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Advanced glycation end-products (AGEs): involvement in aging and in neurodegenerative diseases

Review Article

M. A. Grillo and **S. Colombatto**

Dipartimento di Medicina e Oncologia Sperimentale, Sezione di Biochimica, Università di Torino, Torino, Italy

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Summary. Advanced glycation end-products (AGEs) are formed from the so-called Amadori products by rearrangement followed by other reactions giving rise to compounds bound irreversibly. The structure of some of them is shown and the mechanism of formation is described. Several AGE binding molecules (Receptors for AGE, RAGE) are known and it is thought that many of the effects caused by AGEs are mediated by RAGE. Some of these were shown to be toxic, and called TAGE. The mechanism of detoxification of glyoxal and methylglyoxal by the glyoxalase system is described and also the possibility to eliminate glycated proteins by deglycation enzymes. Compounds able to inhibit AGEs formation are also taken into consideration.

Keywords: RAGE – TAGE – Detoxification – Amadorines

Introduction

A sugar aldehyde or ketone can react with an amino group of proteins, and also with phospholipids and nucleic acids, in a non-enzymatic reaction, giving rise to a Schiff base. The reaction is reversible and occurs until reaching the equilibrium. However the Schiff base is slowly rearranged giving the so-called Amadori product, that is fructosamine. This is the early glycation process and the compounds formed are considered early glycation adducts. However, they can undergo a further rearrangement and eventually dehydration, condensation, fragmentation, oxidation and cyclization reactions, giving rise to compounds bound irreversibly, the so-called Advanced Glycation End-products (AGEs) (Fig. 1).

Long-lived proteins, such as serum albumin, lens crystallin, collagen of the extracellular matrix accumulate AGEs in vivo. When blood sugar is increased, more AGEs are formed and therefore these compounds have been initially connected with diabetes. Later it has been shown that they are involved also in physiologically aging (senile cataracts, arteriosclerosis) and in neurodegenerative diseases, such as Alzheimer disease (AD) and Parkinson disease. AD is characterized by the presence of senile plaques (SP) and neurofibrillary tangles (NFT). AGEs have been identified in both SP and NFT.

Different types of AGEs are known, depending on the compound from which they originate. Takeuchi et al. (2004) recognized six distinct classes of AGEs: those deriving from glucose (AGE-1), from other carbohydrates such as glyceraldehyde (AGE-2) and from α-dicarbonyls, such as glycolaldehyde (AGE-3), methylglyoxal (AGE-4), glyoxal (AGE-5), 3-deoxyglucosone (AGE-6). Glyoxal, methylglyoxal (MG) and 3-deoxyglucosone (3-DG) are formed in the glycation of proteins by glucose (Thornalley et al., 1999); however, glyoxal is also formed in lipid peroxidation, methylglyoxal by the fragmentation of triosephosphates and the catabolism of ketone bodies and of threonine, 3-deoxyglucosone from fructose-3-phosphate. All these compounds can react with the amino group of lysine or the terminal aminogroup of proteins and with the guanidine group of arginine, and also with cystein. Interactions among the compounds formed are following, with formation of cyclic compounds and of aggregates. Moreover, AGEs can propagate free-radical reactions, that may catalyze further damaged proteins, lipids or DNA. It

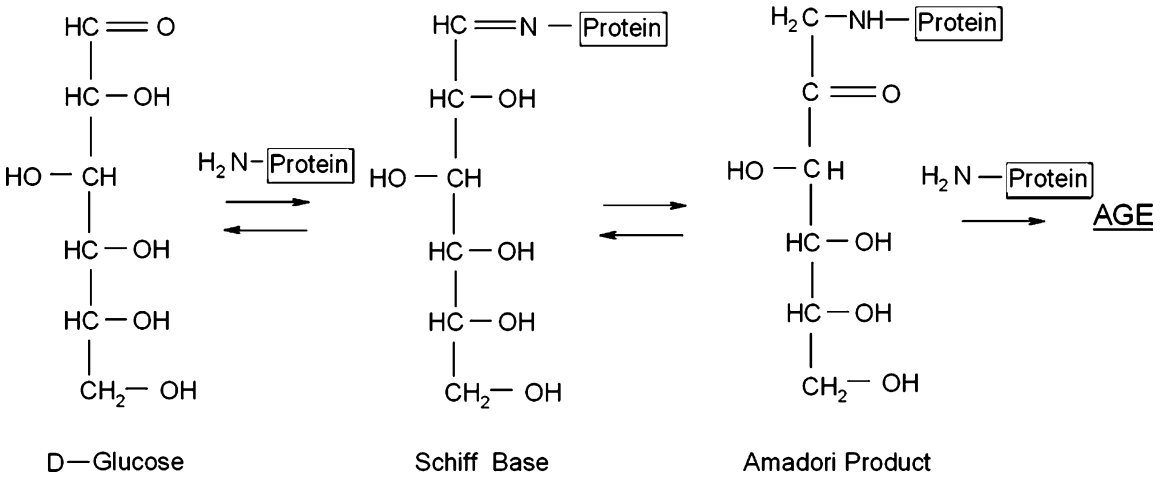

Fig. 1. Protein glycation by glucose

has been suggested that such an oxidative stress occurs on tau protein, contributing to neuronal dysfunction and death (Yan et al., 1994).

Glycation by glucose or other carbohydrates

As already said, glucose can react with aminogroups of protein, giving the reaction shown in Fig. 1. In some cases oxidation is also involved, so that it is possible to distinguish between compounds formed by glycation by others formed by glycoxydation.

From glucose the non oxidative pathway could give rise to pyrraline; in the oxidative pathway to pentosidine and N^6-carboxymethyllysine (CML).

Glyceraldehyde can also be involved. It is formed from glyceraldehyde-3-phosphate, an intermediate of glycolysis, through the polyol pathway, or from fructose, during its transformation by fructokinase. A glyceraldehyde derived AGE is the so called glyceraldehyde-derived pyridinium compound (GLAP), a compound that has been seen to induce oxidative cellular dysfunction. Glyceraldehyde-derived AGEs have been shown initially in AD brain and in the cytosol of neurons (Choei et al., 2004). Later, GLAP has been detected in the plasma protein and in collagen obtained from streptozotocin-induced diabetic rats (Usui et al., 2007).

When glycoxidation occurs, new compounds are formed, such as MG and glyoxal. These in turn can also react with proteins. In this case MG reacts mainly with Arg, less so with Lys and Cys (contrary to what occurs in the glycation with glucose). One compound obtained is CML, formed from fructoselysine, one of the Amadori products, in the presence of metal ions. However, now CML is suggested to be a marker of oxidation rather than of glycation, as it can also be formed during lipid peroxidation besides malondialdehyde and hydroxynonenal adducts to lysine. Moreover, the methylglyoxal-lysine dimer (MOLD), the glyoxallysine dimer (GOLD) and the deoxyglucosone-lysine dimer (DOLD), argpyrimidine (and its tetrahydroderivative) are also formed.

Other compounds formed are pentosidine and vesperlysines (A, B, C). Pentosidine derives from lysine and arginine. It has been found in several tissues, such as plasma and erythrocytes. The pentose which is mainly used appears to be ribose. Vesperlysine A has been shown in the lens of diabetic subjects (Tessier et al., 1999). It derives from ascorbate, ribose and threose.

Pyrraline is also formed from 3-deoxyglucosone and lysine.

Glycation by α-dicarbonyls

Besides hexoses and pentoses, also dicarbonyl compounds can give rise to AGEs: among these MG, glyoxal, 3-deoxyglucosone (3-DG) and glycolaldehyde.

As stated before, MG and glyoxal can be formed by glycoxidation of the Amadori product. But they can be formed also by other pathways. In animal tissues MG has been shown initially to be formed during glycolysis: when hydroxyacetone phosphate is isomerized to D-glyceraldehyde phosphate, the unstable enediolate intermediate can give rise to methylglyoxal, albeit at a very low rate (Richard, 1993). MG is formed also during lipid peroxidation, in the catabolism of threonine and in the oxidation of acetone. It is present also in the food (and also in the cigarette smoke). Moreover, also the spontaneous degradation of glucose in physiological conditions gives rise to glyoxal, MG and 3-DG.

Glyoxal can be formed from glucose by retroaldol condensation activated by deprotonation of the 2- or 3-hydroxy groups. Concurrent oxidative processes forming H_2O_2 (autoxidation of glycolaldehyde to glyoxal and glucose to glucosone) also stimulate glyoxal formation by hydroxyl radical-mediated acetal proton abstraction from glucopyranose and β-elimination reactions (Thornalley et al., 1984).

3-DG and glucosone formation occurs by an initial common activation step, deprotonation of carbon-2: redistribution of the electron density between carbon-1 and carbon-2 leads to the formation of the 1-diol, or redistribution of the electronic density leads to the 2,3-enol and thereby 3-DG.

Methylglyoxal may be formed by fragmentation of 3-DG.

Glyoxal, MG and 3-DG can also be formed from an early glycation product, i.e. the Schiff base. The presence of the aldimine group accelerates the formation of α-oxoaldehydes (Thornalley et al., 1999). In the same time other compounds can be formed in the fragmentation of the hexose moiety, that is erythrose and glyceraldehyde (Zyzak et al., 1995). After the Amadori rearrangement also 3-DG can be formed from fructosamine, in this case by phosphorylation to fructosamine-3-phosphate, followed by spontaneous fragmentation (see below).

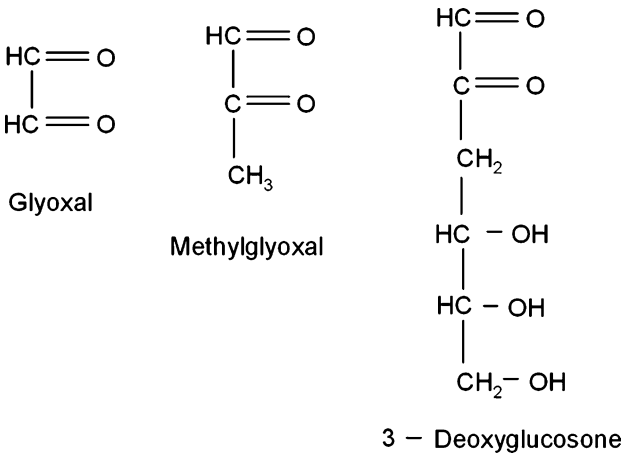

Fig. 2. Chemical structure of compounds involved in glycation

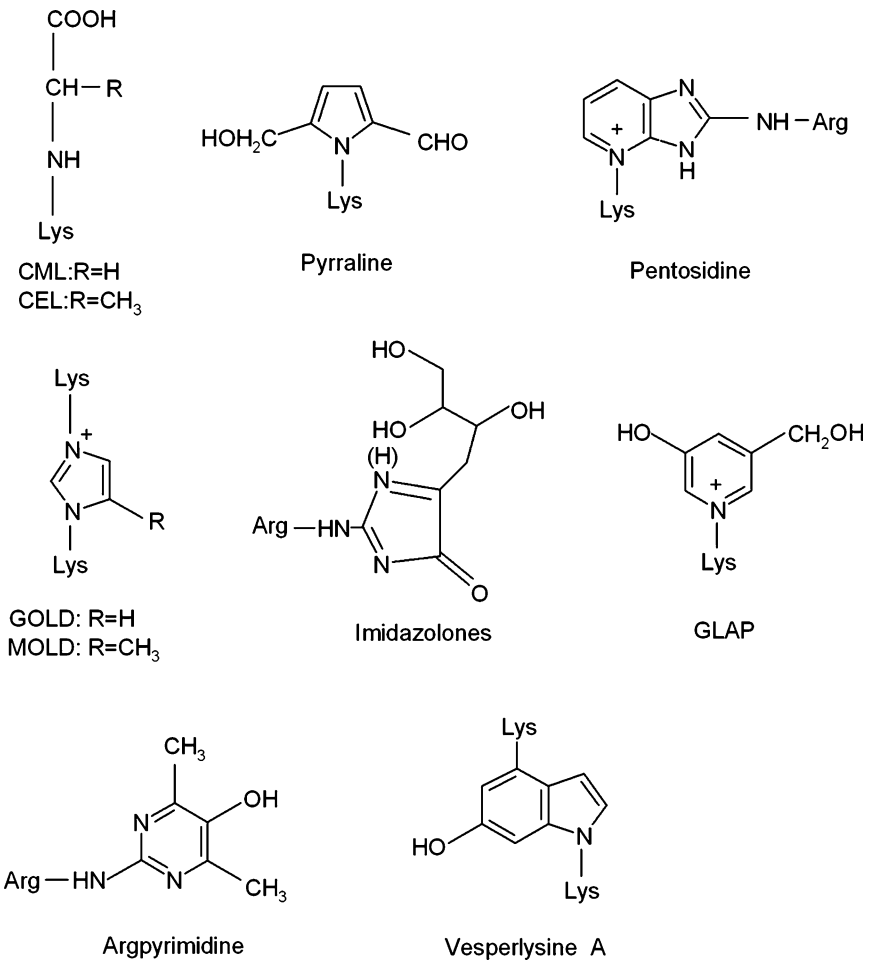

Fig. 3. Chemical structure of various AGEs: *CML* (N-carboxymethyllysine); *CEL* (N-carboxyethyllysine); *GOLD* (glyoxal-lysine dimer): *MOLD* (methylglyoxal-lysine dimer); *GLAP* (glyceraldehyde-derived pyridinium compound); vesperlysine A

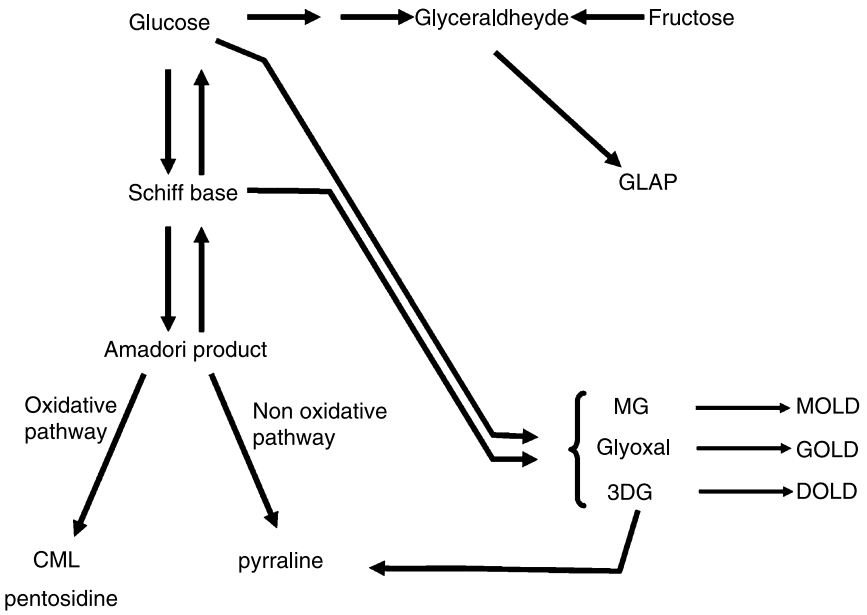

Fig. 4. Schematic formation of AGEs

Glyoxal is formed also in the lipid peroxidation and from threonine.

Glycoaldehyde is formed during the initial stages of protein glycation. Moreover it can be formed also by oxidation of L-serine.

The chemical structure of the α-dicarbonyls involved, and that of some AGEs, which can be formed, are shown in Figs. 2 and 3 respectively. The structure of many other derivatives (not reported) is also known.

In Fig. 4 the reactions involved are summarized.

RAGE

Since the amount of AGEs found in human tissues is less than could be expected by the rate of the reaction glucose/protein, it has been suggested that part of the AGEs formed are removed by normal mechanisms. This has been demonstrated to occur initially in rat liver, where two proteins have been shown able to recognize AGE modified macromolecules (Yang et al., 1991). Experiments in vitro confirmed that AGE proteins could undergo receptor-mediated endocytosis. Later, several AGE binding molecules have been described and it is thought that many of the effects of AGEs are mediated by receptors of AGEs.

Among these, the so-called RAGE (Receptor for AGE) and scavenger receptors expressed by liver sinusoidal cells such as Kupffer and endothelial cells. These liver cells are believed to be important mediators in endocytic uptake of AGE proteins from the plasma, although it has not yet been demonstrated in vivo (Ahmed et al., 2004). RAGE belongs to the immunoglobulin superfamily, having three immunoglobulin-like domains in the N-terminal extracellular segment, one transmembrane region and a short C-terminal intracytoplasmic stretch (Schmidt and Stern, 2000). Binding of AGEs to RAGE initiates cellular signals that activate NF-κB, which results in transcription of proinflammatory factors. AGE-2s, that is those formed from glyceraldehyde, caused more cytotoxic effects in cortical neuronal cells than other types of AGEs (Sato et al., 2006).

The upregulation of RAGE and its ligands in diabetic blood vessels in human subjects and murine cells suggests that AGE-RAGE interaction might affect the initiation and the progression of vascular complications. The participation of RAGE in the pathogenesis of Alzheimer disease has been also confirmed. RAGE is expressed by neuron, microglial cells and astrocytes in the normal human brain. In this tissue there is a highly specialized regulation of RAGE expression, via alternative splicing. Of the three well characterized isoforms of RAGE (full-length RAGE, secretory RAGE (sRAGE), N-truncated RAGE (NtRAGE)), sRAGE is expressed in the brain of control subjects at much higher levels than the other two. These isoforms specifically interact with the various ligands present in the brain (Ding and Keller, 2005). RAGE expression by cortical neurons and glia increases in AD, although this is associated with changes in the relative distribution.

It has been reported that RAGE may be the nerve cell receptor for amyloid β protein (Aβ). The consequences of Aβ ligation of RAGE appear to be different in neurons

and microglia. Whereas microglia are activated, as reflected by expression of cytokines, early neuronal activation is followed by cytotoxicity. The interaction of RAGE with pathological Aβ species would therefore modulate properties of the vasculature and neurons (Schmidt et al., 2001). It has been suggested that RAGE-mediated degradation of Aβ occurs in astrocytes. As Aβ, AGE and RAGE are co-localized in astrocytes of AD brains, it appears that glycated Aβ is taken up via RAGE and is degraded. It is, however, possible that other glycated proteins other than Aβ are present in astrocytes. In any case, it appears that RAGE-mediated Aβ degradation may contribute to neuronal dysfunction and death, resulting in progression of AD (Sasaki et al., 2001).

According to Sato et al. (2006) only AGE-2 and AGE-3 (much less so AGE-1) are bound to RAGE, and they alone contribute to the neuronal toxicity. They proposed therefore to call these Toxic AGEs (TAGEs), to distinguish them from the non-toxic AGEs. As non-toxic AGEs have no direct effect on neural cells, they may accumulate in healthy subjects. The direct neurotoxicity of TAGEs, on the other hand, will stimulate the development of AD. (Sato et al., 2006).

Accumulation of AGEs in brain

In the aging brain AGEs accumulate both intra- and extracellularly.

In AD more AGE adducts have been found in plaque fractions than in preparations obtained from control brain (Picklo et al., 2002). The major protein of the amyloid deposits, that accumulates extracellularly, is Aβ. This consists of 28 extramembranal amino acids plus 11–14 residues of the hydrophobic transmembrane domain from its precursor, Amyloid Precursor Protein (APP) (Dukic-Stefanovic et al., 2001). Polymerization of Aβ is accelerated by AGE-mediated crosslinking. The rate of senile plaque formation is likely to be important for the progression of the disease. The neurofibrillary tangles (NFT) contain a hyperphosphorylated microtubule associated tau protein. In affected neurons of AD brains this tau protein is AGE-modified, whereas in some other neurons or non-demented human brains the protein is soluble and not AGE-modified. The process of transglycation leads in AD to an ''oxidative stress dependent'' tangle formation (Ko et al., 1999). Nitric oxide may participate in the process, as AGEs are co-localized with iNOS (Wong et al., 2001). The presence of RAGE besides AGEs in astrocytes is also very important for the onset and progression of AD.

An increased AGEs level in plasma does not reflect the increased level of cerebral AGEs in AD patients. Cerebral AGEs accumulation in AD appears therefore a highly selective, brain specific event.

Many astrocytes containing many AGEs, RAGE-immunopositive granules and prion protein positive granules have been shown in the brain of patients with the Creutzfeldt-Jacob disease with prion plaques (Sasaki et al., 2002).

Further informations are given by Riederer and Hoyer (2006).

Toxic effects

Associated with the oxidation of Amadori products is the formation of oxygen free radicals. This is due to autoxidation by transition metal-catalysis, followed by dismutation of superoxide to hydrogen peroxide and the generation of hydroxyl radicals by the Fenton reaction. Moreover, AGEs can produce oxygen free radicals through an indirect process, by inducing the release of cytokines.

Another mechanism involved is due to the effect on the susceptibility of proteins to proteolysis and degradation.

Detoxification of oxoaldehydes

Methylglyoxal itself may directly damage neurons by depolarization and production of reactive oxygen species (ROS), followed by apoptosis. Detoxification of glyoxal and MG is therefore important. It may occur by effect of several enzymes: the NADPH-dependent aldose reductase, aldehyde dehydrogenase, 2-oxoaldehyde dehydrogenase and the glyoxalase system. The first two are expressed in the cerebral cortex and other parts; all 4 enzymes are present in the cerebellum. It follows that in different brain regions different mechanisms are involved in detoxification (Picklo et al., 2001). However, in mutant tau transgenic mice, with pathologic similarities with AD, glyoxalase 1 was the only up-regulated gene (Chen et al., 2004).

Glyoxalase

MG is the substrate of the glyoxalase system, present in the cytosol of all mammalian species and in most microrganisms. It is formed of two enzymes: glyoxalase 1 (EC 4.4.1.5) (GLX 1), glyoxalase 2 (EC 3.2.1.6) (GLX 2) and catalytic amounts of GSH. The substrate for GLX1 is the hemi-thioacetale formed through the non enzymatic con-

jugation of MG with GSH. The product of the reaction is S-D-lactoylglutathione, which is then hydrolyzed by GLX2 to D-lactate, while GSH is reformed. D-lactate is further metabolized to pyruvate.

$$CH_3COCHO + GSH \rightarrow CH_3COCH(OH) - SG \rightarrow CH_3CH(OH)CO - SG$$

$$CH_3CH(OH)CO - SG + H_2O \rightarrow CH_3CH(OH)COO^- + GSH + H^+$$

Human GLX1 is a dimer, formed by two similar subunits, so that three alloenzymes are formed. Each alloenzyme contains one Zn^{++}. It has been shown that overexpression of GLX1 prevents the increase of AGEs and increases the concentration of D-lactate. In contrast, decreasing of GLX 1 activity due to the aging process and oxidation stress increases glycation and tissue damage (Thornalley, 2003). Its role has been demonstrated in AD (Wong et al., 2001). GLX1 is upregulated in AD, presumably in a compensatory manner to avoid the increase in methylglyoxal and glyoxal (Khula et al., 2005; Kuhla et al., 2007).

How the enzymatic activity of GLX1 is regulated is not clear. It has been suggested that it is regulated by PKA-mediated phosphorylation (Van Herreweghe et al., 2002). An other hypothesis is that NO might alter its activity, as in AD iNOS, eNOS and nitrotyrosine levels are known to be increased (Lüth et al., 2002).

GLX2 contains a metallo-β-lactamase fold. Contrary to GLX1, which is present in cytosol only, it is present in mitochondria also, though the role of the mitochondrial GLX2 is not clear (Marasinghe et al., 2005). It has been suggested that the mitochondrial GLX2 is involved in the regulation of the redox state (Xu and Chen, 2006). The gene encoding it can be activated and bound by p63 and p73. Upon over expression, the cytosolic form, not the mitochondrial one, inhibits the apoptotic response of a cell to MG (Xu and Chen, 2006).

Physiological substrates are also glyoxal and 4,5-dioxovalerate (DOVA), a compound formed during the oxidative catabolism of 5-aminolevulinate (a heme precursor) and in the reduction of α-ketoglutarate.

As the formation of MG is increased in hyperglycemia due to diabetes a decrease in GSH can induce oxidative damage and glycation, due to a lower activity of GLX1.

Overexpression of GLX1 is associated with clinical multidrug resistance in tumours (Sakamoto et al., 2001). The study of the efficacy of inhibitors of GLX1 has therefore been suggested in cancer chemotherapy (Creighton et al., 2003).

Degradation of the glycated proteins

It is known that altered proteins can be eliminated in eukaryotic cells mainly by lysosomes and proteasomes. However, contrary to the lysosomal system, for which in aging only a reduced activity has been observed, in many cell types proteasomal system activity besides being declined is also affected in other ways. Most cross-linked aggregates which accompany several neurodegenerative diseases may no longer ''fit'' into the proteasome. Moreover accumulation of damaged proteins inhibits the proteasome, and Aβ itself can bind and inhibit it. Therefore, decreased proteolysis during aging and disease can occur in several different ways.

Another possibility to eliminate glycated proteins is by deglycating enzymes (the so-called amadoriases). Three types of enzymes able to deglycate proteins are known: fructoselysine oxidase (Takahashi et al., 1997), fructoselysine-3-kinase (Szwergold et al., 2001) and fructoselysine-6-kinase (Wiame et al., 2002). However, fructoselysine 3-kinase only has been detected in higher organisms. This enzyme phosphorylates Amadori products, giving rise to fructose-3-phosphate. This phosphoester decomposes to regenerate an unmodified lysine residue, inorganic phosphate and deoxyglucosone. Another enzyme, fructosamine-3-kinase related protein, has also been detected in human erythrocytes, with a different specificity, as it catalyses phosphorylation of protein-bound ribulosamine and psicosamines, but not fructosamines (Collard et al., 2004). However, fructosamine kinase is an intracellular enzyme, ATP dependent, and not suitable for deglycation of products in the extracellular matrix. Therefore it does not appear to be very useful for deglycation of proteins. Moreover, 3-deoxyglucosone is again formed. It has been suggested therefore that inhibition of this phosphokinase should protect from the diabetic complications due to AGEs formation (Brown et al., 2003).

Inhibitors of AGEs formation

A few compounds, called by Khalifah et al. (1999) Amadorines, are known which are able to inhibit AGEs formation: aminoguanidine, carnosine and pyridoxamine. Aminoguanidine reacts with Amadori carbonyl groups of glycated proteins and also with dicarbonyl compounds such as glyoxal, MG and 3-DG. Carnosine (beta-alanylhistidine) is a natural dipeptide, found also in brain tissue. Besides being an antioxidant, it has antiglycation properties. Pyridoxamine has been shown to be more effective than aminoguanidine. It does not interact directly with the

carbonyl moiety of the Amadori intermediate, but it interferes with post-Amadori oxidative reactions by binding catalytic redox metal ions (Voziyan et al., 2003). Inhibition of the post-Amadori reactions could also decrease the production of ROS, which are known to be formed during this process. Studies in vitro seem to support this hypothesis (Voziyan and Hudson, 2005). Moreover both aminoguanidine and pyridoxamine are potent inhibitors of NOS and of the Cu-dependent oxidases involved in amine and amino acids metabolism. Pyridoxamine is also able to bind intermediates of lipid peroxidation and prevents alteration of lysine residues and formation of CML, CEL and other derivatives during the oxidation of LDL in vitro.

Recently, polyamines have also been suggested as protectors of proteins from glycation. Experiments in vitro appear to confirm this hypothesis (Gugliucci and Menini, 2003). Besides polyamines, their precursor also, i.e. arginine, is able to inhibit in vitro the synthesis of pyrraline. Further studies to support the suggestion to use these compounds for therapeutic aims however are needed (Méndez and Leal, 2004).

Conclusion

From the data presented it appears evident that glycation might be involved in neuronal death. However, enzymes able to detoxificate glyoxal and methylglyoxal, and also others able to eliminate glycated proteins are present in many tissues. Moreover, the synthesis of AGEs can be inhibited by several amines and also polyamines. By acting on these systems it is therefore possible to have a therapeutic approach to reduce the changes associated with neurodegeneration.

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Authors' address: Maria Angelica Grillo, Dipartimento di Medicina e Oncologia Sperimentale, Sezione di Biochimica, Universita di Torino, Via Michelangelo 27, 10126 Torino, Italy,
Fax: +39-011-6705311, E-mail: mariaangelica.grillo@unito.it