lens (known as the nucleus) and the youngest at the periphery close to the epithelium (known as the cortex; Fig. 1). The lens proteins have a negligible turnover rate and, therefore, proteins at the center of the lens have been present from embryological development and are as old as an individual. It is this property that has attracted researchers to the field of Maillard reaction, as it is believed that long-lived proteins accumulate more Maillard reaction products than short-lived proteins.

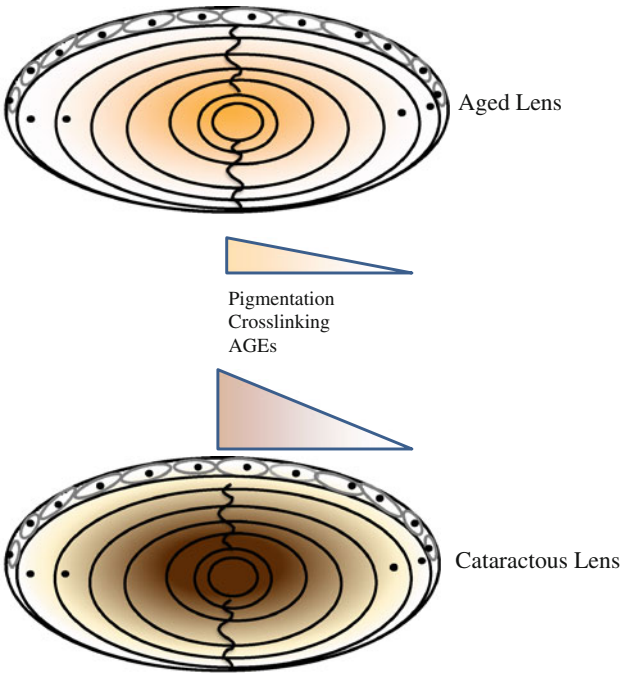


Fig. 1 As lens proteins age, they accumulate pigments, become fluorescent and cross-linked, and their AGE levels increase. Since the outer cortex is younger than the inner nucleus, these changes accumulate more in the nuclear region than in the cortex. The changes are exaggerated in senile cataractous lenses

Significant changes occur in the lens during aging. These include covalent cross-linking and insolubility of proteins, yellow/brown coloration and accumulation of fluorescent products in nuclear proteins (Harding 1991). These changes take place at a relatively slow rate during the first four decades of life, but increase exponentially from the age of 50 years onwards. In senile cataractous lenses, where nuclear sclerosis is a major event, all these

changes are exacerbated (Sell and Monnier 1995). Several biochemical mechanisms have been suggested to explain these changes, including oxidation, truncation, deamidation of proteins and the Maillard reaction (Sharma and Santhoshkumar 2009). In this section of the review, we will focus on the Maillard reaction and elucidate how this reaction might play an important role in aging and cataract formation in the lens.

Maillard reaction of sugars in the lens

The oxygen content in the lens is extremely low relative to the surrounding tissues (McNulty et al. 2004; Shui and Beebe 2008), and glucose levels are also markedly lower than plasma levels (Tomana et al. 1984). Despite this, several oxidative and glucose-mediated modifications accumulate in the aging lens. Indeed, long-lived proteins such as those occurring in the lens significantly accumulate post-synthetic modifications during aging. A major impetus for research into Maillard chemistry in the lens came from the discovery by Monnier and Cerami (1981) that the physico-chemical changes in the aging lens could be duplicated in vitro by simply incubating lens proteins with glucose. Studies immediately after this discovery quickly established that glycation occurs at a higher rate during diabetes in both human (Garlick et al. 1984; Oimomi et al. 1988) and rat lenses (Yano et al. 1989). The fact that diabetic lenses "yellow" at an accelerated rate and that lens fluorescence was shown to be related to glycemic control supported this view (Larsen et al. 1989; Liang 1987; Lutze and Bresnick 1991). The Baynes' group established the structure of an AGE in 1986 (Ahmed et al. 1986). They showed that N^{ε}-carboxymethyllysine (CML) is a terminal stable product derived from the degradation of the Amadori compound and is present in the human lens (Ahmed et al. 1986). CML accumulates to a higher degree in cataractous lenses than in age-matched non-cataractous controls (Franke et al. 2003; Lyons et al. 1991; Tessier et al. 1999).

Another milestone for AGE research was the discovery of pentosidine by Sell and Monnier (1989). Unlike CML, this AGE is a fluorescent protein cross-linking adduct and accumulates in lens proteins with age, especially those which are intensely pigmented (Nagaraj et al. 1991). These discoveries firmly established that AGEs were integral to lens aging and subsequent cataract formation. Indeed, to date, there are more than 15 AGEs that have been found in vivo, with most present in the lens and at higher levels in cataracts.

The finding that glycation could play a role in diabetic cataracts led to further studies to closely examine the relationship between glycation and the degree of glycemic control in diabetic patients. Abraham et al. determined that glycation occurred progressively in diabetic lenses (Perry et al. 1987) and corresponded to degrees of hyperglycemia (Swamy-Mruthinti et al. 1996). Fructose produced from the polyol pathway was found to be a stronger glycating agent than glucose and was proposed to contribute to the AGE burden in cataracts (Suarez et al. 1988; Suarez 1989). These discoveries led to new studies in which the focus was on AGEs and not on the initial glycation products. Subsequent studies showed that pentosidine accumulated to a greater degree in diabetic cataracts than in senile cataracts, although CML levels were similar in the two types of cataracts (Lyons et al. 1991). In diabetic animal lenses, a clear increase in pentosidine and AGEs was observed and was dependent on a glycemic threshold (Nagaraj et al. 1996a, b; Swamy-Mruthinti et al. 1999).

Since these discoveries, other sugar-derived AGEs have been detected in the lens. Pyrraline is another AGE, and it is derived from the reaction of lysine in proteins with 3-deoxyglucosone (3-DG). 3-DG is a dehydrated derivative of the Amadori product found in vivo. This AGE is present at higher levels in cataractous lenses relative to non-cataractous lenses (Nagaraj and Sady 1996), which suggests enhanced degradation of the Amadori product in cataractous lenses. Recent work showed the presence of another protein cross-link derived from glucose and first identified by Lederer's group (Biemel et al. 2002). This protein cross-linking structure is known as glucosepane. Glucosepane arises from the reaction of a dideoxyosone intermediate (which is derived from the long-range carbonyl shift of the Amadori product) with arginine residues in proteins. This AGE is present in higher amounts in senile cataractous lenses when compared with age-matched non-cataractous lenses. Whether this is an intra- or inter-molecular cross-linking structure needs to be verified; nevertheless, its presence in the lens is clearly indicative of the transformation of the Amadori product to a dideoxyosone intermediate. The dideoxyosone intermediate could form many other lysine–arginine cross-linking structures. Thus, because of its potential prominence in AGE synthesis, attempts were made to detect dideoxyosone intermediates. Since dideoxyosone intermediates are inherently unstable, an immunological method was developed wherein a monoclonal antibody against a chemically trapped dideoxyosone was used (Puttaiah et al. 2006). Further studies are needed to appreciate the full scope of dideoxyosones in AGE formation in vivo.

Another interesting observation made recently was that kynurenines, which are tryptophan oxidation products present in the lens, can modulate AGE synthesis. They were found to generate glycation initiators from ascorbate upon UV light irradiation (Ortwerth et al. 2009). 3OH-kynurenine at low concentrations was found to promote pentosidine synthesis from ribose in lens proteins (Nagaraj

et al. 2010). Thus, there may be interplay between the Maillard reaction and tryptophan oxidation in the aging lens.

Maillard reaction by ascorbate in the lens

Ascorbate (vitamin C) levels are high in the lens ($\sim$2 mM) and, in the late 1980s, Ortwerth et al. made a compelling case that ascorbate oxidation products react with lens proteins much the same way as sugars to generate AGEs (Cheng et al. 2001; Linetsky et al. 2008; Ortwerth and Olesen 1988b; Ortwerth et al. 1994; Prabhakaram and Ortwerth 1992; Slight et al. 1990). Ascorbate levels decrease with aging and cataract formation (Lohmann et al. 1986; Tessier et al. 1998), and two studies provided chemical evidence of involvement in lens aging. Firstly, the Baynes' group showed that CML could be formed from ascorbate (Reddy et al. 1995) and, secondly, the Monnier group showed that ascorbate oxidation products were strong precursors for pentosidine (Nagaraj et al. 1991). Further work on ascorbate led to the identification of a lysine–lysine cross-linking adduct, initially named LM-1 (Nagaraj and Monnier 1992), and later found to be similar to a previously identified AGE vesperlysine A (Tessier et al. 1999). An interesting observation on vesperlysine A is that its in vitro formation can be greatly enhanced by the addition of glyoxal and glycoaldehyde to ribose, clearly an indication that a combination of sugar and dicarbonyl reactions can favor AGE synthesis in the lens. Another example for such AGE formation from combination reactions with different carbohydrates is OP-lysine (Argirov et al. 2004), which is synthesized by the reaction of glycoaldehyde and glyceraldehyde with lysine. This product is present in the lens and its levels were found to be elevated in cataractous lenses. Another AGE, ascorbate monoalkylamide, synthesized from ascorbate, has also been reported in the lens (Nagaraj et al. 1999).

Ortwerth's laboratory made some additional remarkable discoveries. First, they found that ascorbate-derived AGEs were photosensitizers and could produce singlet oxygen upon irradiation with UVA light (see below). Second, they found that ascorbate-derived AGEs were the major protein modifications in the human lens; they identified, although did not elucidate the structure of nearly 100 products in the human lens that could be synthesized in vitro from the glycation of lens proteins with ascorbate (Cheng et al. 2006). They also isolated an ascorbate-derived AGE, K2P, which is a lysine–lysine cross-linking adduct (Cheng et al. 2004). K2P levels strictly correlated with protein fluorescence in the lens and K2P was present at high levels in brunescent cataracts. These findings further reiterated a role for ascorbate in the Maillard reactions in the lens. However, even more compelling evidence for ascorbate-mediated Maillard reactions came from a recent study; Monnier et al. developed a transgenic animal line in which a human ascorbate transporter was specifically over-expressed in the lens (Fan et al. 2006). These animals, but not the wild-type counterparts, accumulated significant quantities of ascorbate, its oxidation product dehydroascorbate and ascorbate-derived AGEs in their lenses. Remarkably, the lenses of these animals turned yellow with age, similar to aging human lenses, and this was the first direct demonstration that ascorbate-mediated AGE formation was a major mechanism in the aging lens (Fan et al. 2006).

Ascorbate-derived AGEs in the lens are photosensitizers

Aged and cataractous lens proteins absorb UVA light and generate reactive oxygen species in the presence of molecular oxygen (Lee et al. 1999; Linetsky and Ortwerth 1996; Ortwerth et al. 1995). Largely due to the work in the laboratory of Ortwerth, a new role for AGEs in lens protein damage was discovered. They elegantly demonstrated that the UVA-sensitizing property of the water-insoluble cross-linked proteins of the human lens could be reproduced in vitro by the Maillard reaction of lens proteins with ascorbate. The ascorbate-modified proteins under aerobic conditions produced similar amounts of reactive oxygen species (ROS) during UVA photolysis, with singlet oxygen representing 96% of all ROS produced (Ortwerth et al. 2003). Superoxide and hydrogen peroxide were the additional ROS generated by both human lens proteins and ascorbate-modified lens proteins. In later studies, UVA-sensitizing activity with individual AGEs, such as pentosidine, argpyrimidine, K2P and OP-lysine was demonstrated (Kessel et al. 2005; Ortwerth et al. 1997). It is conceivable that ROS-mediated damage to tryptophan and histidine residues in lens proteins is due to UVA photolysis of AGEs, especially in cataractous lenses. Such damages might also occur even in the absence of oxygen. In the excited state, AGEs can react with ascorbate by a type 1 photochemical mechanism causing its photolysis. This could lead to the formation of dehydroascorbic acid and further to 2,3-diketogulonic acid and L-erythrulose, probably via an ascorbate radical. Depending on the UVA light flux, these reactions could lead to two distinctive molecular events in the aged lenses: under acute doses of UVA light, the reactions could cause bleaching of AGEs (Argirov et al. 2005) and, under UVA light fluxes similar to the ambient UVA, the reactions could produce ascorbate oxidation products, with little or no loss of the lens protein AGEs (Ortwerth et al. 2003). The end effect could be additional AGE formation from ascorbate oxidation products, which could then set off a vicious cycle in which ascorbate-AGEs promote the formation of more AGEs in the lens (Fig. 2).

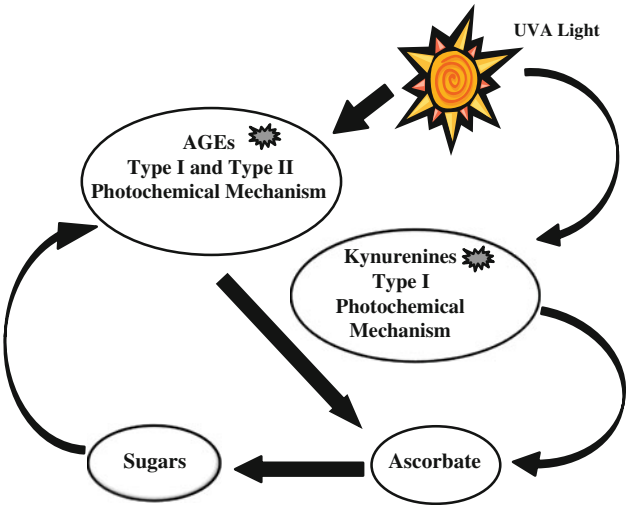


Fig. 2 Ascorbate-derived AGEs through their photosensitization property can promote oxidation of ascorbate, which generates sugars, such as threose and erythrulose, and form additional AGEs in lens proteins. This vicious cycle is likely to enhance AGE formation in aged and cataractous lenses

Maillard reaction by dicarbonyls

Dicarbonyl compounds, such as methylglyoxal (MGO) and glyoxal (GO), are present in the lens and are now established as playing a central role in AGE formation (Lo et al. 1994; Selwood and Thornalley 1993). Most of the MGO is derived from the triose phosphate intermediates of glycolysis, although other minor sources are obtained through the metabolism of acetone and aminoacetone (Thornalley 1993). MGO levels in the lens are higher than in plasma (Haik et al. 1994) and the first MGO-derived AGE to be isolated and characterized was named imidazolysine by our group (Nagaraj et al. 1996a, b), although the Baynes' group identified the very same compound and named it methylglyoxal lysine dimer (MOLD) (Degenhardt et al. 1998). This product is a lysine–lysine cross-link formed by the reaction of two molecules of MGO with two lysine residues. Its formation in the human lens was later established by chromatographic and immunochemical methods (Chellan and Nagaraj 1999; Frye et al. 1998; Shamsi and Nagaraj 1999; Shamsi et al. 2000). Another AGE derived from the reaction of MGO with lysine is the N^{ε}-carboxyethyllysine (CEL), also found to be present in the human lens (Ahmed et al. 1997).

Since MGO is a dicarbonyl compound, it was expected to react avidly with arginine residues and we identified and isolated a fluorescent product in 1996 called argpyrimidine (Shipanova et al. 1997). Immunological and chemical methods clearly established that this product was formed in the human lens and occurred at higher levels during cataract (Padayatti et al. 2001; Wilker et al. 2001). This compound could possibly degrade to ornithine in aged lenses (Sell and Monnier 2004). Thornalley's group identified another type of modification of arginine, namely hydroimidazolones. Three isomers of hydroimidazolone (MGH-1, MGH-2 and MGH-3) were identified and were later found to be present in human lenses. Remarkably, hydroimidazolones were present at relatively high concentrations in the lens, reaching more than 20 nmoles/mg of protein (Ahmed et al. 2003), probably the highest among all known AGEs in the human lens. Lederer's group working independently on the chemistry of MGO reactions identified MODIC, an MGO-derived lysine–arginine cross-linking product and later established its formation in human cataractous lenses (Biemel et al. 2002). Additionally, a more recent study by Monnier's group claimed that lysine residues in lens proteins were oxidized in a dicarbonyl/metal catalyzed oxidation reaction to allysine, a precursor of aminoadipic acid in the human lens (Fan et al. 2009). Thus, MGO appears to be a major protein modifier in the lens.

GO is another dicarbonyl present in the lens. Unlike MGO, GO is derived from lipid and sugar oxidation (Thornalley 2005). GO reacts similarly to MGO with lens proteins and forms glyoxal-lysine dimer (GOLD), and hydroimidazolone and *glyoxal*-derived imidazolium cross-link (GODIC; Fig. 2). Among these products, GOLD and GODIC have already been detected in the human lenses (Biemel et al. 2002). In addition to their direct modification abilities, these dicarbonyls can bring about additional damages through the formation of ROS by the photosensitization of their AGEs by UV light (Argirova and Breipohl 2002).

In summary, sugars, ascorbate and dicarbonyl compounds (Fig. 3) can all generate AGEs through the Maillard reaction in aging and cataractous lenses. Table 1 shows all the AGEs identified so far in the lens and their levels in the human lens.

Maillard reaction and the chaperone function of α-crystallin

An interesting twist on the reaction of GO and MGO with lens α-crystallin enhances its intrinsic chaperone function. α-crystallin constitutes about 50% of the total lens protein and is composed of two subunits: αA-(acidic) and αB-(basic) crystallin (Bloemendal and de Jong 1991). These proteins belong to the family of small heat shock proteins. In 1993, Horwitz first described that α-crystallin exhibits a chaperone-like function (Horwitz 1993). Several subsequent investigations studied the effect of aging and diabetes on the chaperone function of α-crystallin (Derham and Harding 1997; Takemoto and Boyle 1998; Thampi et al. 2002). Abraham's group, based on their work on

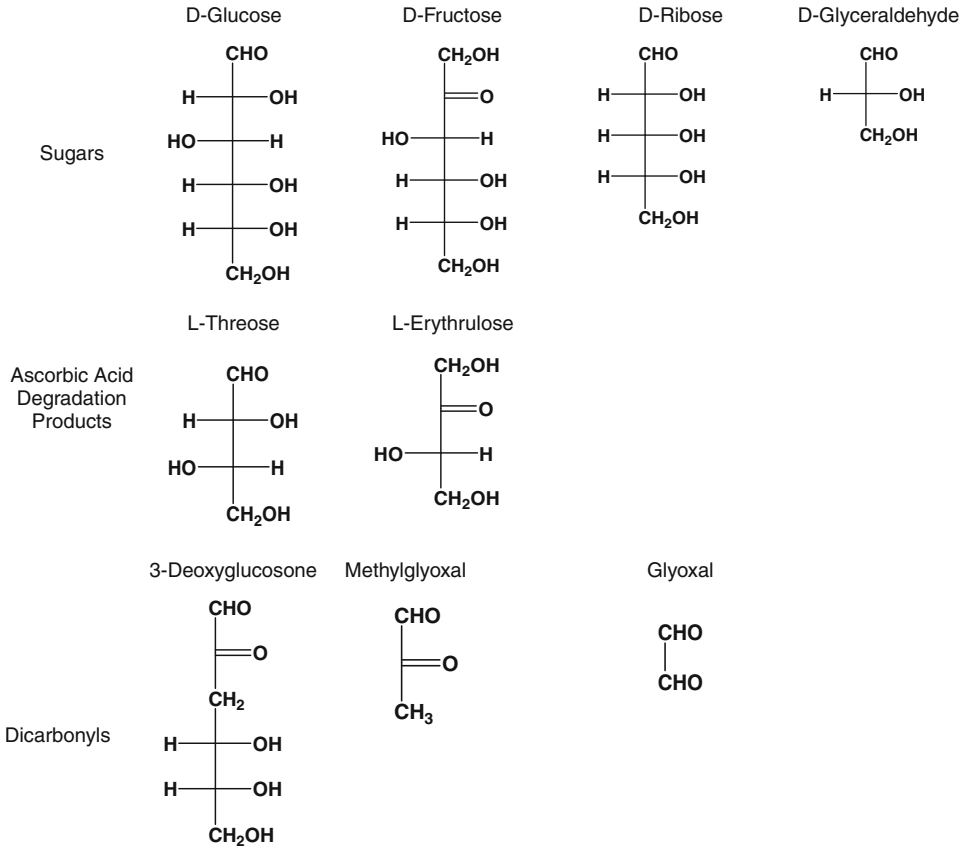


Fig. 3 AGE precursors in the human lens

diabetic rats, concluded that diabetes reduced the chaperone function of α-crystallin (Thampi et al. 2002) and later studies have shown that Maillard reactions by sugars could be the cause for such a reduction in the chaperone function of α-crystallin (Bhattacharyya et al. 2007; Kumar et al. 2007). In light of these findings, we embarked on studies to determine if dicarbonyls affect the chaperone function. Surprisingly, the reaction of MGO and GO with α-crystallin increased the chaperone function (Biswas et al. 2008a, b; Kumar et al. 2004; Nagaraj et al. 2003). This was later found to be due to modification of arginine residues in α-crystallin. Mass spectrometric studies identified R21, R49 and R103 to be modified to argpyrimidine by MGO (Nagaraj et al. 2003). Subsequent studies using site-directed mutagenesis of these arginine residues to alanine showed that while R21A and R103A mutants increased the chaperone function, R49A decreased it (Biswas et al. 2006, 2008a, b). However, the net effect of all three mutations was a gain in the chaperone function. Based on these findings, we concluded that removal of the positive charge from selected arginine residues (by the reaction with MGO or mutation to alanine) resulted in enhancement of the chaperone function of αA-crystallin. Our recent study shows that MGH-1 modification also increases the chaperone function, and that the extent of MGH-1 modification equal to what is found in vivo is sufficient to increase the chaperone function of αA-crystallin (Gangadhariah et al.). Because MGH-1 formation occurs rapidly from the reaction of MGO, it is likely that in vivo MGH-1 could have a bigger role in enhancing the chaperone function of α-crystallin.

MGO modification was also found to inhibit pentosidine synthesis and prevent ascorbate-mediated inactivation of the chaperone function of αA-crystallin (Puttaiah et al. 2007). α-Crystallin, through its chaperone function, also possesses the ability to refold denatured proteins. Reddy's group claimed that MGO-modified α-crystallin loses this function (Kumar et al. 2005); but in our recent study with mildly MGO-modified αA-crystallin, we showed that protein refolding ability was unaffected by mild MGO modification (Gangadhariah et al.). Furthermore, we found that MGO modification of the client proteins made them more resistant to chemical and thermal stress (Biswas et al. 2008a, b). Thus, if α-crystallin and the client proteins are both modified by MGO, a likely scenario in vivo, the combined effect could be that the proteins become even more resistant to denaturation. Altogether, these observations suggest that MGO and GO in the lens can enhance the chaperone function of α-crystallin.

Whether the improvement in chaperone function following MGO modification has a positive or negative influence on the lens is debatable. In the lens, the client

Table 1 AGEs in the human lens

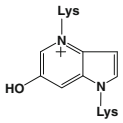
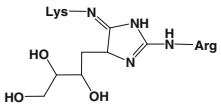
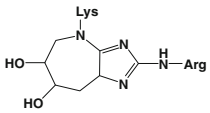
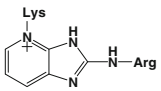
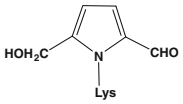
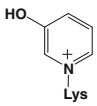
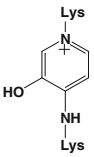
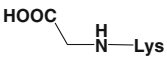
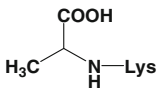
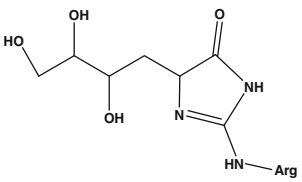
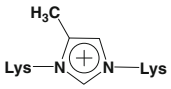
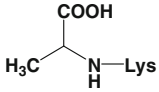
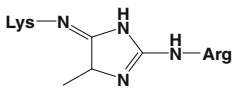
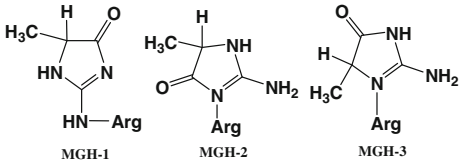
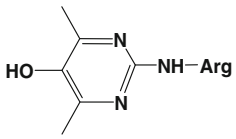
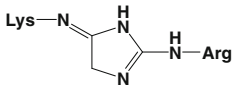
	Age	Structure	Pmoles/mg protein	References
1	Vesperlysine A (LM-1)		2–24	Tessier et al. (1999)
2	DOGDIC		1–8	Biemel et al. (2002)
3	Glucosepane		132–242	Biemel et al. (2002)
4	Pentosidine		2–5 2–22 1–7	Franke et al. (2003) Nagaraj et al. (1991) Tessier et al. (1999)
5	Pyrraline		21–60	Nagaraj and Sady (1996)
6	OP-Lysine		80–520	Argirov et al. (2004)
7	K2P		23–613	Cheng et al. (2006)
8	Carboxymethyllysine		1–5,200 200–3,300 1–5 mmol/mol Lys	Franke et al. (2003) Tessier et al. (1999) Ahmed et al. (1986)
9	Oxalate monoalkylamide		*	Nagaraj et al. (1999)
10	Imidazoline		1–190 AU	Franke et al. (2003)
11	MOLD (imidazolysine)		0.1–0.8 mmol/mol Lys 211–366	Frye et al. (1998) Chellan and Nagaraj (1999)
12	CEL		1.8–4 mmol/mol Lys	Ahmed et al. (1997)

Table 1 continued

	Age	Structure	Pmoles/mg protein	References
13	MODIC		41–97	Biemel et al. (2002)
14	Hydroimidazolones MGH-1, MGH-2 and MGH-3	 MGH-1 MGH-2 MGH-3	1,200–22,300	Ahmed et al. (2003)
15	Argpyrimidine		16–1,500	Padayatti et al. (2001) Wilker et al. (2001)
16	GOLD		2–22 0.04–0.2 mmol/mol Lys	Chellan and Nagaraj (1999) Frye et al. (1998)
17	GODIC		2–43	Biemel et al. (2002)

* Not determined

proteins are likely to be permanently tethered to α-crystallin once they are chaperoned, if there are no mechanisms to dissociate the chaperone–client protein complex. In many cells, larger heat shock proteins, such as the Hsp70-protein complex, are dissociated in an ATP-dependent manner, although such a mechanism has not been documented in the lens. If the chaperone–client protein complexes increase as a result of MGO modification, it may be detrimental to the function of the lens, because more light may be scattered by such protein complexes. This issue needs to be studied further.

Introduction to the retina

The mammalian retina is a highly complex and specialized tissue. Retinal neurons act in concert to receive light and transform chemical stimuli into image-forming signals, which are transmitted through the axons of the optic nerve to the brain. In response to metabolic requirements, the retina closely regulates oxygenation and nutrient balance: a function performed by the intra-retinal microvasculature and the choriocapillaris of the choroid. At the interface between the photoreceptors and the underlying choroid lies the retinal pigment epithelium (RPE; Fig. 4), which rests on a basal lamina known as Bruch's membrane. Together, this RPE–Bruch's membrane complex forms the outer blood retinal barrier, which serves to transport nutrients and waste products into and out of the retina. The RPE also plays a major role in the diurnal visual cycle and is

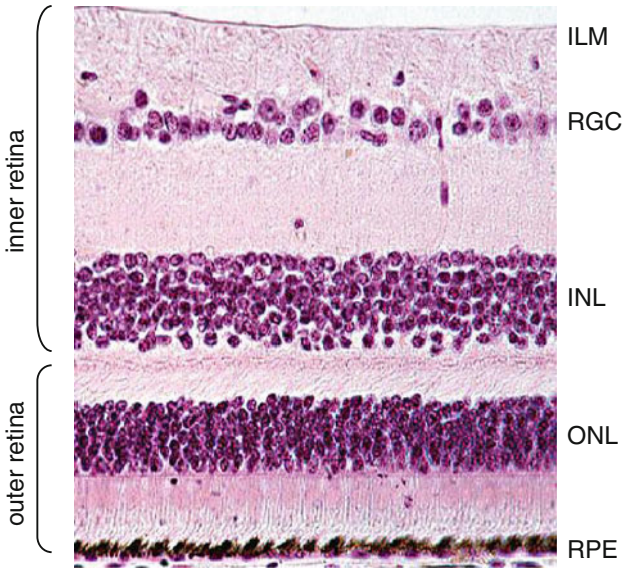


Fig. 4 Histological section of the retina. The inner and outer retina is depicted with the arbitrary cut being between the inner nuclear layer (INL) and the photoreceptor nuclei (the outer nuclear layer; ONL). The RPE rests on Bruch's membrane. Internal limiting membrane (ILM); retinal ganglion cell layer (RGC)

responsible for the uptake, phagocytosis and removal of spent photoreceptor outer segments.

The neural retina shows little regenerative capacity during aging and the cellular manifestations of this process include increased chemical damage to proteins, accumulation of intra- and/or extracellular deposits and decreased efficiency of antioxidant defense. All layers of the retina suffer during the aging process. For example, primary open angle glaucoma (POAG) is associated with aging and manifests as a chronic neurodegenerative disease resulting in progressive loss of retinal ganglion cells and associated optic nerve axons (Harwerth et al. 2008; Parikh et al. 2007). Likewise, the cells of the outer retina also suffer during aging.

AGEs and the retina during aging

As outlined in the early sections of this review, the formation of AGEs in the lens is well established, but comparatively less is known about these adducts in other structures of the aging eye. Perhaps, unsurprisingly, AGEs are known to accumulate with aging and diabetic human cornea (Kaji et al. 2000; Malik et al. 1992), the collagenous network of the lamina cribrosa at the optic nerve head (Amano et al. 2001), the vitreous gel (Stitt et al. 1998) and within the trabecular meshwork (Ganea and Harding 2006). This section of the review concentrates on the retina.

AGEs and cells of the inner retina

AGE formation in the inner retina is best characterized during diabetic retinopathy, and this has been suggested to be an important pathogenic pathway in this condition as previously reviewed (Bhatwadekar and Stitt 2007; Stitt et al. 2002a, b). In the context of aging, AGE adducts accumulate within the collagenous matrix of the lamina cribrosa (Albon et al. 1995, 2000) and this has implications for the well-being of axons of the optic nerve. Indeed, AGE-mediated cross-linking of the lamina cribrosa may reduce flexibility of this matrix and impact on optic nerve head pathology (Albon et al. 1995, 2000). AGE accumulation in human glaucomatous tissues during aging is associated with ganglion cell degeneration (Tezel et al. 2007). The presence of a receptor for AGE, RAGE, on retinal ganglion cells has also been demonstrated (Tezel et al. 2007), although the precise nature of this receptor in these cells remains uncertain. There is potential for RAGE-ligand interactions to contribute to retinal neurodegenerative pathology during aging (Takeuchi and Yamagishi 2008) possibly through age-related activation of RAGE-linked pro-inflammatory pathways.

AGEs and cells of the outer retina

Outer retinal changes in the elderly are collectively referred to as age-related maculopathy (ARM) and, while there may be no visual loss in early ARM, a significant proportion of patients may progress to the late-stage manifestations of age-related macular degeneration (AMD). AMD represents the leading cause of blindness in the developed countries (Klein et al. 2002). Its prevalence is likely to rise as populations show increasing longevity (Beatty et al. 2000). AMD manifests as two clear pathologies: geographic atrophy (GA) and choroidal neovascularization (CNV), termed dry and wet AMD, respectively. Both forms of AMD cause severe, irreversible loss of central vision.

The outer retina consists of the photoreceptors and RPE, and these cells reside in a highly oxygenated and glucose-rich microenvironment. This area of the neuropile is also rich in polyunsaturated fatty acids (PUFA) such as docosahexaenoic acid (DHA), which are highly susceptible to lipid peroxidation (Bazan 1982). This process yields lipid hydroperoxides, which decompose to reactive aldehydes such as acrolein, 4-hydroxynonenal (HNE) or malondialdehyde (MDA).These, in turn, react with proteins to form stable advanced lipoxidation end products (ALEs) and AGEs (Januszewski et al. 2003). With its unusually high levels of PUFAs and presence of various sources of oxidation, the retina provides an ideal environment for the formation of various ALE species. In particular, photoreceptor outer segments are particularly rich in $n-3$ and $n-6$ PUFAs (Catala 2006) and these membranous discs harbor elevated levels of ALEs (Cingolani et al. 2006) with strong links to pathology. Oxidation of DHA is associated with the carboxyethylpyrrole (CEP) adducts in the retina, especially with aging and at significant levels in AMD donors (Crabb et al. 2002a, b; Ebrahem et al. 2006; Gu et al. 2003, 2009; Ni et al. 2009). In addition, ALEs derived from acrolein may be formed endogenously in vivo and its primary adduct, FDP–lysine, has been identified in various cells and tissues, including the RPE (Schutt et al. 2003; Zhang et al. 2005) and photoreceptors (Cingolani et al. 2006). ALE adducts have been implicated in a broad spectrum of molecular pathological events, ranging from misfolding of structural proteins, alteration of transcriptional regulation and changes to enzyme activity, ultimately leading to cell dysfunction (Crabb et al. 2002a, b; Ethen et al. 2007).

AGEs accumulate in and around the RPE where they can appear as free adducts or as AGE-modified proteins in cytoplasmic lipofuscin (Schutt et al. 2003). AGEs have been demonstrated in Bruch's membrane and overlying drusen (extracellular deposits) from aged postmortem eyes (Fig. 5) and at elevated levels in eyes with pre-diagnosed

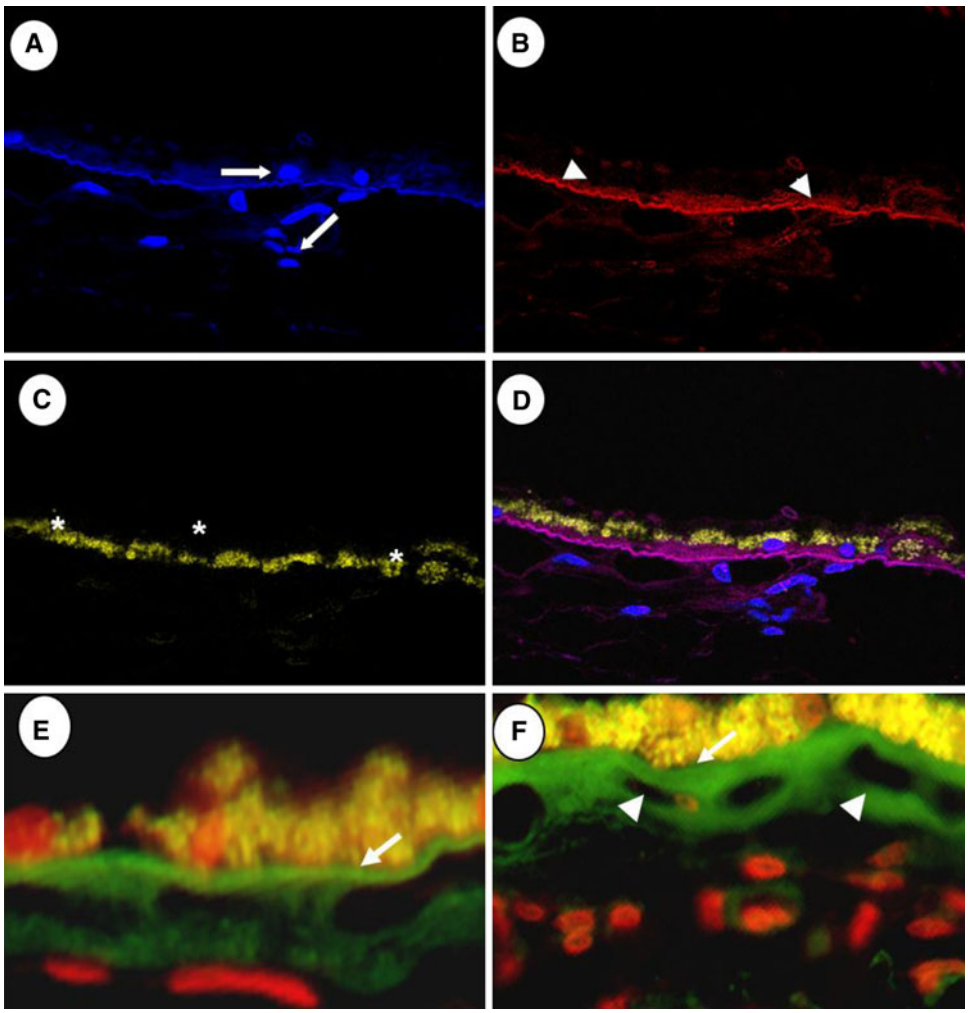


Fig. 5 AGE-linked autofluorescence is present in human Bruch's membrane (88-year-old male). **a** Cell nuclei stained with DAPI (*blue arrows*); **b** localization of fluorescent AGEs within the RPE layer and Bruch's membrane with excitation emission spectra in 400–460 nm range (*red*); **c** RPE autofluorescence (*yellow*) due to presence of lipofuscin (*asterisk*); **d** Composite image of **a–c**; **e** AGE immunoreactivity in human Bruch's membrane and choroid in a middle aged (53 years old) donor; **f** intense AGE immunofluorescence is evidenced in an aged donor (76 years) in Bruch's membrane (*arrow*) with more diffuse immunoreactivity in the matrix around the choriocapillaris (*arrowheads*) (color figure online)

AMD (Handa et al. 1999; Howes et al. 2004; Ishibashi et al. 1998; Schutt et al. 2003; Yamada et al. 2006). RPE, growing on an AGE-modified substrate akin to what happens in normal aging (Glenn et al. 2007), shows depressed lysosomal enzymatic activity and enhanced accumulation of lipofuscin (Glenn et al. 2009), which is an important link between age-related RPE dysfunction and clinical data demonstrating AGE-immunoreactivity within Bruch's membrane and the RPE. AGEs and ALEs can induce pro-angiogenic growth factors in RPE in vitro (Zhou et al. 2005) and, although these responses need to be confirmed in vivo, this could be an important link between advanced glycation, aging and inflammation in the outer retina.

Bruch's membrane thickens as we get older and there is remodeling of its extracellular matrix protein network with a net reduction in hydraulic conductivity and charge selectivity (Binder et al. 2007). There is also reduction in RPE viability with aging and surviving cells contain less melanin and show impaired degradative capacity (Boulton and Dayhaw-Barker 2001; Boulton et al. 2004), which is generally thought to accompany age-related accumulation of autofluorescent material called lipofuscin (Bird et al. 1995). Non-degradable lipofuscin continues to accumulate throughout life (Schutt et al. 2003), while drusen deposits occur between the RPE and inner collagenous layer of Bruch's membrane (de Jong 2006).

Enzymatic and non-enzymatic defenses against glycation in the eye

The eye has high levels of glutathione (Lou 2000) and this can act as a natural anti-glycation agent partly due to its ability to react with reducing sugars and prevent their reaction with proteins, and partly due to its ability to reduce dehydroascorbate to ascorbate (Linetsky et al. 2005; Ortwerth and Olesen 1988a). Yet another mechanism is via GSH-dependent metabolism of MGO (see below). ROS have been shown to increase the formation of some AGEs.

The eye lens has several antioxidative enzymes, including GSH peroxidase, which requires GSH for function. Thus, GSH might indirectly reduce ROS levels and consequently AGEs in the lens. Taurine, present in the lens, may function in a manner analogous to GSH in inhibiting AGE formation (Devamanoharan et al. 1997).

A range of enzymatic systems that provide endogenous protection against dicarbonyls has evolved. In 2001, Szwergold et al. identified fructosamine 3-kinase (Brown et al. 2003; Lal et al. 1993; Szwergold et al. 2001), which converts fructosamine (Amadori product) into fructosamine 3-phosphate. While this enzyme regenerates lysine from the Amadori product, paradoxically, it produces 3-DG as a by-product. 3-DG is a potent glycating agent and can generate AGEs such as imidazoline and pyrraline on proteins.

Another example of endogenous protection is that the glutathione (GSH)-dependent glyoxalase complex (formed from glyoxalase I (GLO1) and glyoxalase II (GLO2) components) acts as a detoxification system for GO and MGO, which are converted to glycolate and D-lactate, respectively (Thornalley 1993, 1998). The Km values for these substrates are relatively low, suggesting that glyoxalase is one of the major factors for inhibiting dicarbonyl-mediated AGE synthesis in the lens. However, in the human lens, glyoxalase I activity decreases with age (Mailankot et al. 2009) along with a decrease in GSH level (Haik et al. 1994). Together, these factors could contribute to a drastic reduction in glyoxalase I activity, which could result in the retention of MGO and consequently formation of MGO-AGEs. Indeed, endothelial cells transfected to over-express GLO1 accumulate less MGO-derived AGEs (Shinohara et al. 1998) and are protected against high glucose-induced responses (Yao et al. 2007). Interestingly, *C. elegans* engineered to over-express GLO1 also contains less AGEs and shows significantly increased life span (Morcos et al. 2008; Schlotterer et al. 2009).

In a recent study, we showed that over-expression of human GLO1 in mouse lenses inhibits AGE formation, implicating the glyoxalase system in controlling AGE formation in the lens (Gangadhariah et al. 2010). Interestingly, though GLO1 mRNA content and activity are increased in the diabetic mouse lens, those increases are insufficient to reduce MGO levels, hinting at the possible existence of other mechanisms in reducing MGO levels (Staniszewska and Nagaraj 2006). With respect to the retina, treatment of human retinal pericytes with high glucose and S-p-bromobenzylglutathione cyclopentyl diester (an inhibitor of GLO1) results in apoptosis concomitant with increases in MGO (Miller et al. 2006). Furthermore, over-expression of GLO1 in these cells could protect against high glucose-induced apoptotsis (Miller et al. 2006). Strategies to enhance carbonyl detoxification in retinal cells could be an important future therapeutic strategy.

Pharmacological inhibition of glycation in the aging eye

To date, few therapeutic options exist for the treatment of AGE-linked aging disorders. The use of so-called 'AGE breakers' to cleave cross-links has been reported in several clinical trials for heart failure, atherosclerosis and renal diseases (Hartog et al. 2007; Huijberts et al. 2008; Jandeleit-Dahm et al. 2008). Breakers such as N-phenacylthiazolium bromide (PTB) were proposed to cleave AGE-derived protein cross-links (Vasan et al. 1996) and has been used in studies of Alzheimer's disease and diabetic retinopathy (Oturai et al. 2000; Vasan et al. 2003). However, this has been disputed (Thornalley and Minhas 1999) and it is currently not clear if pharmacological effects of putative AGE breakers are mediated by cleaving AGEs. Thus far, no reagent has been synthesised that can break specific cross-linking AGEs such as pentosidine, glucosepane and K2P (1-(5-amino-5-carboxypentyl)-4-(5-amino-5-carboxypentyl-amino)-3-hydroxy-2, 3-dihydropyridinium) (Cheng et al. 2005; Monnier et al. 2005; Sell et al. 2005).

Several pharmacological agents have been tested for inhibition of the Maillard reaction and many of these have been evaluated in the eye. Aminoguanidine is highly effective in inhibiting AGE formation associated with cataract development (Harding 1992; Swamy-Mruthinti et al. 1996) and diabetic retinopathy (Agardh et al. 2000; Gardiner et al. 2003; Hammes et al. 1991; Kern and Engerman 2001). Aminoguanidine has been evaluated in a multi-center clinical trial where it failed to achieve statistically significant lowering of serum creatinine, urinary albumin but showed positive signs toward slowing the progression of overt nephropathy and retinopathy (Bolton et al. 2004). However, it is now known that aminoguanidine is not a specific AGE inhibitor and also acts as an effective iNOS inhibitor (Ren et al. 2008). Other related nucleophilic compounds have also shown beneficial effects in terms of inhibiting AGE formation in the lens (Fan and Monnier 2008). Pyridoxamine also inhibits AGE formation in diabetic lenses (Padival and Nagaraj 2006) and protects against diabetic retinopathy (Stitt et al. 2002a, b). Carnosine has been found to be very effective against experimental cataract, and it can also inhibit AGE formation in vitro (Reddy et al. 2005). Dietary caloric restriction delays cataract formation in mice (Taylor et al. 1989), which might inhibit AGE formation in the lens similar to effects seen on the skin collagen AGEs (Cefalu et al. 1995; Sell et al. 2003).

Conclusion

Advanced glycation plays an important role in age-related ocular disease, but more research is still needed to fully appreciate the precise pathogenic mechanisms with which these adducts are involved. As our populations become skewed toward greater longevity, aging disorders of the eye are becoming ever more prevalent and this has important, far-reaching implications for morbidity and quality of life in the elderly. Undoubtedly, we have the best understanding about AGEs and their role in lens pathology. Lens proteins are probably the longest-lived proteins in our body and therefore they accumulate significant quantities of post-synthetic modifications. To date, there are more than 15 AGEs that have been found in vivo; remarkably, most are present in the lens. It is clear that AGEs progressively accumulate with age in the lens and at a higher rate in cataractous lenses. Pharmacological inhibitors of AGEs have been found to inhibit cataract development, although their mode of action needs to be verified. Long-term reduction of AGE formation by dietary manipulations or lifestyle changes might reduce AGE levels and help retain clarity of the lens. It is important to recognize that our understanding of AGEs is still at its infancy. At present, we are probably barely touching the surface of this complex reaction. Just as a reminder, Ortwerth in one of his last papers before his retirement identified nearly 100 compounds in the lens that could be generated in vitro from the Maillard reaction of ascorbate (Cheng et al. 2006). All that we know now is that they are ascorbate-derived AGEs, but we do not know anything about their chemistry and synthetic pathways.

To a lesser extent, the retina also accumulates AGEs, but nevertheless such adducts may have significant pathogenic consequences for this neurosensory tissue. With novel pharmacological inhibitors of AGEs becoming available, there is hope that advanced glycation can be manipulated therapeutically. There is plenty of work that lies ahead. With progress being made toward understanding cataractogenesis, glaucoma and age-related retinal degeneration, combined with the ability to regulate Maillard chemistry in vivo, we could be close to preventing these conditions and therefore enhance the prospects of life-long vision.

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