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Advanced glycation end products (AGEs) in diabetes

Introduction

Life style in the industrialized countries has dramatically changed over the last 100 years. Due to theses changes as well as an increase in hygienic standards and a medical progress, best-performance life expectancy has constantly increased with an apparent rate of three months per year for the last 160 years. However, in recent years, the incidence of civilization-associated diseases has also increased. Especially, the incidence of diabetes has nearly doubled over the last 20 years. Whereas in the USA the incidence has been around 3 cases per 1000 inhabitants during the 80s and 90s it has increased to about 7.5 per 1000 today (CDC, 2007). According to the WHO, there are currently 151 million people suffering from diabetes worldwide and this number may rise to 221 million in 2010 and about 300 million in 2025. This goes along with a significant gain in average body weight and frequency of obesity. Olshansky and others discussed, that due to these changes, life expectancy will not increase further on, but unfortunately will decline in the future (Olshansky et al., 2005).

In diabetes and obesity, protein modifications which are caused by high concentrations of reactive aldehydes such as carbohydrates and α-oxo-aldehydes accumulate to large amounts and are believed to play a major role in the pathogenesis of major diabetic complications such as nephropathy and vascular disease. This non-enzymatic formation of so called advanced glycation endproducts (AGEs) is also observed during normal ageing and occurs endogenously in as well as outside of every cell. In the course of normal "healthy" ageing, increasing amounts of AGEs can also be detected in many tissues with further increase in patients with diabetes. Additionally, to the endogenously formed AGEs, we incorporate a significant amount of AGEs with food, but the contribution of these exogeneous AGEs to pathophysiological processes is largely unresolved.

Structure and origin of AGEs

In 1912 Maillard first observed a browning reaction by heating glycine and glucose (Maillard, 1912). This reaction, now called Maillard reaction, is the driving force of AGE formation. Advanced Glycation Endproducts are considered as a heterogeneous group of compounds that arise non-enzymatically by the reaction of reducing sugars and other α-carbonylic compounds with amino groups, not only within proteins but also lipids and nucleic acids.

The paradigm for these reactions is the condensation of glucose with a lysine residue on a protein (Fig. 1). The

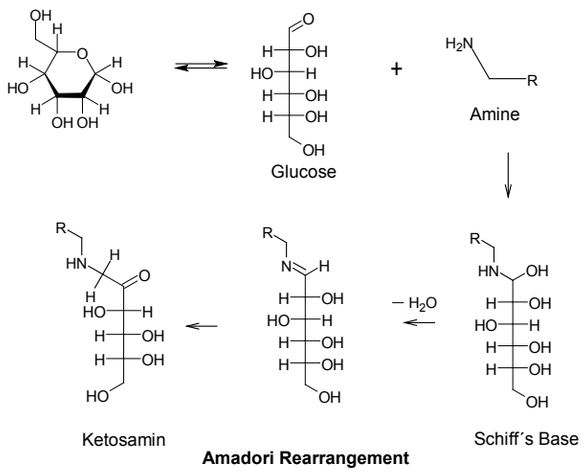

Fig. 1: Scheme for the early stages of AGE-formation. After a Schiff´s base is formed, it undergoes the Amadori-rearrangement and forms the more stable ketosamine.

Schiff´s base typically undergoes a so-called Amadori rearrangement resulting in a fructosamin (ketosamin) structure. The Amadori product is stable for several weeks. This is the reason why one of the best known Amadori products, HbA1c, the adduct of hemoglobin and glucose, can be used as a major indicator for hyperglycemia. Further rearrangements, oxidations and eliminations are needed to finally form the members of the highly heterogeneous group of AGEs.

Sugars differ in their ability to react with amino groups. Generally, the small sugar (oxo-aldehyde) molecules are more reactive than sugars with more carbon atoms (Bunn and Higgins, 1981). Reactivity also depends on the proportion of molecules in the more reactive open chain conformation and furanose ring structures (Franks, 1987). For example, fructose is about 10-fold more reactive than glucose. Important acceptors are amino acids like lysine or arginine or amino groups on nucleobases and lipids.

Besides monosaccharides, α-oxo-carbonylic compounds contribute significantly to AGE-formation as they

are far more reactive than sugars (Lo et al., 1994). This carbonyl-stress can be caused by several mechanisms (Fig. 2). α-oxoaldehydes are side products of glycolysis

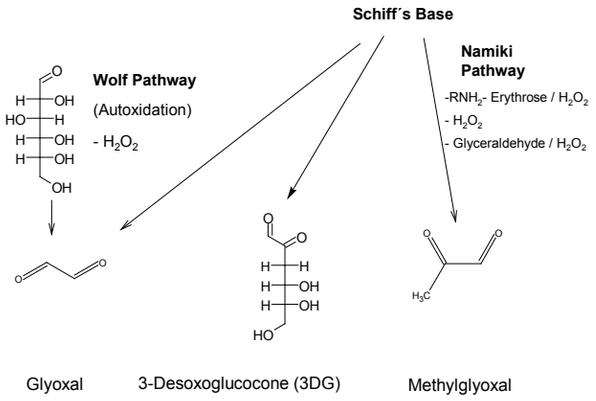

Fig. 2: Formation of reactive α–oxo aldehydes from the Schiff´s base. Note that H_2O_2 is also formed in these pathways. Other possible reactions exist to form methylglyoxal from glycolysis intermediates and glyoxal from fatty acid metabolism.

and amino acid degradation. Triosephosphates, which are intermediates of glycolysis can be non-enzymatically degraded to form oxoaldehydes. In the case of glyceraldehyde 3-phosphate the reaction product is methylglyoxal. The degradation of serine and cystein can lead to the formation of glycolaldehyde or 2-hydroxyl propanal, a process that requires ROS formed by the gp91phox NADPH oxidase (Anderson and Heinecke, 2003). Furthermore, slow oxidative degradation of monosaccharides leads to the formation of α-oxoaldehydes and hydrogen peroxide which represents the so called Wolff-pathway (Thornalley et al., 1984).

If the Schiff´s base does not undergo the Amadori rearrangement, elimination reactions can occur that release the primary amine and reactive dialdehydes such as glyoxal, glucosone and methylglyoxal are formed (Hayashi and Namiki, 1980; Ferreira et al., 2003). These reactions, which are known as Namiki pathway can also release hydrogenperoxide and thereby increase oxidative stress conditions.

AGEs can be classified by their ability to show fluorescence or to form cross links on proteins (Fig. 3). Some authors also discriminate between toxic and non-toxic

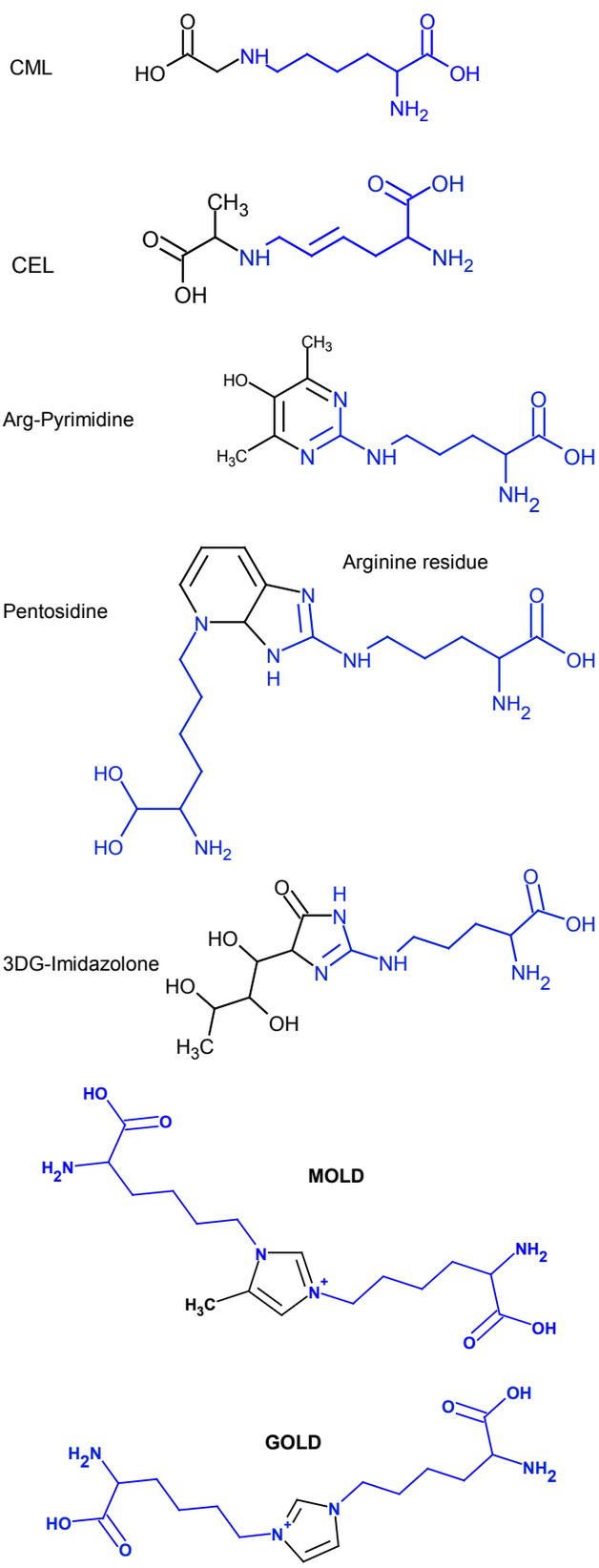

Fig. 3: Examples for common AGE-structures. Amino acid derived atoms and bonds are drawn in blue. Examples for "simple", aliphatic AGEs: CEL, Carboxyethallysine, CML, Carboxymethyllysine and aromatic AGE: 3DG-Imidazolone, 3-deoxyglucusone-imidazolone.

Fluorescent AGEs are Arg-Pyrimidine and Pentosidine. Pentosidine forms also cross links comparable to MOLD (methylglyoxal induced lysine dimer) and GOLD (glyoxal derived lysine dimer).

AGEs. Compounds such as CML and CEL or pyrralline are not fluorescent, do not cross link proteins and are considered as non-toxic AGEs. Toxic AGEs are usually derived from glycolaldehyde or glyceraldehyde but not from glucose and their structures remain to be elucidated (Sato et al., 2006a,b).

Processed food also contains high amounts of AGEs, or in this case the so-called Maillard reaction products (MRPs). However, many AGE-structures can be formed endogenously and exogenously as well. It is obvious that high temperatures, as used in the deep frying process together with the "Western-style diet", which is rich in red meat, starch and sweat, favours the formation of MRPs. A major difference between food processing and endogenous formation of AGEs is the appearance of polymeric, high molecular mass components, the melanoidines. As many of these compounds contribute to colour and flavour of food, they are essential components of cooking. Parallel to the Maillard reaction, brown food pigments are also formed by caramelization. Caramelization involves reactions of sugars at temperatures that are usually higher than needed for the Maillard reaction. The typical caramelization process occurs, when a dry sugar such as sucrose is heated to a characteristic caramelization temperature (i.e. 160°C for sucrose). Brown pigments are then formed by a series of hydrolysis, dehydration and polymerisation processes (Greenshields and Macgillivray, 1972).

As with many compounds that are present in food, it is not absolutely clarified if, or which MRP/AGE components are absorbed in the intestine, however, in case of fluorescent AGEs it was shown that at least a small proportion enters the blood stream and is subsequently secreted with the urine. Food derived AGEs/MRPs are undoubtedly affected by digestive enzymes and also by the bacteria of the gut. It is expected that mainly low molecular mass compounds are taken up, however, larger molecules might also be able to cross the intestinal barrier; or will at least be able to affect enterocytes or immune cells in the gut.

Biological "activity" of AGEs

AGEs can have impact on the function of biological systems by several means. Modifications on proteins can clearly alter structure, enzymatic activity and biological half-life (Friguet et al., 1994; Bulteau et al., 2001). If DNA is modified the consequence can be mutations, and if membrane lipids are hit, this might affect transport and signalling processes. Last, but not least, AGEs can act through specific receptor molecules.

For several enzymes it has been shown that the presence of an AGE-modification alters, if not destroys activity. One example is methylglyoxal-modified serum albumin, which exhibits drastically impaired esterase activity and reduced ketoprofen binding compared to unmodified albumin (Ahmed et al., 2005).

Extracellular proteins are well known targets for AGE-modifications. Proteins such as collagen have a relatively long biological half-life and are directly exposed to high levels of glucose outside the cell. Interestingly, modified collagen becomes more resistant to degradation by matrix metalloproteinases (MMPs) which causes accumulation of AGE-modified collagens in the ECM. The occurrence of AGE cross links such as GOLD or MOLD results in stiffening of the ECM which often compromises organ function and is associated with several chronic diseases such as diabetes, vascular diseases, retinopathy, arthritis and also Alzheimer´s syndrome.

Although glycation seems to be a rather unspecific reaction, it seems that some proteins are prone to become the major modified protein in a cell. It is not clear whether this is simply a consequence of exposure of reactive residues on the surface or in the catalytic site of the proteins, or whether it reflects physiological functions such as a protective mechanism. Examples for predominantly modified proteins include several heat shock proteins. In case of HSP-27 a higher anti-apoptotic effect became evident after methylglyoxal modification. In stem cells the HSC-70 protein was described as the mostly modified protein (Hernebring et al., 2006). In yeast cells, only a few proteins are found to be modified by methylglyoxal (Gomes et al., 2005, 2006). These proteins include enolase, phosphoglycerate mutase and aldolase, all involved in glycolysis. Additionally, very similar to mammals, three heat shock proteins, involved in protein salvage were glycated (HSP 71/72, HSP 26). Although enolase was inhibited by methylglyoxal modification, the glycolytic flux was not affected (Gomes et al., 2006) showing that yeast glycolytic machinery is resistant to glycation that results from the high glycolytic activity in these cells.

According to an early hypothesis, the formation of AGE-modifications might have regulatory functions as it reflects physiological states, such as glycolytic activity of cells. This is clearly in contrast to the modern view that focuses on the association of AGE-formation with pathophysiological processes. However, in a recent study, it could be shown that high glycolytic flow caused increased modification of the transcriptional corepressor mSIN3a by methylglyoxal, which resulted in coupling of glycolytic activity to changes in gene expression, namely angiopoetin-2 transcription (Yao et al., 2006, 2007a,b).

The finding that embryonic stem cells contain large amounts of glycated proteins that are rapidly eliminated when differentiation processes occur (Hernebring et al., 2006) showed that, in this case, glycation is not generally deleterious to the cells and may even be involved in maintaining the undifferentiated state.

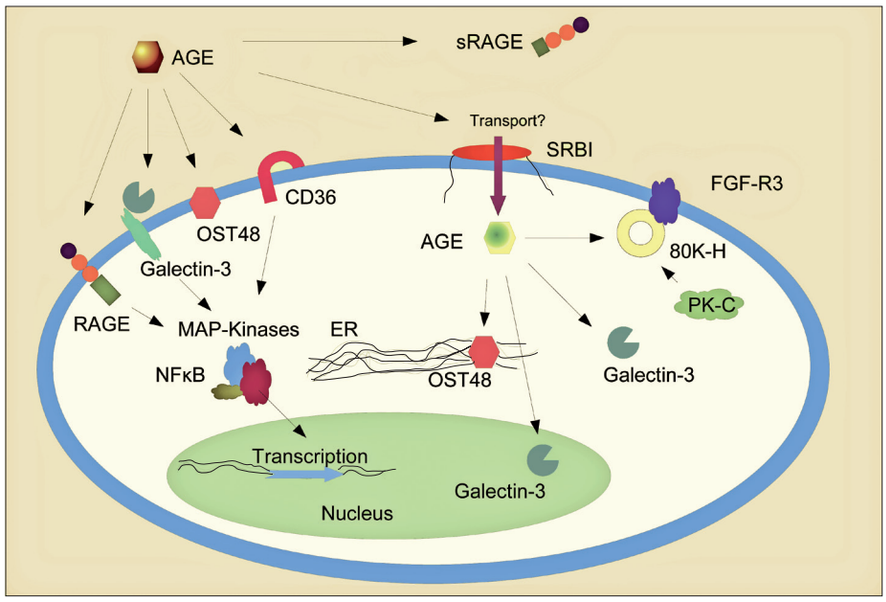

Fig. 4: AGE signalling. Common players involved in AGE-signalling. Main AGE-binding molecules are RAGE and soluble RAGE. AGE-R1 to –R3 may form an AGE-receptor complex. However for these molecules, all possible subcellular localizations and the uptake of AGEs are shown. AGEs signalling occurs through MAP-kinases and NFkB. Additional signals, which are not shown here, are the JAK/STAT-pathway, rho-GTPases, phosphoinositol 3 kinase and reactive oxygen produced by the gp91phox NADPH-oxidases.

Cells possess specific binding and receptor molecules for AGEs (Vlassara, 2001). The major and best known receptor for AGEs is the "Receptor for AGEs", RAGE or synonymous AGER (Schmidt et al., 2000) (Fig. 4), but other binding proteins have also been described. These are oligosaccharyltransferase (OST48, AGE-R1), 80K-H (AGE-R2) (Li et al., 1996), galectin-3 (AGE-R3) (Vlassara et al., 1995b), CD36 (Ohgami et al., 2001, 2002; Kuniyasu et al., 2003), and scavenger receptors IIa and –b (Takata et al., 1988, 1989). RAGE is a member of the immunoglobulin receptor family and binds several ligands such as AGEs, HMGB-1, S100 proteins or amyloid beta peptide. Binding of agonists like the AGEs to RAGE results in activation of NADPH-oxidases and other less well described pathways that lead to increased production of reactive oxygen species (ROS). Furthermore, activation of ERK, p38 MAP-Kinase, JAK/STAT-pathway, rho-GTPases and phosphoinositol 3 kinase was linked to RAGE activation (Bierhaus et al., 2005). The major downstream target of RAGE is the proinflammatory NFκB-pathway, which in turn leads to elevated RAGE expression and perpetuation of the cellular inflammatory state (Bierhaus et al., 2006). This inflammatory state is characterized by the production of inflammatory cytokines such as IL-6, TNFα, MCP-1 strongly depending on the cell type analyzed. A secreted form of RAGE is the product of alternative splicing of the RAGE-RNA. This soluble RAGE (sRAGE) seems to play an antagonistic role in RAGE signalling as sRAGE bind circulating AGEs, thus competing for binding with the other AGE-receptors (Bierhaus et al., 2005).

The functions of other receptors are far less understood. In 1994, it was shown that methylglyoxal-modified albumin is substrate for a specific endocytotic process (Westwood et al., 1994). Putative AGE-binding, transport molecules like CD36 (fatty acid translocase) and scavenger receptor class B (SRBI) are considered to be involved in uptake and degradation of AGEs rather than in signalling processes (Marsche et al., 2007). Nevertheless, CD36 is coupled to signalling pathways such as tyrosine kinases and NFκB and can contribute to AGE-signalling.

AGE-R1 was already known as oligosaccharyl transferase (OST48) before AGEs binding was observed (Li et al., 1996) and is localized to the lumen of the ER. AGE-R1 might be involved in mitigating cellular toxicity of AGEs as overexpressing this receptor in mesanglial cells showed decreased AGE-induced-RAGE-dependent MAP-kinase and EGF-receptor phosphorylation and also NFκB activation (Lu et al., 2004). AGE-R2 was described as 80K-H protein (Li et al., 1996) which is an intracellular substrate of protein kinase C (Goh et al., 1996) and, as a link to glucose metabolism and diabetes, this protein is involved in GLUT-4 trafficking (Hodgkinson et al., 2005). AGE-R3, also called galectin-3, is a soluble galactose binding lectin and associated with development of several types of cancers. It can either be secreted and bound to integrins (Fukushi et al., 2004; Lippert et al., 2007) or localized to the cytoplasm and nucleus (Gaudin et al., 2000; Hughes,

2001; Deschildre et al., 2007), which is mediated by importins (Nakahara et al., 2006). From KO-mouse studies it was deduced that galectin-3 has also a protective function in AGE-induced glomerular injury (Iacobini et al., 2003, 2004). Taken together, several AGE-binding molecules exist involved in binding, signalling and degradation of AGEs. The effects of the presence of AGEs will therefore depend on the occurrence of these receptors on the individual cell type. It is also not well described if these binding molecules differ in their binding characteristics towards different AGE-modifications. It has also been proposed that AGE-receptors -R1, R2 and R3 molecules form an AGE-receptor complex (Vlassara et al., 1995b).

AGEs and diseases

The presence of AGEs is correlated with several important diseases. As diabetes is often accompanied with hyperglycemia and oxidative stress, an accelerated rate of AGE-formation is observed (Fig. 5). This glycation reaction contributes to morbidity of diabetes, end-stage kidney and heart diseases, and it is also involved in the pathophysiology of Alzheimer´s disease, arthritis and ageing.

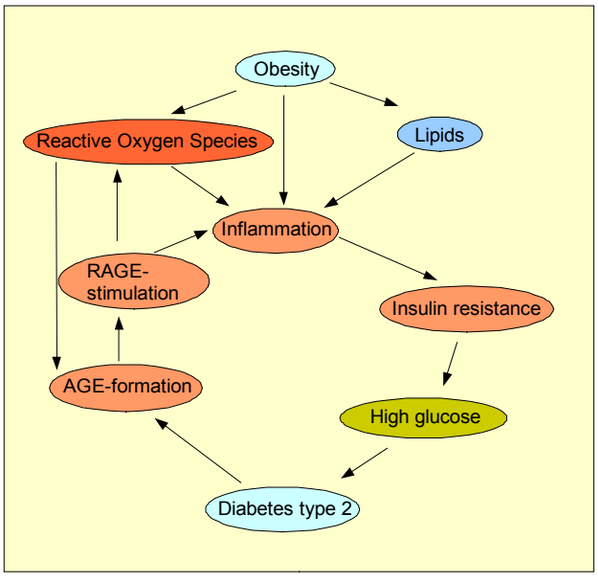

Fig. 5: Postulated relationship between obesity, diabetes and the formation of AGEs.

Diabetic nephropathy

Diabetic nephropathy is a major cause of end-stage renal disease. Pathophysiologically, it is characterized by thickened glomerular basement membrane, increased mesangium, renal tubular cells and podocytes (Dronavalli et al., 2008). This is accompanied by increased AGE deposition in this structures. Interestingly, not only these endogenous deposition of AGEs contributes to renal disease, but also increasing the amounts of exogenous AGE-molecules in the plasma caused thickening of the glomerular basement membrane, due to increased expression of components of the extracellular matrix and growth factors such as TGF-ß (Vlassara et al., 1994). An indication for a major role of AGEs in this process is that overexpression of RAGE in a diabetic mouse model increased renal defects (Yamamoto et al., 2001), whereas ablation of galectin-3 increased susceptibility to diabetic and AGE-induced nephropathy (Iacobini et al., 2005). In addition, RAGE-deficient animals showed amelioration of diabetic nephropathy (Myint et al., 2006). Other factors involved in the development of diabetic nephropathy are protein kinase C activation (Cooper, 2004), reactive oxygen species (Vasavada and Agarwal, 2005; Nishikawa et al., 2007) and cytokines. A functional decline of the nephrons will cause a further accumulation of advanced glycation end products, because the kidney is the major organ involved in clearance of AGE-modified residues (Miyata et al., 1998). A reduction in AGEs resulted in decreased disease signs (Forbes et al., 2001, 2003).

Diabetic eye disease

The eye is influenced by diabetes at several levels. Firstly, the predominant protein of the lens, crystalline, can be modified by AGE-moieties resulting in lens ageing and cataract formation. α-Crystalline is a protein that belongs to the small-heat-shock proteins of the chaperone family. As described above, such proteins are common targets for glycation and already a single modification was found to alter crystalline´s chaperone activity, and thus might also influence the transparency of the lens (Bhattacharyya et al., 2007). Retinopathy is another form of microvascular disease that correlates with the deposition of AGE-modified proteins. Diabetic retinopathy occurs in more than 60 % of people suffering from long term diabetes (Fong et al., 2004; Khan and Chakrabarti, 2007) and leads to degeneration of the retina and, finally, blindness. Like nephropathy, retinopathy involves characteristic damage of the microvessel wall, correlated with cytokine production and oxidative stress (Madsen-Bouterse and Kowluru, 2008). AGE deposition seems to be correlated with the development of the disease (Murata et al., 1997; Hammes et al., 1999; Stitt, 2001; Barile and Schmidt, 2007). AGE-deposits are found in the basement membrane and the retinal pericytes in rats (Stitt et al., 1997) and the optic nerve head (Amano et al., 2001). Glycated proteins can induce dysfunction and death of retinal pericytes (Stitt et

al., 2004). In addition, pharmacological inhibition of glycation was shown to prevent retinopathies (Ino-ue et al., 1998; Chen et al., 2004).

Cardiovascular diseases

Diabetes is also associated with a significant acceleration of atherosclerosis (Mazzone, 2007; Mazzone et al., 2008). That this is at least partially due to glycation was already demonstrated by an early study by Brownlee (Brownlee et al., 1986): Pharmacological inhibition of AGE formation using aminoguanidine resulted in reduced cross linking of proteins in arterial walls. *Vice versa*, the administration of exogenous AGEs to levels found in diabetics, induced atheroma formation in rabbits (Vlassara et al., 1995a). These data are further corroborated by the expression pattern of receptors of AGEs in atherosclerotic plaques. CD36 is expressed on macrophages as a major receptor for oxidised LDL (Endemann et al., 1993). CD36 is expressed in atherosclerotic lesions and considered to trigger the formation of macrophages into foam cells, a major event in the development of atherosclerosis. AGE-binding to CD36 can further accelerate this process by triggering tyrosine phosphorylation and NFκB activation. SRBI is essential for the reverse cholesterol transport as HDL. SRBI recognises AGEs and binding of AGE interferes with the uptake of acetylated HDL and suppresses SRBI-mediated efflux of cholesterol from cells (Ohgami et al., 2003). These observations suggest that AGEs inhibit cholesterol reflux (Miyazaki et al., 2002) which is considered as proatherogenic. Another fact that shows involvement of AGEs or AGE-related signalling in atherosclerosis are data on the soluble form of RAGE. In a model of accelerated atherosclerosis in diabetic mice deficient for apolipoprotein E, treatment with the sRAGE completely suppressed diabetic atherosclerosis in a glycemia- and lipid-independent manner (Park et al., 1998). Epidemiological studies demonstrated that low levels of sRAGE in plasma are correlated with a higher risk for cardiovascular mortality (Koyama et al., 2005, 2007, 2008). In another population study, it was shown that the AA/GA genotypes of the RAGE +557G>A polymorphism are associated with a significantly decreased risk of coronary heart disease (Yoon et al., 2007).

Inflammation and diabetes

Activation of RAGE results in the activation of the transcription factor NFκB which is a major regulator of inflammation and the immune response. RAGE is therefore involved in the regulation of inflammatory state, which is characterized by the expression of cytokines such as IL-6 and TNF-alpha. More than 100 human genes carry NFκB binding sites (Pahl, 1999). Besides growth factors, most of the interleukins and some of the interleukin receptors, TNF and TNF-receptors cell adhesion molecules, extracellular matrix proteins and apoptosis related genes are among the proven target genes of NFkB.

Inflammation is discussed at least to contribute to insulin resistance in diabetes type 2. Obesity results in a "low grade chronic inflammation" via TNF-α and ROS. TNF-α impairs insulin action in many model systems and knock out mice have improved insulin sensitivity (Uysal et al., 1997; Wellen and Hotamisligil, 2005). Given the fact that AGE-formation and RAGE activation are elevated in diabetes, a vicious circle can be postulated that would lead to further increased insulin resistance (Fig. 5).

Role of AGEs in cancer

Many studies have shown a link between diabetes and cancer (Strickler et al., 2001; Jee et al., 2005; Abe and Yamagishi, 2008). In these studies associations between diabetes and non-Hodgkin's lymphoma (Chao and Page, 2008), liver (Chen et al., 2008), colorectal (Berster and Goke, 2008; Hart et al., 2008), endometrial, breast, and renal cell cancers have been observed. For other cancers no effect or even a reduction of risk was observed, i.e. for prostate or lung cancers (Calton et al., 2007; Leitzmann et al., 2008; Wigle et al., 2008).

A possible explanation that fits well to epidemiological data lies in the elevated levels of insulin and insulin-like growth factor in diabetic patients. This hyperinsulinemia is due to insulin resistance and therapeutic insulin supplementation. According to this hypothesis, insulin may act as a growth factor for cancer cells (Yu et al., 1992; Schoen et al., 2005; Gunter et al., 2008). But this might not be true for all types of cancers. Non-Hodgkin's lymphoma is linked to chronic inflammation and altered immune function both of which are also associated with diabetes (Chao and Page, 2008). In other cancers, where no association with diabetes was observed, one can assume that insulin or IGF do have less impact on growth rate on the affected cells.

AGE-signalling was associated with certain tumours because RAGE activation causes cell activation, growth factor expression and activation of NFκB (see above). According to this hypothesis, in prostate cancer RAGE and its ligand amphoterin were found to be overexpressed and blockade of RAGE resulted in reduced tumour cell growth. Similar data were obtained for colon and gastric cancers. In contrast, lung tumours, which are highly invasive, expressed reduced levels of RAGE (Bartling et al., 2005). Additionally, the expression of the "endogenous secretory RAGE" (esRAGE) which is considered as a decoy receptor, preventing signalling through RAGE

was also found to be reduced in most lung cancers (Franklin, 2007; Kobayashi et al., 2007). Interestingly, normal lung tissue already expresses high amounts of RAGE. Taken together, these data suggest that RAGE might become a useful target for cancer therapies (Logsdon et al., 2007).

Biological detoxification

There are several enzyme systems described that can influence glycation processes in vivo (Fig. 6). Namely, there are glyoxalase I, together with aldehyde dehydrogenases that detoxify carbonylic compounds. Fructosamine 3-phosphokinase can catalyse the removal of fructosamine glycation adducts from proteins by phosphorylating protein bound and free fructosamine. However, in case of fructosamin 3-phosphokinase (F3K), despite the release of a free lysine, one molecule of 3-deoxyglucosone is produced that needs to be detoxified, otherwise it will be able to attack another free amino group and restart the glycation reaction. A recently developed F3K knockout mouse confirmed the prediction that F3K is indeed involved in deglycation reactions (Veiga da-Cunha et al., 2006; Van Schaftingen et al., 2007) as the animals exhibited 2.5-fold higher fructosamin conjugated haemoglobin and other proteins than control mice.

In the glyoxalase reaction methylglyoxal is added spontaneously to glutathione. The adduct, a hemithioacetal, is isomerized by glyoxalase I into 2-hydroxyacylglutathion derivatives. These substances are then converted by glyoxalase II to the corresponding α-hydroxyacids and

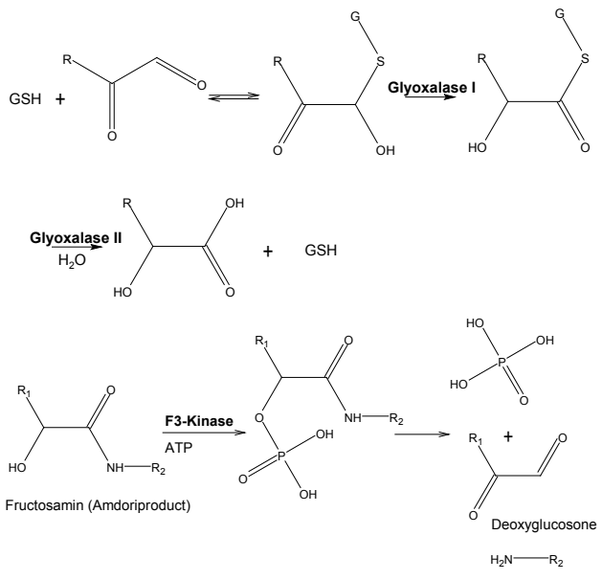

Fig. 6: Scheme of the detoxification reaction catalysed by the glyoxalase system (upper panel) and F3-Kinase (lower panel). GSH : reduced glutathion.

glutathione is recycled (Thornalley, 1998). If the cells are under oxidative stress and glutathione concentration is low, the antiglycation defence mediated by the glyoxalase system can become insufficient, which establishes another link of oxidative stress and glycation (Amicarelli et al., 2003).

However, in case of glyoxalase I adverse effects of higher expression can be expected, as several aggressive tumours show a correlation between multidrug resistance and glyoxalase I expression (Mannervik et al., 1990; Antognelli et al., 2006). Glyoxalase I inhibitors are therefore potential antitumour drugs (Tsuruo et al., 2003). Glyoxalase I together with gluthathione reductase I, was also linked to anxiety in transgenic mice. Local overexpression in brain resulted in anxiety-like behaviour whereas glyoxalase I inhibition by RNA interference decreased these manners (Hovatta et al., 2005). It was not analysed whether these manipulations also resulted in changes in advanced glycation end products in brain.

Preventing AGE-formation by nutrition and pharmacotherapy

Due to the fact that accumulation of AGEs is correlated with the development of major diseases, AGE-formation and deposition is generally considered as problematic. Several strategies to avoid AGE formation or to break present AGE-cross links have therefore been developed. In case of diabetes, strict control of plasma glucose levels is critical. A well established measure for sufficient glucose control is the amount of HbA1c, the Amadori product of haemoglobin. Fructose is often used as a glucose replacement in the nutrition of diabetics. But as fructose is even more reactive than glucose, high blood concentrations should also be avoided. The typical plasma concentration is 1mg/dL which is significantly lower than glucose levels (app. 100 mg/dL). Fructose levels can rise to up to 10mg/dL which his still low compared to glucose concentrations (Macdonald et al., 1978; Bohannon et al., 1980). The rate of glycation by fructose is about 10-times higher than with glucose, thus, the 10-fold lower concentration might result in comparable rates of glycation (Bunn and Higgins, 1981; McPherson et al., 1988) which was already shown for rats, where fructose-rich food increased glycation of haemoglobin, the amounts of lipoxidation products and collagen modifications (Levi and Werman, 1998). From this point of view, the use of the alternative sweetener fructose should be handled with care (Gaby, 2005).

As pointed out above, food contains significant amounts of AGE-related Maillard reaction products (MRP), such as melanoidins. Our current knowledge on the possible health effects still remains scarce, although

research on this aspect has been intensified during recent years (Somoza, 2005). In the context of this review the interplay of exogenous AGEs and the endogenous AGE-formation is of particular interest. From many studies it is known that food AGEs/MRPs are absorbed to about 30% by the digestive tract, depending on the modification (Koschinsky et al., 1997; Foerster and Henle, 2003; Somoza, 2006). MRP-modified proteins will undergo proteolysis and are further metabolized by the bacteria of the gut (Ames et al., 1999). It is therefore proposed that MRPs enter the blood stream as low molecular mass compounds, such as glycation free adducts, but the transport mechanism is unknown and might be different for individual compounds. Transport might well be mediated only by diffusion, as a recent study showed that early-, as well as advanced glycation-modified lysine was transported neither by the major peptide carrier (PEPT-1) nor by carriers for neutral amino acids (Grunwald et al., 2006). In case of renal clearance, glycation free adducts are usually efficiently excreted. On the other hand, in the case of renal dysfunction, an AGE accumulation was observed. Again, it is not known if any carrier molecules are involved.

Another option to reduce AGE formation is the choice of nutritional fat. High fat intake generally enhances AGE formation, especially in visceral tissue (Li et al., 2005) and the consumption of unsaturated fatty acids (Portero-Otin et al., 2003) increased the amounts of lipoxidation dependent MDA-adducts in all organs and the amounts of CML-adducts in brain but not in kidney and liver, which might reflect the metabolic differences of these organs.

It is not clear, however, if the consumption of MRP/AGEs has always harmful effects under normal health condition. It might even be beneficial, as an induction of detoxifying enzymes has been observed that could result in increased chemopreventive potential (Hofmann et al., 2001; Faist et al., 2002; Lindenmeier et al., 2002; Somoza et al., 2003). Consistent with the antioxidative properties of MRPs (Cioroi, 2000; Daglia et al., 2000; Borrelli et al., 2002; Morales and Babbel, 2002; Wagner et al., 2002), an inhibition of lipid peroxidation and increase of total antioxidant capacity of plasma was found (Esposito et al., 2003) after coffee consumption (a model for high AGE intake). It can therefore be speculated that some exogenous MRPs are able to reduce endogenous AGE-formation. On the opposite, these substances are ligands to AGE-receptors and, therefore, potentially proinflammatoric (Zill et al., 2001), which could result in enhanced production of reactive oxygen species followed by glycoxidation and increased endogenous AGE formation. Nevertheless, it was shown that uptake of AGEs via food might have unfavourable effects on the endothelium (Negrean et al., 2007; Uribarri et al., 2007b), inflammation and ageing (Uribarri et al., 2007a). Also, mice that were fed a diet low in AGEs exhibited an extended life-span (Cai et al., 2007).

Other nutritional factors, like the consumption of substances with antioxidative potential are also possible inhibitors of AGE formation because of the assumed inhibition of glycoxidation and lipoxidation processes. This was shown for the phytoestrogens daidzein, genistein and also resveratrol (Mizutani et al., 2000a,b) in case of rat vascular smooth muscle cells. For curcumin, the major constituent of the spice turmeric, which has antioxidant as well as NFκB inhibitory activity (Farid et al., 2005), it was shown that it prevented methylglyoxal related damage in embryonic stem cells (Chan et al., 2005; Hsuuw et al., 2005). Other components that have been suggested to prevent AGE formation are garlic extract (Ahmad and Ahmed, 2006) and green tea (Babu et al., 2006). However, data on this topic are rare and there is a definite need for further investigations.

A pharmacologic approach for the prevention of AGE-formation is the use of carbonyl traps. Promising substances are pyridoxamine, aminoguanidine and the well-known metformin. Pyridoxamin, also known as vitamin B6, scavenges α-dialdehydes as well as lipid peroxidation intermediates (Voziyan et al., 2003; Voziyan and Hudson, 2005; Reddy and Beyaz, 2006). Aminoguanidine, also known as Pimagedine, has similar properties as pyridoxamine. It scavenges α-dialdehydes and also peroxynitrite and was shown to be beneficial for diabetic rats (Stadler et al., 2005). However, in a clinical trial, adverse side effects were observed and the substance was withdrawn from the clinical evaluation process (Bolton et al., 2004). Metformin has long been used in treatment of type-II diabetes. As a bisguanidine it has the potential to react with methylglyoxal. Its mechanism in reducing blood glucose levels is not fully understood, but it seems to interfere with AMP-activated protein kinase (Shaw et al., 2005).

Preformed AGE-crosslinks can also be cleaved by the so-called AGE-crosslink breaking drugs, of which ALT-711 (Alagebrium) is the most promising for therapeutical use (Fig. 7). It has been used in several animal and human studies, where it was able to improve many diabetes and ageing associated defects. Treatment with ALT-711 reduced stiffness of arteries and myocardium which is associated with diabetes and ageing (Wolffenbuttel et al., 1998; Asif et al., 2000; Kass et al., 2001; Vaitkevicius et al., 2001). With respect to nephropathies, extracellular matrix accumulation was prevented by ALT-711 (Thallas-Bonke et al., 2004) and the substance was able to prevent, and even reverse diabetic nephropathy in obese mice (Peppa et al., 2006). In elderly patients with diastolic heart failure, ALT-711 treatment resulted in improved ventricular diastolic heart filling and also improved quality of life score (Little et al., 2005).

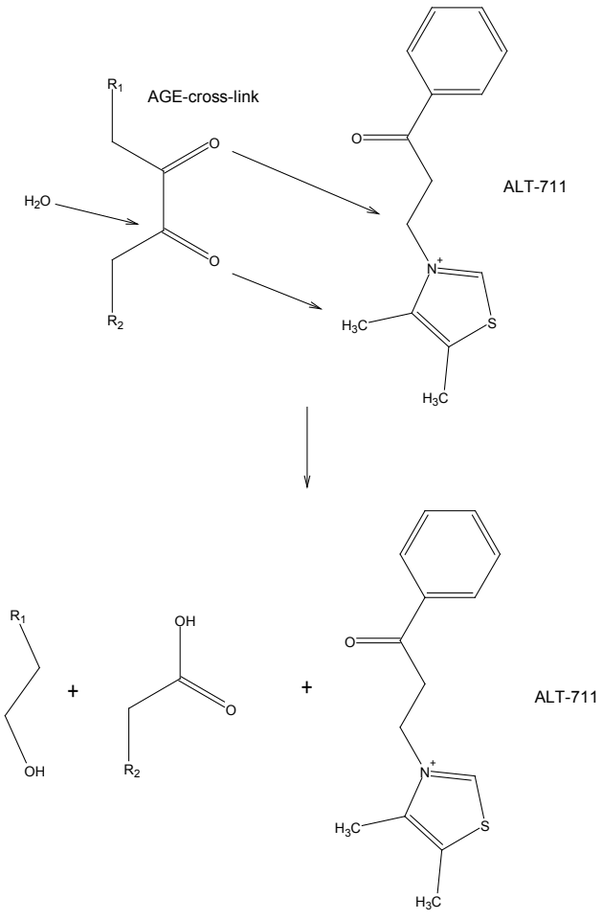

Fig. 7: Reaction catalyzed by the cross link breaker ALT-711

Conclusions

The term advanced glycation end products represents a variety of structurally highly diverse compounds. As reactive carbohydrates are the major cause of the AGE formation reaction, AGEs are on the one hand closely related to diabetes and on the other hand, are discussed to be a major cause of diabetes associated diseases. They can either be formed endogenously or incorporated from food, and are often associated with disease progression. Modulating AGE-formation and deposition is therefore a promising tool in treatment or prevention of several diseases ranging from diabetic complications over atherosclerosis to cancer and also ageing (Fig. 8). In case of AGE-rich nutrition, the antioxidative potential of melanoidins might have positive effects, but further research on this topic is needed to identify components of promising pharmacological value.

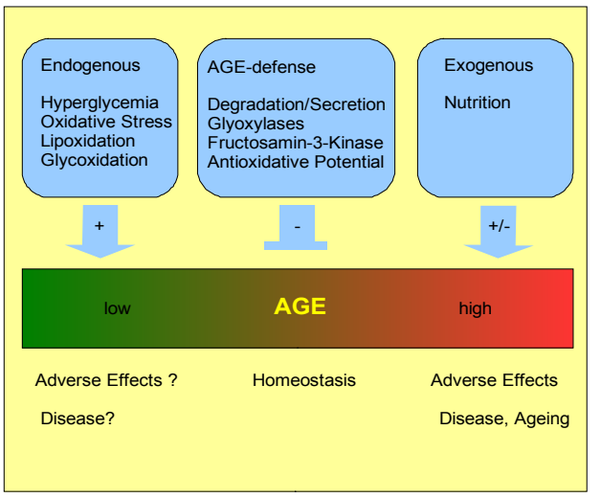

Fig. 8: Biological effects of AGEs. AGEs are formed endogenously or uptake occurs from food. Several AGE-defense mechanisms occur which should result in steady state levels, which may relate to disease and age status.

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