

Review

## THE ROLE OF ADVANCED GLYCATION END PRODUCTS IN VARIOUS TYPES OF NEURODEGENERATIVE DISEASE: A THERAPEUTIC APPROACH

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**Abstract:** Protein glycation is initiated by a nucleophilic addition reaction between the free amino group from a protein, lipid or nucleic acid and the carbonyl group of a reducing sugar. This reaction forms a reversible Schiff base, which rearranges over a period of days to produce ketoamine or Amadori products. The Amadori products undergo dehydration and rearrangements and develop a cross-link between adjacent proteins, giving rise to protein aggregation or advanced glycation end products (AGEs). A number of studies

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Abbreviations used: A $\beta$  – amyloid beta; AD – Alzheimer’s disease; AFGPs – alkylformyl glycosylpyrroles; AG – aminoguanidine; AGEs – advanced glycation end products; AKR – aldo-keto-reductase; ALI – arginine lysine imidazole; ALS – amyloid lateral sclerosis; ALT – 711-alagebrium chloride; APP – amyloid precursor protein; BSE – bovine spongiform encephalopathy; CD-36 – cluster of differentiation 36; CFD – Creutzfeldt-Jakob disease; CML – N $\epsilon$ -carboxymethyllysine; Cu, Zn-SOD-1 – copper-zinc superoxide dismutase 1; DETAPAC – diethylenetriaminepentaacetic acid; 3DG – 3-deoxyglucosone; EGCG – (-)-epigallocatechin gallate; FAP – familial amyloid polyneuropathy; FN3K – fructosamine-3-kinase; GAPDH – glyceraldehyde-3-phosphate dehydrogenase; GOLD – glyoxal lysine dimer; GSH – glutathione; GSK-3 – glycogen synthase kinase-3; IL-1 $\beta$  – interleukin-1 $\beta$ ; IFA – isoferulic acid; LBs – Lewy bodies; LRRK-2 – leucine-rich repeat kinase 2; MG – methylglyoxal; MOLD – methylglyoxal lysine dimer; MSR type II – macrophage scavenger receptor types II; NADPH – nicotinamide adenine dinucleotide phosphate; NF- $\kappa$ B – nuclear factor- $\kappa$ B; NFTs – neurofibrillary tangles; OM – *origanum majorana*; OST-48 – oligosaccharyltransferase-48; PD – Parkinson’s disease; PM – pyridoxamine; PrPC – cellular prion protein; PTB – phenacylthiazolium bromide; RAGE – receptor of advanced glycation end products; ROS – reactive oxygen species; SNCA – synuclein alpha; sRAGE – soluble receptor of advanced glycation end products; TTR – transthyretin; TK – transketolase; TNF $\alpha$  – tumor necrosis factor- $\alpha$ ; TPP – thiamine pyrophosphate

have shown that glycation induces the formation of the  $\beta$ -sheet structure in  $\beta$ -amyloid protein,  $\alpha$ -synuclein, transthyretin (TTR), copper–zinc superoxide dismutase 1 (Cu, Zn-SOD-1), and prion protein. Aggregation of the  $\beta$ -sheet structure in each case creates fibrillar structures, respectively causing Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, familial amyloid polyneuropathy, and prion disease. It has been suggested that oligomeric species of glycated  $\alpha$ -synuclein and prion are more toxic than fibrils. This review focuses on the pathway of AGE formation, the synthesis of different types of AGE, and the molecular mechanisms by which glycation causes various types of neurodegenerative disease. It discusses several new therapeutic approaches that have been applied to treat these devastating disorders, including the use of various synthetic and naturally occurring inhibitors. Modulation of the AGE-RAGE axis is now considered promising in the prevention of neurodegenerative diseases. Additionally, the review covers several defense enzymes and proteins in the human body that are important anti-glycating systems acting to prevent the development of neurodegenerative diseases.

**Keywords:** Aggregation, Advanced glycation end products, Glycation in Alzheimer's disease, Glycation in Parkinson's disease, Glycation in amyotrophic lateral sclerosis, Glycation in familial amyloid polyneuropathy, Glycation in prion diseases, Glyoxylases, AGE inhibitors

## PROTEIN GLYCATION

Protein glycation occurs through a complex series of very slow reactions in the body, including the Amadori reaction, Schiff base formation, and the Maillard reaction. These give rise to the formation of advanced glycation end products (AGEs). In the first step of AGE synthesis, a non-enzymatic condensation reaction occurs between  $\alpha$ -amino or N-terminal group of a protein, lipid or nucleic acid [1] and the carbonyl group of a reducing sugar. This step is followed by a highly reversible nucleophilic addition reaction that results in the development of a Schiff base [2], which is formed relatively quickly [3]. Then, over a period of weeks, slow chemical rearrangements in the Schiff base occur, leading to the synthesis of stable and highly reversible ketoamine (Amadori product) [2, 4–6]. Finally, the Amadori products undergo dehydration and rearrangements and develop a cross-link between adjacent proteins, forming a protein aggregate or advanced glycation end products [7]. Fig. 1 shows the pathway of AGE synthesis [7] and Fig. 2 shows the structures of some of the AGEs described below.

Pentosidine is one of the major AGEs that occur in vivo. Pentosidine has been identified in lipofuscin pigments of Alzheimer's disease (AD) and aged brains [8]. Immunological studies indicate that pentosidine and other AGEs are co-localized with astrocytes and microglial cells, and their activation may enhance oxidative stress, which consequently leads to AD [9, 10]. Pentosidine is primarily synthesized from lysine, arginine, and ribose [2].

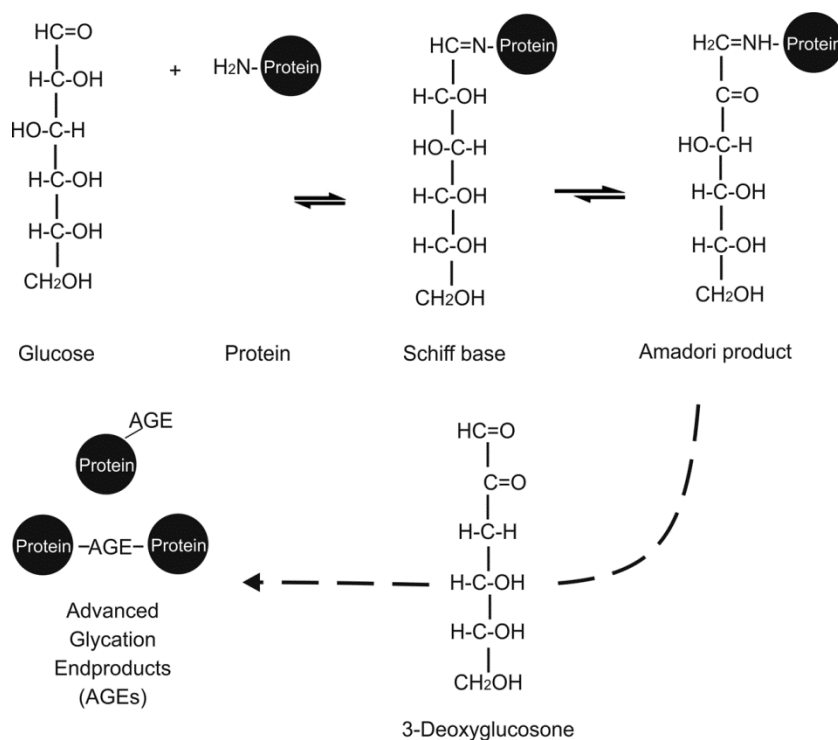


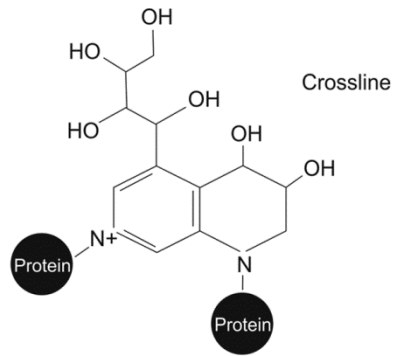
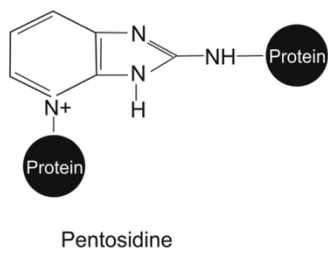
Fig. 1. The pathway of AGE formation via a dicarbonyl intermediate (adapted from [7]).

The AGE-like crossline was first identified in the kidneys of diabetic rats and can be formed both *in vitro* and *in vivo* [11]. Crossline formation occurs from the reaction between glucose and free amino group(s) such as the epsilon amino group of lysine.

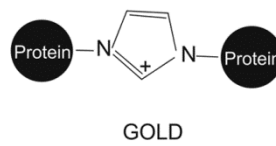
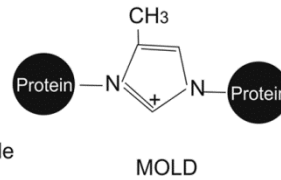
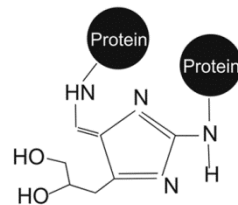
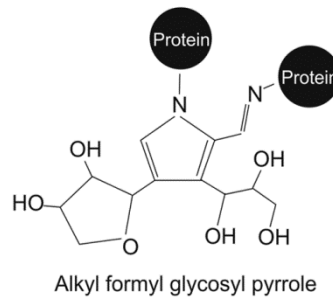
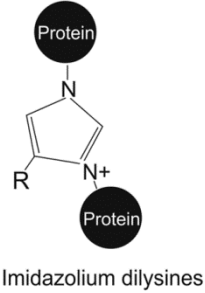
AGEs such as pyrraline are generally implicated in AD and other age-related diseases such as cataracts. Pyrraline is synthesized either through the reaction of glucose with the amino group of protein or through the reaction of 3-deoxyglucosone and lysine.

*N*ε-carboxymethyllysine (CML) is thus far the most important AGE that occurs *in vivo* [12]. It has been extensively studied and implicated in neurodegenerative disorders [10]. CML is produced through an oxidative breakdown of Amadori products or a metal-catalyzed oxidation reaction between polyunsaturated fatty acids and protein. Non-fluorescent crosslink AGEs, such as glyoxal lysine dimer (GOLD) or methylglyoxal lysine dimer (MOLD), are synthesized by reactions between two molecules of glyoxal derivatives with two lysine residues (Fig. 2). These AGEs are detectable *in vivo*. Similarly, AGEs like alkyl formyl glycosyl pyrroles (AFGPs) are formed through the reaction between two sugar molecules with one alkylamine molecule that mimics the lysine residue. Furthermore, it has been suggested that AFGP crosslinks may not play an important role *in vivo* [13]. Non-fluorescent crosslink AGEs such as arginine-lysine imidazole (ALI)

## Fluorescent Cross-linking AGEs



## Non-Fluorescent Cross-linking AGEs



## Non-Cross-linking AGEs

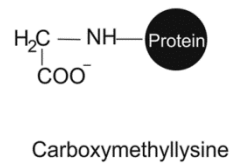
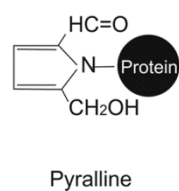


Fig. 2. The structures of different types of AGE.

are produced through the reaction of Amadori dione with an arginine residue. As this illustrates, AGEs are highly heterogeneous in nature, and the mechanisms by which they are produced are only partially understood.

Alternative pathways of AGE formation to the Maillard reaction include the carbonyl stress pathway, where oxidation of sugars and/or lipids generates a dicarbonyl intermediate, which binds amino acids and forms AGEs [14, 15]. Another mechanism of AGE formation is the aldose reductase-mediated polyol pathway. Glucose entering the polyol pathway may directly form AGEs via 3-deoxyglucosone AGE intermediates, but this reaction depletes NADPH and glutathione, and the resultant oxidative stress indirectly increases AGE formation [16].

Since these glycation reactions were slow, it was believed that this process predominantly affected long-lived proteins. However, it was later found that even short-lived compounds such as lipids, nucleic acids, and intracellular growth factors are glycated [17]. The side-chains of arginine and lysine residues, the N-terminal amino groups of proteins, and the thiol groups of cysteine residues are the main targets of protein glycation. The reaction depends on several factors, including the concentration and reactivity of the glycation agent. Increases in the concentration and reactivity of the glycating agent accelerate the glycation process. The buffer composition, oxygen levels, physiological pH, temperature, nature of metal ions present, and the unfolding of the protein [18–20] also affect the glycation reaction. The accessibility of glycating residues and the pK of amino acid residues in the vicinity of the glycating residue also influence the glycation reaction [17].

AGE-modified proteins also interact with specific receptors, including the macrophage scavenger receptor, MSR type II, OST-48, 80K-H, galectin-3, CD36, and RAGE [21–25], leading to the activation of cellular pathways. RAGE belongs to the immunoglobulin superfamily and can bind a broad repertoire of ligands, such as AGEs, A $\beta$  fibrils, transthyretin, and amphoterin, and proinflammatory cytokine-like mediators of the S100/calgranulin family [26]. The interaction of A $\beta$  with RAGE induces neuronal stress and the activation of different signaling pathways [27].

## GLYCATION IN ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is one of the most common neurodegenerative diseases. It affects 5% of people aged 65–75 and almost 50% over 85 [28]. AD occurs primarily because of protein aggregation. The characteristic features of this disease are progressive loss of memory, speech, and the ability to recognize people and objects. The dysfunction involves degeneration of neurons, especially in the forebrain and hippocampus. Most AD cases are sporadic and only 6% show a genetic origin [29]. The majority of genetic cases are related to the presence of the  $\epsilon$ 4 allele of apolipoprotein E (ApoE $\epsilon$ 4) and also to mutations in the amyloid precursor protein (APP) [30]. A recent report suggests that

glycation plays a key role in the formation of amyloid protein. For instance, it was found that glycation converts albumin, a globular protein with largely  $\alpha$ -helical structure, into a  $\beta$ -pleated sheet structure and the quaternary structural element known as the cross- $\beta$  conformation [31].

AGEs are also formed from the reaction of reactive carbonyl or dicarbonyl compounds with lysine or arginine groups on proteins [32], and are present in  $\beta$ -amyloid plaques and NFTs [33, 34]. AGEs play an important role in AD. The plaque fractions of AD brains contain higher levels of AGEs than samples from age-matched controls [35]. Furthermore, immunohistochemical methods have convincingly demonstrated that AGEs are present in NFTs and senile plaques [36]. Although some authors suggested that AGEs are very late markers of the disease [37], it is now widely accepted that they are active participants in the progression of the disease [38].

RAGE plays an important role in AD, because it recognizes A $\beta$  [39]. Interestingly, A $\beta$ -, AGE- and RAGE-positive granules were co-localized in one part of a single astrocyte, suggesting that glycated A $\beta$  is taken up via RAGE to be degraded via the lysosomal pathway in astrocytes [40].

A link between diabetes mellitus and AD was recently postulated because humans with diabetes show a greater deposition of brain AGEs and RAGE, which may mediate a common pro-inflammatory pathway in neurodegenerative disorders. Immunohistochemical studies of human postmortem samples showed that patients with the combination of AD and diabetes had higher AGE levels, increased numbers of  $\beta$ -amyloid dense plaques, higher RAGE- and tau-positive cells, and major microglial activation in their brains when compared to the brains of patients with AD alone. [41].

A $\beta$  aggregation follows a nucleation-dependent polymerization mechanism, which is significantly accelerated by AGE-mediated crosslinking [42]. The A $\beta$  aggregation consists of two distinctive stages, an initial, slow, nucleus-formation step, followed by a rapid elongation phase. The nucleus-formation stage is a reversible process involving oligomer formation. Once the oligomers reach a critical size, a fast, linear elongation of the aggregates or fibril formation can occur via the addition of  $\beta$ -amyloid peptides to the ends. The fibril-formation step is an irreversible process. Finally, these fibrils grow and form amyloid plaques.

Li et al. speculated that A $\beta$ -AGE formation may exacerbate neurotoxicity [43]. Indeed they found glycation of A $\beta$  exacerbated neurotoxicity with upregulation of RAGE and activation of glycogen synthase kinase-3 (GSK-3). This pathway was inhibited and reversed by the RAGE antibody or GSK-3 and consequently prevented neuronal damages. They then authors found that A $\beta$  is also glycated with age-dependent elevation of AGEs in Tg2576 mice, which showed loss of cognitive function. The glycation of A $\beta$  in mice was inhibited via aminoguanidine administration for 3 months, and the results showed improvement in cognitive function [43]. Thus, these studies revealed that the

glycated A $\beta$  amyloid is more toxic than non-glycated A $\beta$  amyloid [43]. More recently, both in vitro and in vivo studies have shown that amyloid precursor protein (APP) expression is upregulated by AGEs, leading to their increased  $\beta$ -amyloid levels. The increase in  $\beta$ -amyloid levels could be effectively blocked with the ROS inhibitor, N-acetyl-L-cysteine [44].

Neurofibrillary tangles (NFTs) are most common primary marker of AD. NFTs are the aggregates of hyperphosphorylated microtubule-associated tau protein. Using a monospecific antibody, AGEs have been co-localized with paired helical filament tau in neurofibrillary tangles in sporadic Alzheimer's disease. Such neurons also exhibited evidence of oxidative stress and neuronal dysfunction [45]. This causes toxicity in NFTs. AGEs can also cause toxicity through RAGE-mediated GSK-3 activation, which induces tau protein hyperphosphorylation and consequently impairs synapse signaling and memory in rats [46]. Methylglyoxal also glycates A $\beta$  and promotes the formation of  $\beta$ -sheets, oligomers and protofibrils and increased the size of aggregate [47]. Furthermore, it has been shown that glyoxylase I is involved in the catabolic pathway of methylglyoxal [48]. This enzyme levels decrease in the late stage of AD [49]. This leads to a build-up of high carbonyl stress, which increases the levels of AGEs, oxidative stress, inflammation, plaque and tangle formation, and finally apoptosis.

Similarly, the AGE-derived product glyceraldehyde occurs in the cytosol of neurons in the hippocampus and parahippocampal gyrus and elicits carbonyl stress by inhibiting the catalytic activity of glyceraldehyde-3-phosphate dehydrogenase (GAPDH), meaning that glyceraldehyde and then methylglyoxal accumulate in the brain [50]. This results in a vicious cycle and consequently leads to AD [50–52]. From these studies, it is evident that glycation plays an important role in AD.

## GLYCATION IN PARKINSON'S DISEASE

Parkinson's disease (PD) is another very common form of neurodegenerative disease characterized by resting tremors, rigidity, slow movements, and postural and autonomic instability. PD involves degeneration of dopaminergic neurons in the *Substantia nigra* of the midbrain and other monoaminergic neurons in the brain stem [53]. In a similar vein to other neurodegenerative diseases including Alzheimer's disease (AD), the etiology of PD is complex, including genetic and environmental factors and crosstalk between these. Only a few cases of purely genetic or environmental PD have been reported; most cases involve both factors [54]. Genes such as  $\alpha$ -syn, Parkin, DJ-1, and Pink1 have been identified and determined to play an important role in the development of PD [55–57]. Environmental factors also lead to the onset of PD, including brief exposure to pesticides, herbicides and heavy metals, increased stress, and brain injuries [54–58]. Some of the autosomal dominant PD genes are SNCA (alpha-synuclein) and LRRK2 (leucine-rich repeat kinase 2).

SNCA primarily exists in a natively unfolded state in the cytoplasm or is associated with the lipid bilayer membrane [54]. Mutations in  $\alpha$ -syn may change the protein conformation, thereby abolishing the membrane-binding ability and favoring self-aggregation and the formation of more LBs [59]. Glycation of  $\alpha$ -synuclein is one of the important factors that leads to aggregation and the formation of LBs and thus to PD [53].

Glycation was first reported in the *Substantia nigra* and locus coeruleus of peripheral LB [60]. Glycation is also found in cerebral cortex, amygdala, and *Substantia nigra* of healthy subjects, but the levels are higher in PD patients than in age-matched control subjects. RAGE was also found to be expressed in PD patients. The AGEs are co-localized with  $\alpha$ -syn and accelerate the aggregation process of the protein [61].

Alpha-syn has a total of 15 lysine residues and these are all candidate sites for glycation [61]. The glycation of  $\alpha$ -syn influences the nucleation of protein aggregates [61] and induces  $\alpha$ -syn oligomerization, thereby stabilizing oligomers. This is an important pathological modification of  $\alpha$ -syn, because oligomeric species of  $\alpha$ -syn are now considered to be more toxic than  $\alpha$ -syn aggregates [53]. Guerrero et al. proposed that glycated  $\alpha$ -synuclein may exert toxic effects in neuronal cells through multiple mechanisms [53]. For instance,

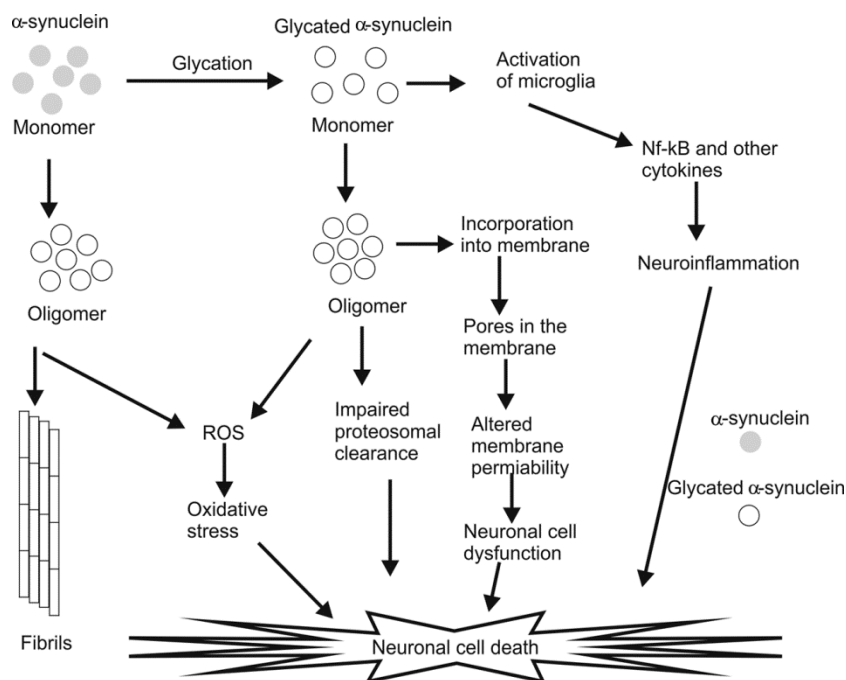


Fig. 3. The role of glycation in  $\alpha$ -synuclein aggregation and neurotoxicity (adapted from [53]).



$\alpha$ -syn oligomers may interact with the membrane and form annular pores in the membrane, thereby altering membrane permeability (Fig. 3), which can cause a loss of cell homeostasis and neuronal cell dysfunction. Secondly, both oligomeric and monomeric species of the glycated  $\alpha$ -syn are believed to generate ROS in the cell and increase oxidative stress. This leads to a vicious cycle and neuronal cell death. Thirdly, glycated  $\alpha$ -syn oligomers may be resistant to proteasomal clearance, and thus cause proteasome dysfunction and neuronal cell death. The cells with proteasome dysfunction proceed to autophagy and are eliminated. Fourthly, glycated  $\alpha$ -syn may exert the toxic effect by activating microglia and instigating neuroinflammation. Finally, glycated  $\alpha$ -syn may interact with RAGE and trigger the release of NF- $\kappa$ B. These signaling proteins activate signaling cascades in the brain and damage neuronal cells. NF- $\kappa$ B also regulates RAGE expression by inducing the expression of RAGE proteins. Increased expression of RAGE receptors means more glycated  $\alpha$ -syn binding and release of NF- $\kappa$ B. Due to this, it forms a feedback loop, meaning continuous activation of RAGE receptors, which activate the inflammatory pathway (Fig. 4) and lead to neuronal cell death [53]. Enhanced inflammation and RAGE expression in PD suggest that the glycation mechanism of  $\alpha$ -syn may operate only in the disease condition leading to neuronal cell death (Fig. 3) [53]. These studies suggest that glycation is involved in PD.

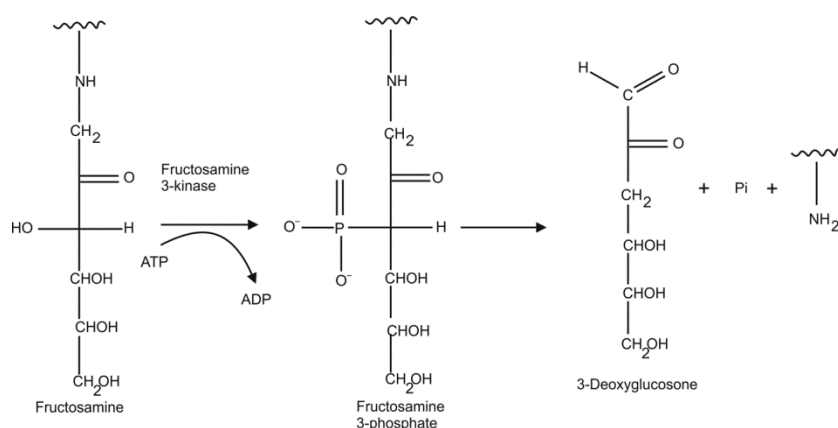


Fig. 4. The deglycation reaction catalyzed by fructoseamine-3 kinase.

## GLYCATION IN AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is a very common motor neuron disease. It is the third most common neurological cause of human death [62]. ALS is polygenic and multifactorial in origin [63], and causes selective loss of upper and lower motor neurons of the brain and spinal cord. It is characterized by progressive muscle weakness, atrophy, and spasticity [64]. ALS is both sporadic and inherited in nature. Inherited cases are

mostly associated with missense mutations in copper–zinc superoxide dismutase 1 (Cu, Zn-SOD-1) [65]. This implies that oxidative stress plays an important role in the disease development.

Glycation was first detected in the spinal cord and brain of ALS patients. Chou et al. postulated that glycation could be involved in the time-dependent cross-linking of neurofilament protein [66]. The subunits of neurofilament protein contain multiple Lys-Ser-Pro sequences. Glycation of these lysine residues impairs the self-assembly process and thereby promotes cross-linking in the neurofilament protein, which leads to ALS. Studies have revealed that AGE levels were higher in the presence of the Cu, Zn-SOD-1 mutation, while in control human and mouse subjects, AGE immunoreactivities were virtually absent [67].

Strikingly, the levels of soluble RAGE (sRAGE), a C-terminal truncated isoform of RAGE, are significantly lower in the serum of ALS patients [68]. sRAGE lacks the transmembrane-anchoring domain and was found to ameliorate the deleterious effects of RAGE by forming a complex with the ligand. This allowed it to be degraded through the lysosomal pathway [69]. Therefore, one conspicuous role of sRAGE is to protect humans from ALS. This indicates that low sRAGE levels may be a risk factor for ALS.

Glycation is generally thought to be a random process. However, in Cu, Zn-SOD-1 protein glycation occurs specifically at Lys122 and Lys128 [70]. These results suggest that glycation is responsible for the oxidative stress, which culminates in ALS. Recently, it has been established that CML concentration is significantly increased in serum and cerebrospinal fluid of ALS patient, which may represent diagnostic tool [71]. These data suggest that glycation is involved in ALS.

### **GLYCATION IN FAMILIAL AMYLOID POLYNEUROPATHY**

Familial amyloidotic polyneuropathy (FAP) is an autosomal dominant neurodegenerative disease characterized by the formation of amyloid fibril deposits that are mainly composed of transthyretin (TTR), which is present in various organs and tissues [72, 73]. TTR is normally an innocuous protein responsible for the transport of thyroxin hormone and retinol. FAP is associated with point mutations in TTR, a homotetrameric protein mainly produced in the liver and found in the plasma, cerebrospinal fluid, and saliva. More than 80 TTR point mutations are associated with amyloidotic diseases, and the most widely accepted disease model suggests that TTR tetramer instability is related to point mutations.

However, this model fails to explain two observations. First, native TTR also forms amyloids in systemic senile amyloidosis, a geriatric disease. Secondly, the age onset of disease varies by decades for patients bearing the same mutation. In fact, some mutation carrying individuals are asymptomatic throughout their lives. These results suggest mutations only accelerate the process and therefore non-genetic factors, such as protein glycation, play an important role in disease development [74]. The glycation hypothesis in FAP is supported by research

showing that methylglyoxal-derived AGE is found in FAP patients. The glycated TTR may contribute to cytotoxicity via a mechanism involving oxidative stress, or by interaction with RAGE [75–77]. Interaction between TTR fibrils and RAGE results in the translocation of NF- $\kappa$ B to the nucleus, where it promotes the induction of tumor necrosis factor- $\alpha$  (TNF $\alpha$ ) and interleukin-1 $\beta$  (IL-1 $\beta$ ) [77]. The activations of these markers were abrogated by an anti-RAGE antibody or by sRAGE [76]. Thus, these studies suggest that glycation plays an important role in FAP.

### GLYCATION IN PRION DISEASES

Prion diseases are fatal neurodegenerative diseases that can be spontaneous, genetic, or infection-related. Spontaneously occurring prion diseases are mostly age-related in nature. Prions are proteinaceous infectious particles, containing host-encoded prion protein (PrP). In prion diseases, cellular prion protein (PrPC) becomes misfolded and thereby accumulates and aggregates. PrPC plays a key role in long-term memory formation. Neuronal loss, vacuolation, microgliosis, astrogliosis, and spongiform alterations are the characteristic features of amyloid diseases, including Creutzfeldt-Jakob disease (CJD), bovine spongiform encephalopathy (BSE), and scrapie [78]. CJD is both sporadic and genetic in nature [79]. The ‘protein only’ hypothesis states that these diseases are caused by the conversion of natively folded PrPC into non-native state, which is resistant to degradation by proteinase K (PrPres). However, the exact mechanism is still the subject of considerable discussion [80]. Interestingly recent findings indicate that PrP(C) is involved in signal transduction [81].

The pathological role of advanced glycation end products and the receptor for AGE in CJD was recently studied in the occipital lobe of three patients using anti-AGE and anti-RAGE antibodies [82]. These studies revealed a colocalization of PrP-positive granule AGEs and RAGE. The authors hypothesized that glycation would advance over time and like A $\beta$ , PrP would be degraded through the lysosomal pathway. These astrocytes also contained PrP-positive granules and several AGE- and RAGE-immunopositive granules. From these data, it is evident that RAGE may form a complex with glycated PrP, leading to degradation through the lysosomal pathway.

The mature form of human PrP contains 21 arginine and lysine residues. Glycation of PrP is not a random process: only lysines 23, 24 and 27 and arginine 37 are specifically glycated [83]. Glycation in prion protein results in a cross-linked structure, which is resistant to protease degradation and therefore may induce oxidative stress. One interesting observation is the higher occurrence of glycation in diglycosylated PrPres. This presumably occurs because diglycosylated residue might alter the microenvironment of the Lys residues, enhancing their susceptibility to glycation. Another interesting observation is that the oligomerized form of glycated PrP is more pathogenic than non-oligomerized PrP.

The mechanism by which AGEs cause the formation of PrPSc remains unknown, but two hypotheses exist [83]. The first states that all AGE modification occurs at the time of PrPSc formation. The second suggests that glycation only occurs after the formation of PrPSc. Thus, glycation plays a key role in the pathogenesis of prion diseases, because glycation would provide enhanced protection for the PrPSc molecules against cellular degradation.

### **GLYCATION AND THE DECLINE OF COGNITION IN OLDER ADULTS**

As mentioned above, glycation plays a key role in AD, PD, and other neurodegenerative diseases. Recent studies suggest that glycation is involved in cognitive decline in older adults. In one study, a higher level of CML staining was found in the cortical neurons and vessels of older adults. The patient's death/disease progression was associated with severe cognitive impairment and a history of diabetes and cerebrovascular disease but minimal AD pathology, suggesting that accumulation of AGEs may contribute to vascular dementia [84]. Yaffe et al. also reported that a high peripheral AGE level is associated with greater cognitive decline in older adults with and without diabetes [85]. The advanced glycation end product precursor methylglyoxal was also reported to play an important role in cognitive decline and neurodegeneration in older people [86]. These data conclusively suggest that glycation plays an important role in cognitive decline in older adults.

### **DIETARY AGEs AND NEUROTOXICITY**

Diet is an underappreciated source of the bodily pool of potentially toxic AGEs [87]. The dietary AGEs include reactive AGE precursors (e.g., 1-or3-deoxyglucosone, methyl glyoxal, and pentosidine) and non-cross-linking AGEs, such as pyrroline, *N*<sub>ε</sub>-carboxymethyllysine (CML), carboxyethyllysine, and their derivatives [88–92]. Diet-derived AGEs are similar to native AGEs with respect to their biological activities. Both generate pro-oxidants and activate pro-inflammatory pathways [87, 93]. Thus, ingested glycoxidation products can accelerate free radical generation and oxidative and carbonyl stress [94].

Recent studies have demonstrated that a diet rich in AGEs also affects the chemistry of the brain, leading to accumulation of misfolded beta amyloid protein. However, mice eating a diet low in AGEs did show an ability to prevent the production of damaged amyloid. Furthermore, humans over 60 showed a link between high levels of AGEs in the blood and cognitive decline [95].

### **THERAPY FOR AGE-MEDIATED NEURODEGENERATIVE DISEASES WITH SYNTHETIC INHIBITORS**

Several novel inhibitors have recently been discovered. They react with and thereby cap the free amino groups of proteins and prevent sugar attachment. Examples of these inhibitors are aldehyde, pyridoxal-phosphate, or the

acetylating agent aspirin. Diclofenac, an anti-inflammatory drug, could also protect proteins from sugar attachment thanks to its non-covalent interactions with proteins such as serum albumin. Results suggest that diclofenac specifically blocked at least one of the major glycation sites of human serum albumin [96].

Some inhibitors are scavengers of free carbonyl. They react with free carbonyl groups, including those of aldose and ketose sugars, and inactivate these sugars before they react with proteins. These compounds act at more than one step of the Maillard reactions. For instance aminoguanidine (AG) reacts with the carbonyl group of Amadori compounds. However, AG and other hydrazine drugs, such as hydralazine, isoniazid, and gentamicins, are either toxic or show adverse side effects because of the depletion of essential carbonyls, such as pyridoxal-phosphate (vitamin B6). Thiol-based antioxidants like glutathione can also act as a carbonyl scavenger. Besides this, there are some dicarbonyl scavengers including AG and L-arginine that trap reactive dicarbonyl intermediates, including glyoxal, glycoaldehyde, and glucosones, to form substituted triazines. Thus, these drugs are powerful therapeutic agents for treating neurodegenerative maladies.

The ROS and free transition metal ions are known to play an important role in the formation of advanced glycation end products. These autoxidative glycosylation and glycooxidation reactions can be efficiently inhibited by redox-metal chelators [97–99] including DETAPAC (diethylenetriaminepentaacetic acid), phytate, and penicillamine. Therefore, these redox-metal chelators could be used in the therapy of neurodegenerative diseases.

Various AGE inhibitors that inhibit Amadori adduct formation have been designed. For example, pyrrolidine was attached to sugar-derived moieties of glycosylated proteins and thereby blocked the reactive sites from further polymerization reactions [100, 101]. Similarly, penicillamine has also been reported to decrease the formation of Amadori products [102, 103] and reduce the AGE levels [104]. Besides these drugs, there are numerous cross-link breakers that break existing cross-links, e.g., thiazolium compounds such as phenacylthiazolium bromide (PTB) and Alteon's ALT-711. These compounds are chemically related to thiamine (vitamin B1), and have been reported to inhibit AGE formation. Alagebrium chloride (ALT-711) was the first compound in the thiazolium class to break established AGE-related protein cross-links. The prototypic AGE cross-link breakers, such as N-phenacylthiazolium bromide (PTB) [105], cleave covalent AGE-derived protein cross-links. Other potent cross-link breakers are curcumin [106] and ALT-946 [107, 108].

AG is a prototype therapeutic agent that has been used for the prevention of AGE formation. It is a small hydrazine-like molecule that inhibits AGE formation through a mechanism involving quenching of the carbonyl groups of the Amadori-product. In cultured cortical neurons, dicarbonyl compounds, including methylglyoxal (MG) and 3-deoxyglucosone (3DG), can cause production of reactive oxygen species, which in turn causes neuronal toxicity.

Co-treatment (but not pretreatment) with AG protected neurons from the neurotoxicities of dicarbonyl compounds [109]. Methylglyoxal is also toxic to the neuroblastoma cell line SHSY5Y, which could be completely abolished by AG [110].

Tenilsetam, also termed (R) CAS 997: (+/-)-3-(2-thienyl)-2-piperazinone, is successfully used for the treatment of patients suffering from Alzheimer's disease [111]. In vitro tenilsetam inhibited AGE crosslink and glucose- and fructose-induced polymerization of lysozymes. Nucleation-dependent polymerization of A $\beta$ , the major component of plaques in patients with Alzheimer's disease, is significantly accelerated by AGEs in vitro. Formation of AGE-crosslinked amyloid  $\beta$  peptide aggregates was inhibited by the AGE-inhibitor tenilsetam [42], which is covalently attached to glycated proteins and blocks the reactive sites for further polymerization reactions. Most likely, it reacts with Amadori products.

Drugs like metformin [112–114] and buformin [115] also showed the potential to protect proteins against in vitro glycation and cross-linking [116, 117]. Furthermore, a series of compounds, such as calcium antagonists [118], amlodipine [119], kinetin [120], quinine [121], and synthetic 6-dimethylaminopyridoxamine [122], retarded or suppressed AGE formation possibly due to radical scavenging properties.

In one study, the inhibitory activity of isoferulic acid (IFA) on fructose- and glucose-mediated protein glycation and the oxidation of bovine serum albumin (BSA) was investigated [123]. The data showed that IFA inhibited the formation of fluorescent advanced glycation end products (AGEs) and non-fluorescent AGE, such as N $\epsilon$ -(carboxymethyl) lysine or CML, and reduced the level of fructosamine. IFA also prevented the protein oxidation of BSA as indicated by decreasing protein carbonyl formation and protein thiol modification. Furthermore, IFA suppressed the formation of  $\beta$ -cross-linked amyloid structures of BSA. Therefore, IFA is a promising anti-glycation agent, which can be used for the prevention of diabetes and neurodegenerative diseases.

Although the synthetic compounds mentioned above are powerful drugs that inhibit AGE formation or break cross-links, they can also have severe side effects. For example, AG, which was the first inhibitor used in clinical trials, had its Phase II trial terminated due to adverse side effects including gastrointestinal disturbance, anemia, and flu-like symptoms [124–126].

### **THERAPY OF AGE-MEDIATED NEURODEGENERATIVE DISEASES USING NATURALLY OCCURRING AGE INHIBITORS**

Therapy using synthetic inhibitors often has side effects. Naturally occurring AGE inhibitors have been investigated as an alternative mode of therapy. The AGE-dependent signal transduction uses free radicals as a 'second messenger'. This pathway is activated in neurodegenerative diseases and could be inhibited by naturally occurring compounds, such as  $\alpha$ -lipoic acid [127]. Thiamine is a water-soluble complex of vitamin B1. It also possesses anti-glycation activity

through dual mechanisms. Firstly, thiamine is converted in the cell to thiamin pyrophosphate (TPP), which is a co-enzyme for transketolase (TK). This conversion is a rate-limiting step of the pentose phosphate pathway [128]. Binding TPP to TK activates TK and decreases the accumulation of glyceraldehyde-3-phosphate and fructose-6-phosphate formed from the glycolytic pathway, thus preventing AGE formation [129]. Secondly, thiamine can directly quench reactive carbonyls [130] due to the unique reactivity of its thiazolium nucleus [131] with a mechanism similar to that used by thiamine in enzymatic catalysis [132].

PM (4-(aminomethyl)-5-(hydroxymethyl)-2-methylpyridin-3-ol), a derivative of vitamin B6, is an effective inhibitor of both in vivo and in vitro of protein glycation and lipoxidation [133]. It inhibits the glycation reaction through different mechanisms, including chelation of metal ions [98], neutralization of radical species [133], and scavenging of carbonyl species.

Plant-derived polyphenols might also offer therapeutic opportunities to delay the progression of AGE- and RAGE-mediated neuroinflammatory diseases, including Alzheimer's disease [134]. For example curcumin and resveratrol have the potential to prevent AD because of their anti-amyloidogenic, anti-oxidative, and anti-inflammatory properties [135]. Furthermore, naturally occurring compounds such as (-)-epigallocatechin gallate (EGCG) may also exhibit protective effects against AGE-induced injury of neuronal cells through its antioxidative properties, as well as by inhibiting AGE- and RAGE-mediated pathways, suggesting a beneficial role for tea catechin against neurodegenerative diseases [136].

Of the commonly consumed juices (pomegranate, cranberry, black cherry, pineapple, apple, and concord grape), pomegranate juice and two of its major constituents were found to be most potent inhibitors of fructose-mediated protein glycation [137]. Genistein, a naturally occurring isoflavone derived from soy products, demonstrated significant trapping effects of MGO and consequently formed mono- and di-MGO adducts [138]. Thus, this compound has the potential to prevent neurodegenerative diseases. An extract of the leaves of *Origanum majorana* also inhibits AGE formation. The antiglycation activities were due to the antioxidant activities and their ability to trap reactive carbonyl species such as methylglyoxal. These results demonstrate that *O. majorana* has significant effects on in vitro AGE formation, and surprisingly it was found to be more a potent glycation inhibitor than AG [139].

### **BLOCKADE OF THE LIGAND–RAGE AXIS**

RAGE activation plays central role in the pathogenesis of some diseases, including diabetes, atherosclerosis, Alzheimer's disease, and chronic airway diseases. In view of this, the AGE–RAGE axis is now considered to be a more promising drug target. Hence, compounds that inhibit RAGE-mediated signals possess beneficial effects in various pathologies.

One therapeutic approach involves the inactivation of ligands. For instance, sRAGE that is present in the body binds to circulating AGEs, thereby preventing it from binding to RAGE. In other words, it inactivates the ligand and results in the prevention of various pathologies including AD [140]. Another therapeutic approach involves inactivating RAGE. High molecular weight substrate analogs, low molecular weight inhibitors, or anti-RAGE antibodies can inactivate the receptor. Due to complexities of molecular interactions between AGE–RAGE, most studies have focused on amyloid  $\beta$ -peptide ( $A\beta$ ) as an antagonist [141]. The interest in  $A\beta$  as a RAGE ligand stems from the fact that the  $A\beta$ –RAGE axis is involved in AD and thus represents an emerging drug target. In particular, in the brain endothelium, RAGE mediates the influx of circulating  $A\beta$  into the brain, while in neurons, it mediates  $A\beta$ -induced oxidant stress and  $A\beta$  intraneuronal transport, causing mitochondrial dysfunction. The  $A\beta$ –RAGE interaction also activates nuclear factor- $\kappa$ B (NF- $\kappa$ B), which plays a crucial role in various inflammatory responses.

In a mouse model of AD the drug FPS-ZM1 was found to be quite effective in inhibiting RAGE-mediated influx of circulating  $A\beta_{40}$  and  $A\beta_{42}$ ,  $\beta$ -secretase activity,  $A\beta$  production and microglia activation and neuroinflammation. It normalized the cognitive function and cerebral blood flow responses [141]. Using ligand-based drug design, a novel series of 4, 6-disubstituted 2-aminopyrimidines have been developed as RAGE antagonists [142]. In transgenic mouse models of AD, one of the antagonists, 4, 6-bis (4-chlorophenyl) pyrimidine analogs significantly lowered the concentration of toxic soluble  $A\beta$  in the brain and improved cognitive function. This drug binds directly to RAGE and inhibits the RAGE- $A\beta$  interaction [142]. Similarly, studies on the interaction of a series of truncated versions of  $A\beta$  with RAGE lead to prevention of full-length  $A\beta$  from binding to RAGE [143]. Furthermore, pretreatment of rat primary cultured cortical neurons with endogenous anti-RAGE antibodies isolated from transgenic APPSWE-PS1 mice expressing human presenilin 1 (A246E variant) and a chimeric amyloid precursor protein prevented  $A\beta$  1-42 induced neurotoxicity [144].

Agents that downregulate RAGE expression are also considered to be powerful therapeutic agent for treating AD. For example, *Ginkgo biloba* extract, a traditional Chinese medicine (EGb761), downregulated RAGE expression in immortalized mouse endothelial cells and protected the brain from hypoxic damage and ROS generation [145, 146].

### **CARNOSINE PREVENTS GLYCATION**

Carnosine is a naturally occurring dipeptide found at high levels in brain tissue and the innervated muscle of mammals, including humans. It has strong antioxidant, metal chelating and anti-glycation properties and thus has strong protective functions. It extends the cultured human fibroblast lifespan, kills transformed cells, protects cells against aldehydes and amyloid peptide



fragments, and inhibits *in vitro* protein glycation (formation of cross-links, carbonyl groups and AGEs) and DNA/protein cross-linking. Carnosine protects neurotoxicity caused by glycated  $\beta$ -amyloid peptide (A $\beta$ 25-35) to rat brain vascular endothelial cells (RBE4 cells). The homologs of carnosine such as  $\beta$ -alanine and homocarnosine, could also act as therapeutic agents, but these are not as effective as carnosine. Thus, it is postulated that carnosine acts as both an anti-glycating and antioxidant agent that protect RBE4 cells from Alzheimer's disease [147].

### ENZYMES INVOLVED IN DEFENSE AGAINST AGEs

Several enzymes in the human body act as a defense mechanism against glycation. For example, fructosamine-3-kinase (FN3K) phosphorylates fructosamines on the third carbon, making them unstable and causing them to break from proteins (Fig. 4). This enzyme was simultaneously discovered by two independent research groups [148, 149]. Fructosamine-3-kinase (FN3K) has been reported to prevent glycation [150–152]. The role of FN3K as a protein repair enzyme was confirmed in an experiment with FN3K-deficient mice that showed approximately 2.5-fold higher levels of hemoglobin-bound fructosamines than control mice [153].

Additionally, there are two more important enzymes that are involved in the defense mechanism against glycation and prevented accumulation of  $\alpha$ -oxoaldehydes: aldose reductase and glyoxalase I and II. Recently, the role of aldose reductase *in vivo* in the mammalian metabolism of AGE precursors has been studied. The enzyme catalyzed the reduction of  $\alpha$ -oxoaldehydes. In mice aldose reductase AKR1B3 catalyzed reduction of AGE precursors. However, the antiglycating reaction was diminished in the heart of aldose reductase-null mice [154]. In the presence of both 3-DG and human umbilical vein endothelial cells, the enzyme AKRs reduced 3-DG to 3-deoxyfructose. The reaction was abolished by an AKR inhibitor [154].

The glyoxalase system consists of two enzymes: glyoxalase 1 and glyoxalase 2 and GSH cofactor. The system catalyzes the conversion of  $\alpha$ -oxoaldehyde into the corresponding  $\alpha$ -hydroxyacids. For example, in the presence of cofactor GSH, glyoxalase 1 catalyzes the conversion of MG to glutathione-methylglyoxal hemithioacetal, which isomerizes to S-D-lactoylglutathione. S-D-lactoylglutathione is a substrate for glyoxalase 2 and is converted to D-lactate and GSH [155, 125]. The term  $k_{cat}/K_m$  is a measure of catalytic efficiency of enzyme where  $k_{cat}$  is catalytic constant and  $K_m$  is the Michaelis-Menten constant. The value of  $k_{cat}/K_m$  for glyoxalase 1 is approximately 100-fold higher than aldose reductase, so the glyoxalase system is more effective at MG detoxification than aldose reductase. In AD, glyoxalase 1 is upregulated and maintains the physiological level of  $\alpha$ -oxoaldehydes [156]. However, in the late stage of AD, the glyoxalase I level is decreased. Furthermore, in both age- and AD-affected brains the level of glyoxalase1 correlated with AGE deposits [49].

## DIETARY RESTRICTIONS OF AGEs

Recent studies suggest that age-related dementia may be causally linked to high levels of dietary AGEs [95]. Therefore, a reduce intake of food-derived AGEs may be an effective strategy to prevent neurodegenerative diseases [95].

## CONCLUSIONS AND FUTURE PROSPECTS

These studies have conclusively demonstrated that AGEs are complex and heterogeneous in nature. Their mechanism of formation is only partially understood. AGEs play an important role in various neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, amyloid lateral sclerosis, familial amyloid polyneuropathy, and prion diseases. In all of these, pathological amyloid glycation induces the formation of a  $\beta$ -sheet structure in the amyloid- $\beta$ -protein,  $\alpha$ -synuclein, TTR, SOD1 protein, and prions and causes these neurodegenerative diseases. More recently, it has been suggested that oligomeric species of glycated  $\alpha$ -synuclein and prion are more toxic than fibrils alone. A number of AGE-inhibitors have been discovered that inhibit the glycation pathway. These inhibitors are either synthetic or natural. The inhibitors cap the amino groups of proteins, scavenge free carbonyls or dicarbonyls, block Amadori adducts, break existing cross-links, chelate metal ions, and possess anti-amyloidogenic, anti-oxidative, and anti-inflammatory activities. Thus, they can inhibit glycation reactions.

The AGE-RAGE damaging axis is now considered to be a promising drug target. The main molecular approaches used to inhibit RAGE activation are inactivation of the ligand, inactivation of RAGE and downregulation of RAGE expression. Additionally, there are defense enzymes and protein present in the body, such as glyoxylase systems I and II, fructose-3-kinase, aldose reductase, and carnosine. These enzymes and protein protect the neuronal cell from glycation and carbonyl stress. The formation of toxic oligomeric species could be controlled by blocking conformational changes in monomeric species of these pathological proteins using novel inhibitors. More efficient drugs could be designed to be more hydrophobic so that it can easily cross the lipid-bilayer membrane of the brain and prevent efficiently neurodegenerative diseases. Using combination therapies, novel drugs could be designed that simultaneously target multiple pathways and may obviously be more efficient than those drugs that modify a single pathway and thereby decrease the risk of side effects.

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