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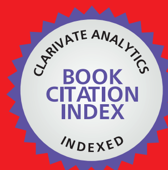

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Role of Glycation in Amyloid: Effect on the Aggregation Process and Cytotoxicity

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Abstract

Although the aggregation process of amyloidogenic proteins has been widely studied in vitro and many physiological factors have been identified, the molecular mechanisms underlying the formation of aggregates in vivo and under pathological conditions are still poorly understood. Post-translational modifications are known to affect protein structure and function. Some of these modifications might affect proteins in detrimental ways and lead to their misfolding and accumulation. Reducing sugars play an important role in modifying proteins, forming advanced glycation end-products (AGEs) in a nonenzymatic process, called glycation. Recently, much attention has been devoted to the role played by glycation in stimulating amyloid aggregation and cellular toxicity. Proteins in amyloid deposits are often found glycated, suggesting a direct correlation between protein glycation and amyloidosis.

AGE products increase in aging and are considered a marker for several diseases such as Alzheimer disease and diabetes. In addition to directly affecting the protein structure and function, AGEs also induce cellular toxicity.

This chapter focuses on the molecular effects induced by glycation in the amyloid aggregation of several protein models. In particular, both the structural effects induced by glycation and their consequence on cellular toxicity will be extensively described.

Keywords: amyloid aggregation, protein glycation, AGEs, cellular toxicity

1. Introduction

Reducing sugars play an important role in modifying proteins, forming advanced glycation end-products (AGEs) in a nonenzymatic process, called glycation. This process is different

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from glycosylation; indeed, these two post-translational modifications affect the structure of the target protein in a different way. Glycosylation is a selective protein modification, driven by specific enzymes, that is generally associated with a gain of function (or stabilization) of the target protein. Nonenzymatic glycation is a nonselective modification, and it is generally associated with a loss of function of the target protein due to modifications of its native structure. While glycosylation is a well-controlled cellular mechanism, nonenzymatic glycation depends on the exposure of free amino groups in the polypeptide chain, concentration of the sugar, and oxidative conditions. Glycation is a pathological process that is highly relevant in diabetes patients, as it plays a crucial role not only in diabetic complications but also in the normal aging process. Increasing evidence suggests a link between diabetes and neurodegenerative processes such as Alzheimer and Parkinson diseases [1]. In this respect, much attention has been recently devoted to the role played by nonenzymatic glycation of proteins in stimulating amyloid aggregation and toxicity. The observation that proteins in amyloid deposits, such as β-amyloid, tau, prions, transthyretin, and β_2-microglobulin, are often found glycated in patients suggests a direct correlation between protein glycation and amyloid formation [2–8]. This is thought to be associated with the formation of cross-links that stabilize protein aggregates. Indeed, AGEs formation can not only interfere with the regular functioning of the proteins to which they are attached but also induce the formation of covalent cross-links with close proteins. In addition, glycation can affect the protein degradation process [9], and, being an abnormal modification, it has been found to induce some proteins to misfold and, thus, promote protein aggregation [10–12].

Moreover, the AGE-modified proteins are tightly involved in physiopathological cellular mechanisms. Once formed, AGEs interact with specific cellular receptors leading to the activation of different signaling pathways. The most studied AGE-receptor, known as RAGE, is a multiligand receptor belonging to the immunoglobulin superfamily [13, 14]. The activation of RAGE regulates key cellular processes such as inflammation, apoptosis, proliferation, autophagy, and recently it has been associated with the pathogenesis of amyloidosis [15, 16]. In neurons, glia, and endothelial cells, RAGE is also the binding site for Aβ peptide on the cell surface and mediates Alzheimer's disease pathology [15, 17, 18].

2. Protein glycation

The nonenzymatic glycation of protein amino groups by reducing sugars (also called Maillard reaction) is a chemical reaction common to all cell types: glycated products slowly accumulate in vivo, leading to several different protein dysfunctions caused by alterations of their integrity [19, 20]. The process begins with a nucleophilic addition reaction between a free amino group of a protein and a carbonyl group of a reducing sugar, forming a reversible intermediate product (Schiff's base). Side-chains of arginine and lysine residues and the N-terminal amino group of proteins are the main targets of protein glycation. The process depends on several conditions, such as the concentration and reactivity of the glycation agent, the presence of catalytic factors (metals, buffer ions, and oxygen), the physiological pH, temperature, and the half-life of each protein. All reducing sugars can participate in

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glycation reactions and, among them, D-ribose is the most active form, and its intracellular level can be quite high. D-glucose is the less reactive form and its intracellular concentration is negligible, while dicarbonyl compounds, such as methylglyoxal and glyoxal, are far more reactive. These compounds are intermediates of glycation reaction, but can also be generated by various oxidative processes and be formed through other metabolic pathways such as glycolysis and catabolism of threonine and ketone bodies. The levels of D-ribose in the blood are estimated around 20 mg/L in healthy individuals, while that of D-glucose are around 6–10 g/L. Once formed, the Schiff's base can convert into a stable ketoamine by Amadori rearrangement (**Figure 1**). This reaction is reversible, depending on the concentration of the reactants. The late stage of the process is an irreversible cascade of reactions involving enolization, dehydration, condensation, oxidation, fragmentation, and other rearrangements, leading to the formation of AGEs [21]. Glucose, Schiff's base, and Amadori product, can also exhibit auto-oxidation reactions that are responsible for free radicals and highly reactive carbonyl compound production. These compounds can react with other amino acid side-chains and further contribute to post-translational modifications. Unlike organic syntheses, AGEs formation does not produce well-defined products but a large number of structures. The pathways leading to several AGEs are extensively outlined in [22]. Glycation reaction produces very reactive intermediates that can promote the formation of intramolecular and intermolecular cross-links within AGE-modified protein monomers. However, the reaction can also evolve into AGE protein adducts unable to form covalent cross-links (**Figure 1**).

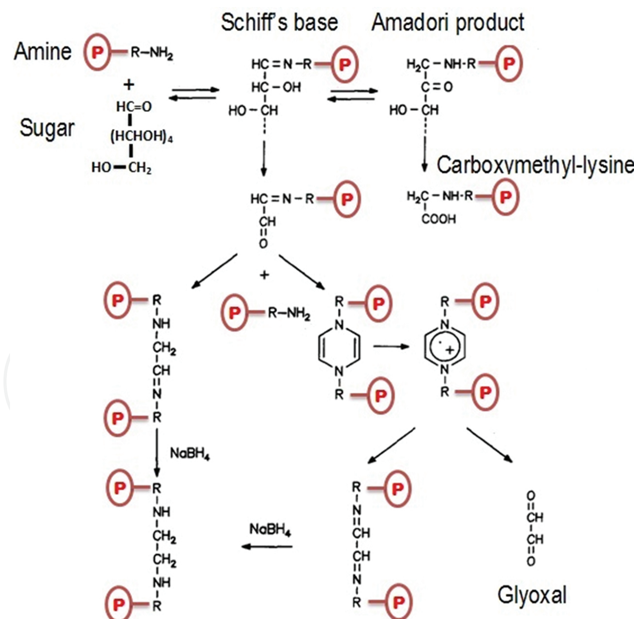

Figure 1. Simplified reaction scheme of some chemical processes involved in AGE formation. The reaction between a free amino group of a protein and the carbonyl group of a reducing sugar leads to the production of the Schiff's base that can turn into a stable ketoamine by Amadori rearrangement. Glycation reaction can evolve to AGE derivatives, forming, that is, di-aminoethyl bridge, or not forming, that is, carboxymethyl-lysine, intramolecular and intermolecular protein cross-links. Adapted from Glomb and Monnier [23].

3. Differential effects of glycation on protein aggregation and cytotoxicity

Several proteins related and not related to misfolding diseases have been so far examined to investigate the effect of glycation on their propensity to aggregate and form amyloid structure.

3.1. Proteins related to misfolding diseases

3.1.1. Aβ-peptide

Aβ-peptide is crucially involved in Alzheimer's disease as the main component of the amyloid plaques found in the brains of Alzheimer patients. This peptide results from the amyloid precursor protein (APP), which is cleaved by beta-secretase and gamma-secretase. Although carbohydrates are directly involved in the formation of neurofibrillary tangles and senile plaques in the brains of the patients with Alzheimer disease (AD) [24–26], their influence on the mechanism of Aβ peptide aggregation and induced cell toxicity is still controversial. Vitek et al. [10] reported, for the first time, that plaque fractions of AD brains contained about threefold more AGE adducts than preparations from healthy, age-matched controls. This observation was further corroborated by immunohistochemical studies on postmortem tissues that identified AGEs as major components of amyloid plaques [27]. Studies in vitro have shown that AGE-modified Aβ peptide-nucleation seeds induce fast aggregation of the soluble Aβ peptide compared to nonmodified seed material [10]. Aggregation of the Aβ peptide follows a nucleation-dependent polymerization process, consisting of two steps, an initial slow nucleus formation, followed by a rapid growth phase. The formation of a nucleus is a reversible process dependent on the concentration of the peptide monomer; thus, it is likely that the initiation of the process at a subthreshold concentration may be started by irreversible covalent cross-linking of the glycated monomers [10]. The AGEs species that enhance nucleation were suggested to be the relatively early glycation products as evidenced by the time course over which glucose accelerated the formation of Aβ peptide aggregates. Successively, it has been reported that glycation by fructose also promotes amyloid aggregation in vitro of Aβ peptide. During the aggregation process, both nucleus formation and aggregates' growth were accelerated by AGE-mediated cross-linking [28, 29]. Specifically, an increased content of oligomeric forms at the expense of fibrillar species was detected when Aβ peptide was incubated in the presence of glucose or fructose [29]. These species resulted to improve cell viability probably due to the stabilization of the oligomeric forms. Indeed, the mechanism by which Aβ induces toxicity is intimately associated to the conformational state of the peptide, the fibrillar forms rather than the soluble oligomers result more toxic to cells [30]. However, increasing evidence has recently shown that soluble oligomers are also cytotoxic, both in vitro and in vivo [31, 32]. The idea that all amyloid oligomers are intrinsically toxic has recently been questioned by a number of evidence showing that, depending on the growth conditions, the same protein/peptide can generate structurally different oligomers endowed with different stability, hydrophobic exposure, compactness, and cytotoxicity [33]. Aβ oligomers display a high degree of polymorphism with different structural, biophysical, and cytotoxic properties. In particular, Aβ oligomers have been classified as A+ and A-, with A+ more toxic than A- oligomers, possibly as a consequence of the increased exposure of hydrophobic residues

that would favor their interaction with the plasma membrane [34, 35]. In this respect, glycation could affect the structural and physicochemical features of amyloid oligomers as well as their interaction to the cell membrane and, consequentially, induce different cytotoxicities. Also, glycation by methylglyoxal promotes the formation of β-sheets, oligomers, and protofibrils in Aβ peptide as well as the increase in size of the oligomers, suggesting an enhancement of intermolecular and intramolecular interactions which stabilizes the aggregate species [36].

Aβ peptide has been identified as a ligand of RAGE, and the Aβ–RAGE interaction triggers the activation of different signaling pathways responsible for the neuronal cell death [37]. RAGE is overexpressed in the AD brains, and its upregulation has been shown to mediate Aβ-induced oxidative stress, activation of transcription factor Nf-κB, and apoptosis [38, 39]. Recently, Li et al. [40] have reported that fully glycated Aβ peptide (long incubation with methylglyoxal) exacerbates the neuronal toxicity by the upregulation of RAGE and subsequent activation of death-signaling pathways. These apparently contrasting effects of the cytotoxic properties of the glycated Aβ could be explained, assuming that glycation induces two different mechanisms in time: an immediate cytoprotective effect, likely associated with the structural properties of the oligomers, and a toxic effect at longer times associated to AGE formation.

3.1.2. β_2-Microglobulin

β_2 microglobulin (β_2M) is a major constituent of amyloid fibrils deposited in patients with hemodialysis-associated amyloidosis. This type of amyloidosis is a common and serious complication in patients on long-term hemodialysis.

Glycation seems to promote amyloid aggregation in β_2M. In particular, D-ribose has been shown to rapidly induce human β_2M to generate AGEs and form aggregates in a time-dependent manner [41]. The process takes few days in vitro and proceeds through the formation of covalent cross-links that are likely to favor protein aggregation. Ribosylated β_2M was highly oligomerized compared to unglycated protein, and had a granular morphology [41]. Furthermore, once ribosylated β_2M aggregates have been formed, they are difficult to be degraded by proteases and can persist in human tissues for a long period. These oligomeric aggregates show significant cytotoxicity to human neuroblastoma and fibroblast cells. Indeed, the exposure of cells to ribosylated β_2M aggregates resulted in a significant increase of intracellular reactive oxygen species (ROS), and thereby induced apoptosis [41]. Inhibition of fibril extension in vitro was reported for β_2M also upon glycation with D-glucose [42]. As glycated β_2M is found as a major component of the amyloid deposits in hemodialysis-associated amyloidosis [2], these findings suggest that glycation could promote the formation of stable β_2-microglobulin aggregates in vivo that contribute to the cell dysfunction and death, thus playing an important role in the pathogenesis of β_2M-associated diseases.

3.1.3. Insulin

Insulin is a small protein hormone that is crucial for the control of glucose metabolism. Monomeric insulin undergoes amyloid aggregation in vivo, and insulin amyloid-like fibrils are the hallmark of a clinical condition observed in insulin-dependent diabetic patients, called insulin injection amyloidosis.

Glycation of insulin has been reported to differentially affect protein structure, stability, and aggregation, depending on the glycating agent and/or environmental conditions. This protein is intimately associated with glycemia and is vulnerable to glycation by glucose and other highly reactive carbonyls, especially in diabetic conditions [43]. Glycated insulin is unable to regulate glucose homeostasis in vivo and to stimulate glucose transport and adipose tissue lipogenesis [44].

In vitro experiments have shown that insulin can be glycated by glucose to be able to react with Lys29 in the C-terminal region of chain B and with N-terminus of chains A and B [45, 46]. Glucose induces the formation of glycated insulin adducts having different structural features, depending on the experimental conditions used. In particular, glycation in reducing conditions is able to induce insulin oligomerization, thus accelerating amyloid formation. On the contrary, glycation in nonreducing conditions strongly inhibit amyloid formation in a way proportional to the glycation extent [47]. Probably, under the latter conditions, insulin adducts possess a higher internal dynamics that prevent formation of the rigid cross-β core structure, thus reducing the ability to form fibrils. Human insulin can also be glycated by methylglyoxal able to react with a single site, that is, Arg22 of the B-chain. This modification promotes the formation of native-like aggregates and reduces the ability of human insulin to form fibrils by impairing the formation of the seeding nuclei. These aggregates are small, soluble, nonfibrillar, and retain a native-like structure. The lag-phase of the nucleation-dependent polymerization process increased as a function of methylglyoxal concentration [48]. Also, using ribose as the glycating agent, the insulin's native conformation is preserved and does not evolve in amyloid aggregates, because ribosylation impairs the α-helix to β-sheet transition, maintaining the protein in a soluble monomeric state [49]. Again, the effects may be ascribed to a higher dynamics in glycated insulin leading to impairment in the formation of the rigid cross-β structure. However, ribose-glycated insulin strongly affects the cell viability, triggering a death pathway involving the activation of apoptotic signaling, intracellular reactive oxygen species (ROS) production, and activation of the transcription factor Nf-κB [49].

3.1.4. α-Synuclein

α-Synuclein is a natively unfolded protein which is found in the typical amyloid fibrillar form in the intraneuronal Lewy bodies (LBs) in Parkinson's disease (PD). Several factors such as metals, oxidative stress, failure of proper protein degradation, and mutations are associated to the altered protein conformation and function [50, 51]. Post-translational modifications like phosphorylation and glycation are known to affect the α-synuclein aggregation process [52]. Glycation was first reported to be present in the substantia nigra and locus coeruleus of peripheral LBs [53]. Increased accumulation of AGEs was detected in neuronal LBs and glial cells in the frontal cortex of early-stage PD brains, suggesting a role for AGEs in the disease

[54]. Moreover, AGEs and α-synuclein were found similarly distributed and colocalized in early LBs in the brains of PD patients [6, 55]. Intracellular accumulation of AGEs precedes α-synuclein-positive inclusion body formation, and extracellular AGEs accelerate the process of intracellular α-synuclein-positive inclusion body formation [56].

In vitro studies showed that AGEs promote cross-linking of α-synuclein. The protein contains 15 lysine residues making it a target for glycation at multiple sites. Glycation with both methylglyoxal and glyoxal induces oligomerization of α-synuclein and inhibits the formation of amyloid fibrils [57, 58]. Under aggregation conditions, glycated α-synuclein promoted the β-sheet conversion and the formation of spherical aggregates which were similar to oligomeric intermediates in their size and morphology, but no further elongation to fibrils was observed. Moreover, protein fibrillization was significantly suppressed by the seeding of modified α-synuclein species [57]. However, AGEs formation did not alter the secondary structure: the glycated α-synuclein showed similar random coil conformation as the native protein [57, 58]. Similar results were obtained with D-ribose: ribosylation of α-synuclein promotes the formation of molten globule-like aggregates and not fibrils. Moreover, these aggregates induce oxidative stress in cell models and result in high cytotoxicity. Changes in secondary structure upon ribosylation were not detected in α-synuclein. However, conformational changes in the tertiary structure occurred as suggested by change in intrinsic fluorescence and exposure of hydrophobic patches [59]. The glycation-induced folding alterations might affect the aggregation kinetics of α-synuclein inducing oligomerization and stabilize oligomeric aggregates.

Choi and Lim [60] reported, in a mouse model of parkinsonism, that α-synuclein is modified by AGEs in vivo. The authors showed that an oligomeric form of α-synuclein is linked to Nε-(carboxymethyl)lysine (CML) and Nε-(carboxyethyl)lysine (CEL) suggesting that the AGEs modification is involved in the aggregation of the α-synuclein in vivo.

These results indicate that glycation of α-synuclein results in the formation of oligomeric or globular structures that are the more toxic aggregate forms. Thus, it is likely that, in a glycation-prone environment, more cytotoxic α-synuclein aggregates or oligomers are formed contributing to the pathogenesis of PD.

3.1.5. Lysozime

Hen egg white lysozyme (HEWL) has also been used to study the impact of glycation on protein structure and aggregation. HEWL is a structural homolog of human lysozyme, responsible for systemic amyloidosis disease and, for this reason, it is considered a very good model for amyloid aggregation studies. HEWL undergoes glycation in vitro, and potential glycation sites are considered to be the N-terminal α-amino group, ε-amino group of lysine residues, and guanidino group of arginine residues [61]. Glycation of HEWL has been tested over a prolonged period in the presence of D-glucose, D-fructose, and D-ribose [62, 63]. Among the tested sugars, D-ribose resulted to be the most effective one, and glycation has been found to promote formation of cross-linked oligomers but no fibrillar species in HEWL. More recently, ribosylation of HEWL in the early phase of the process has been studied by complementary high-resolution techniques [64]. These studies indicate that ribosylation modifies the

protein surface in HEWL without altering the overall structure but affecting its hydrophobic surface. Such modifications lead to the formation of native-like spherical oligomers, able to affect cell viability, which further evolve into insoluble native-like protofibrils [64].

3.2. Proteins not related to misfolding diseases

3.2.1. Albumin

Human serum albumin (HSA) is the most abundant protein in human plasma or serum (around 60% of total proteins). Serum albumin is known to be capable of self-assembling in amyloidogenic aggregates under particular experimental conditions (pH, temperature, concentration, and isoelectric point) and is a widely used model for the study of amyloid aggregation. Both HSA and bovine serum albumin (BSA) have been shown to be efficiently glycated in vitro by different glycating agents. Glycation and AGE modifications of serum albumin induce structural changes that depend on the chemical reactivity of the modifying reagent and the concentration used for in vitro glycation. However, glycation has been shown to promote strong conformational changes affecting both secondary and tertiary structures. Such modifications in tertiary structure have been revealed by complementary spectroscopical techniques: circular dichroism (CD), Fourier transform infrared (FTIR), nuclear magnetic resonance (NMR), and fluorescence spectroscopy [65–69]. In particular, the microenvironment of Trp214 seems to be strongly affected by glycation as indicated by fluorescence and NMR spectroscopy [66, 69]. Such conformational changes in the tertiary structure could be a consequence of molecular rearrangements after the formation of AGE products. Indeed, some of these AGEs forming covalent cross-links within adjacent protein strands require conformational changes which produce more apolar and tight molecules with respect to the native protein. Besides, the accessibility of the hydrophobic regions in the protein has been shown to increase with glycation [67, 68]. Modification at the secondary structure level can be detected only at longer times of incubation with glycating agents. This could be due to the fact that glycation is likely to induce loss of tertiary structure before that of secondary structure, as suggested by comparing intrinsic fluorescence and far-UV CD results in glycated albumin [65, 66, 70].

Glycation-induced protein misfolding promotes the formation of amyloid-like aggregates in serum albumin [12, 71, 72]. These amyloid-like deposits appear as densely staining granules under atomic force microscopy and are able to bind the amyloid-specific dye thioflavin T. Also, they were shown to induce high cytotoxicity that triggers cell death by activation of cellular signaling cascades. In fact, independent experiments have shown that aggregates of glycated BSA are able to induce ROS-mediated oxidative stress and apoptosis in both neurotypic SH-SY5Y and MCF-7 cells. These results indicate that glycation of serum albumin results in the formation of oligomeric or globular structures that are the more toxic aggregate forms [68, 72].

These observations could have important implications, as serum albumin, being a circulating protein, is likely undergoing glycative alteration in the case of diabetes pathology and hyperglycemia. For instance, antioxidant activities of serum albumin were impaired in patients with diabetes.

3.2.2. Apomyoglobin

Apomyoglobin (i.e., heme-free myoglobin) is a small, soluble α-helical protein able to form amyloid fibrils under particular experimental conditions. In addition, an apomyoglobin mutant, that is, W7FW14F, is able to form amyloid fibrils in physiological conditions of pH and temperature, and for this reason this protein is a good model for the study of amyloidosis [73–78].

Wild-type apomyoglobin is rapidly glycated in vitro by different glycating agents, and glycation has been shown to induce strong conformational changes, affecting both secondary and tertiary structures. In particular, glycation induces partial loss of the helical content in apomyoglobin without promoting an α to β transition, typical of the amyloid aggregates. Glycation induces strong modifications in the tridimensional organization, as suggested by the loss of ability of the glycated protein to bind the prosthetic group [79]. Such modifications eventually lead to the formation of oligomeric species, stabilized by intermolecular cross-links, able to affect cell viability as observed for amyloid prefibrillar oligomeric aggregates, specifically, cell exposure to fully glycated wild-type apomyoglobin-induced ROS-mediated apoptosis [79].

At the same time, glycation has been shown to affect the aggregation kinetics in the W7FW14F apomyoglobin mutant, able to form amyloid fibrils in physiological conditions [73–78]. In particular, glycation accelerates the formation of harmless amyloid fibrils in the apomyoglobin this amyloidogenic mutant [76]. A plausible explanation for such faster kinetics could be related to a higher tendency of the mutant to form intermolecular links upon glycation able to reduce the flexibility of aggregation-prone regions and thus favor the subsequent step of fibril elongation.

Although apomyoglobin is not related to any amyloidogenic diseases, it represents a suitable model for studying the role of glycation in amyloid aggregation. Indeed, due to the different aggregation propensities of the native protein and the W7FW14F mutant in physiological conditions, this protein model allows to dissect the effect of glycation in promoting amyloid aggregation and contributes to the aggregation kinetics. The above results indicate that glycation can be considered not only a triggering factor in amyloidosis but also a player in later stages of the aggregation process.

4. Molecular effects of glycation on amyloid aggregation process

The overall evidences on several model proteins indicate that AGE modifications may alter the folding state of proteins and their solubility, thereby influencing protein aggregation. The main outcome of this study is that the effect of glycation on amyloid aggregation cannot be generalized. Indeed, being a post-translational modification, it differentially affects the aggregation process in proteins by promoting, accelerating, and/or stabilizing on-pathway and off-pathway species (**Figure 2**). Molecular basis of such modulation are still poorly understood. Most of the evidence indicate that glycation strongly affects the tertiary structure of the

target protein promoting the formation of globular amyloid-like deposits [62, 72]. Depending on the protein involved, glycation induces chemical modifications of the positively charged side chains (mostly lysine, arginine, and N-terminus), thus affecting the protein charge and favoring the exposure of its hydrophobic surface. This effect could trigger native-like aggregation favoring the formation of small oligomers that, being stabilized by the AGE-derived covalent cross-links, do not evolve into amyloid fibrils. Recent evidence indicates that glycation promotes the formation of the amyloid oligomeric species in several model proteins (**Figure 2B**). However, glycation does not necessarily induce protein oligomerization. Due to the complexity of the glycation reaction, some AGE adducts might not evolve to the formation of protein cross-links. In this case, glycation seems to stabilize the monomeric form thus inhibiting the amyloid aggregation process as observed for ribosylated human insulin (**Figure 2C**). Moreover, the cross-links of AGE-derived oligomers do not necessarily show amyloid properties (**Figure 2D**). However, AGEs-modified proteins are always able to affect cell viability, irrespective of amyloid properties.

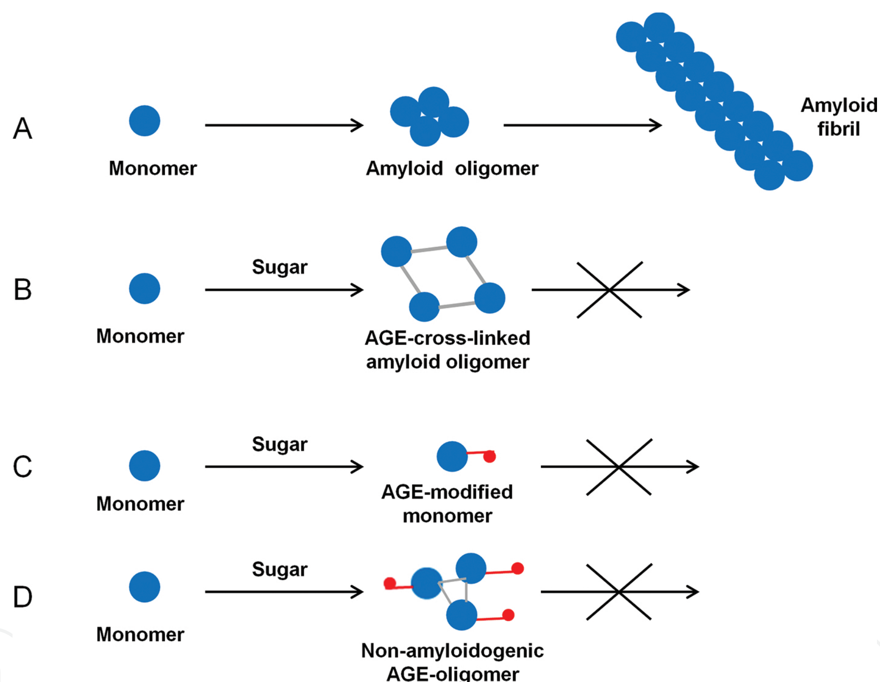

Figure 2. Effects of glycation in amyloid aggregation. Protein monomers are shown as blue dots, AGE-derived cross-links are shown in gray, and AGE modification are shown in red. (A) Typical amyloid aggregation pathway. Possible effects induced by glycation: (B) promote the formation of amyloid oligomeric species stabilized by covalent cross-links; (C) stabilize the monomeric form thus inhibiting amyloid aggregation; (D) promote the formation of cross-linked nonamyloidogenic oligomers.

5. Role of glycation in the amyloid-induced cell toxicity

The effect of glycation on the aggregation process has important implications in the pathological mechanisms involved in amyloid diseases. In most proteins, glycation has been shown

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to stabilize the aggregates in the oligomeric forms. This modification has important pathological implications as oligomeric species are known to be far more toxic than the fibrillar aggregates [80, 81]. The oligomeric species may interact with the cell membrane, altering its permeability and leading to cell homeostasis imbalance and neuronal cell dysfunction [82]. Recent evidence indicates that the amyloid oligomer toxicity is not strictly related to the oligomer properties, but rather a behavior that results from a complex interplay between the structural properties of both oligomers and cell membrane taken as a whole. Indeed, oligomers of comparable size but different structure and biophysical properties can display different toxicities, possibly as a consequence of the increased exposure of hydrophobic residues that would destabilize them and favor the interaction with the plasma membrane [83]. In this respect, glycation could affect structural and physicochemical features of amyloid oligomers as well as their interaction to the cell membrane and subsequently modulate and/or induce the cell toxicity. Also, the glycated oligomeric species can induce formation of reactive oxygen species, worsening the oxidative stress in the cell and further promoting protein glycation. Moreover, protein glycation leads to the formation of AGEs which have a pathological role in several diseases [84–86]. AGE adducts may therefore activate, through interaction with RAGE receptor, inflammatory response generally associated to amyloid toxicity [13]. The AGE–RAGE binding results in the activation of NADPH-oxidases that leads to an increased production of ROS. A key downstream target of RAGE is the proinflammatory Nf-κB pathway, which in turn leads to high RAGE expression, producing a feedback loop in which continuous activation of RAGE keeps the cellular inflammatory state activated [14, 87].

Glycated proteins are also resistant to proteasomal degradation; once proteins become glycated at their exposed lysine residues, clearance by the ubiquitin–proteasome system would be impaired, because ubiquitination at lysine residues, a modification that targets proteins to the proteasome for degradation, might be impeded. Thus, accumulation of proteins as aggregates or as depositions or inclusions in tissues might be favored after glycation.

Taking into account the above considerations, protein glycation can be considered a key dynamic contributor to these multifactorial diseases. In fact, it can both promote the formation of pathological oligomeric species and directly trigger cell dysfunction, damage, and death through the AGEs formation. For these reasons, AGEs are considered key therapeutic targets in amyloidosis, and anti-AGEs drugs are objects of intense ongoing research. Specifically, three main strategies have been developed to counteract the AGEs' effects: (i) to prevent the formation of AGEs; (ii) to break cross-links after their formation; (iii) to prevent AGEs' negative effects.

In vitro and in vivo experiments have shown that many compounds including aminoguanidine, antioxidants such as vitamin C and vitamin E, pyridoxamine, thiamine and its synthetic derivative benfotiamine, alpha-lipoic acid, taurine, pimagedine, aspirin, carnosine, metformin, pioglitazone, and pentoxifylline are able to inhibit AGE formation. Some of these compounds have already been used in clinical practice and some others are under clinical trials. Compounds that have been shown to break existing AGE cross-links mainly include alagebrium (and related ALT-462, ALT-486, and ALT-946) and N-phenacylthiazolium bromide. Studies with the aim to counteract the negative effects of the AGEs mainly involve

the use of natural products as polyphenols, such as resveratrol and curcumin and some flavonoids [88–90].

However, although in vitro and in vivo studies have shown the beneficial effects of various coumpounds, the potential clinical value of these interventions remains to be established. In fact, it seems that safety and/or efficacy in clinical studies with these compounds are still a concern.

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