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Glycation, Antiglycation, and Deglycation: Their Role in Aging Mechanisms and Geroprotective Effects (Literature Review)

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Abstract—The biochemistry of glycation and its role in the disruption of cell metabolism and development of age-related pathologies have been reviewed in this manuscript based on literature data published, for the most part, in the last 5 years. The effects of antiglycation and deglycation actions of endogenous enzymes, as well as of exogenous chemical compounds of natural and synthetic nature on the process of aging, were evaluated.

Keywords: glycation, aging, advanced glycation end products, glycation inhibitors, advanced glycation end products breakers

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CHEMISTRY OF GLYCATION

The search for universal molecular mechanisms responsible for aging of organisms of different biological species remains one of the main areas of study in gerontology. Traditionally, spontaneous nonenzymatic processes—so-called "parametabolic processes"—have been considered as biochemical tools of aging. This term reflects their random, difficult to control, and often undesirable nature, contrary to the regulated and biologically significant enzymatic metabolic pathways [7]. Parametabolic processes cause accumulation of biologically inert macromolecules in cells that have a lifetime comparable with the cell lifetime, which is essential for terminally differentiated cells incapable of proliferation [17].

Glycation (nonenzymatic glycosylation) [3, 13, 16, 17, 53], which was first described by the French chemist Louis Camille Maillard in 1912 as the interaction of proteins and carbohydrates (a reaction of amino acids with sugars, later named the "Maillard reaction") occurring in cooking, may be considered as one of such processes [3, 13, 16, 17, 53]. Although Maillard's studies in food chemistry have continued to be important up to the present day, the true significance of the discovered phenomenon became clear only in the second half of the 20th century, when the first evidence of glycation in live systems was reported [4, 10, 60].

Bibliometric analysis shows that there has been exponential growth in the number of publications on glycation in the last 20 years (Fig. 1). The correlation between the glycation and aging continues to generate considerable interest. In particular, the number of peer-reviewed publications with the term *glycation* in the PubMed database increased 17-fold during this time, while the number of publications containing a combination of terms the *glycation* and ag(e)ing or senescence increased by more than 11 times.

Today the process of glycation is commonly regarded as a nonenzymatic modification of proteins, nucleic acids, and phospholipids by monosaccharides and reducing oligosaccharides, as well as by carbonyl compounds, which are products of their degradation. This allows considering glycation as part of a more general phenomenon, carbonyl stress, which is char-

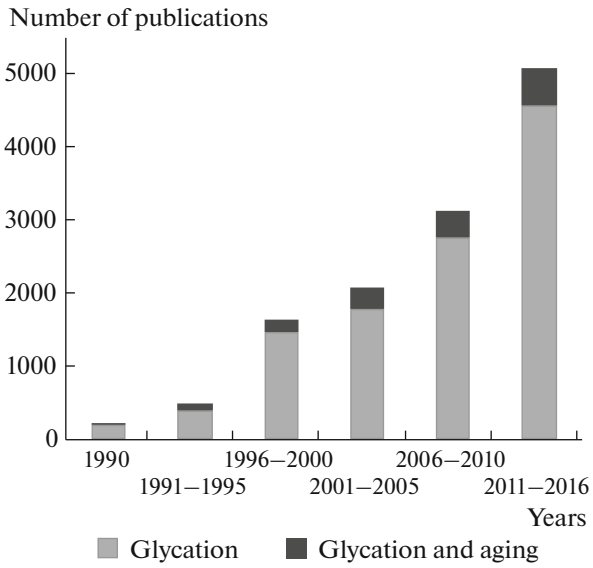

Fig. 1. Growth of number of publication on problems of glycation and aging.

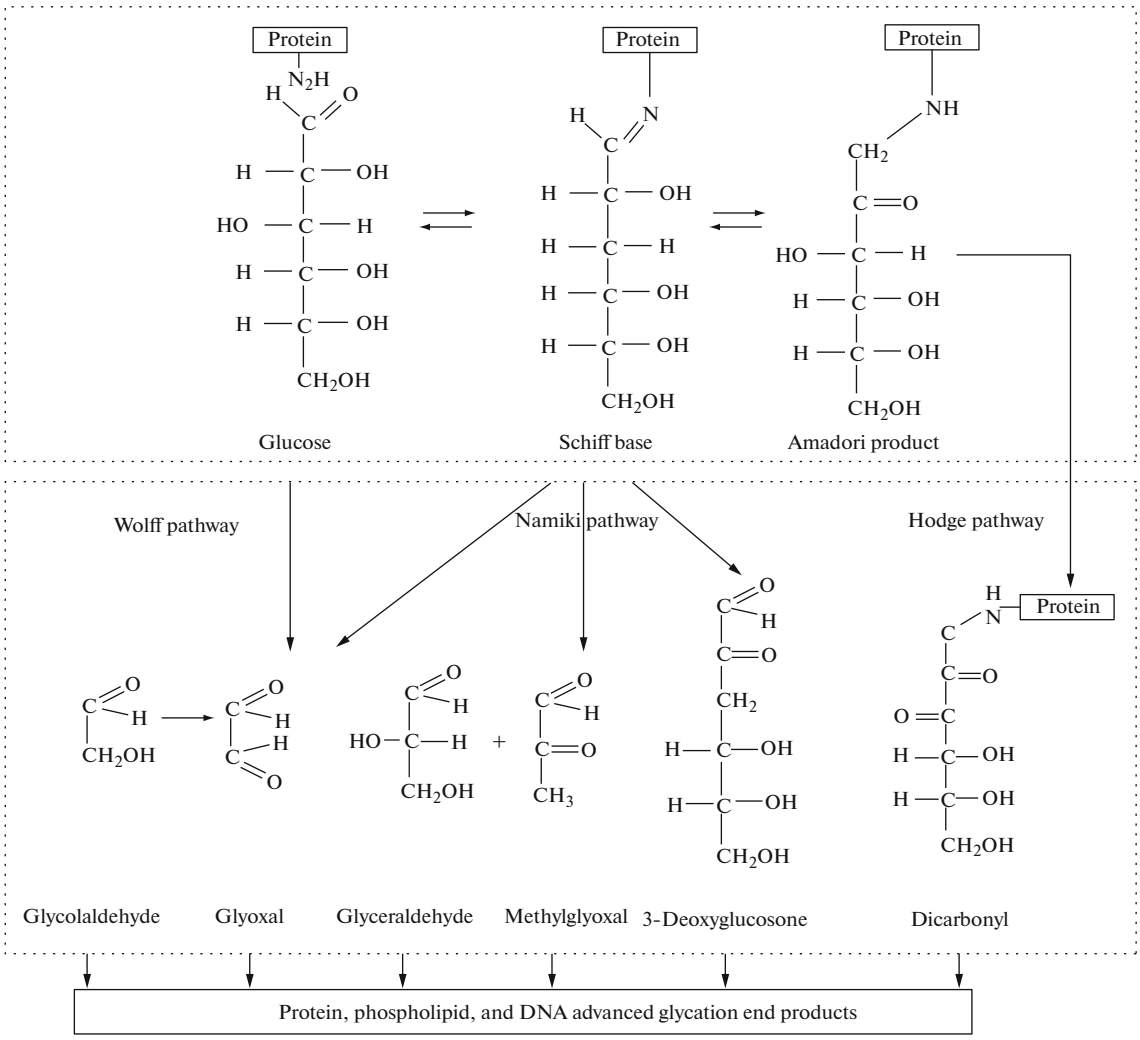

Fig. 2. Stages and products of glycation reaction.

acteristic of both eukaryotes and prokaryotes [8, 11, 47]. Accumulation of irreversible products of glycation in the cells and intercellular matrix results in disruption of the metabolism of cells, tissues, and organs typical for aging organisms, as well as it plays the role in pathogenesis of a number of socially significant age-related disorders [4, 10, 17, 35, 37, 47, 53, 60]. The search for inhibitors of glycation is considered, in its turn, as a promising strategy in the fight against aging [7, 13].

The chemistry of glycation has been investigated in great detail. At present, three stages are recognized in the glycation process. The first stage involves formation of the Schiff base, which represents a primary product of interaction of monosaccharides with protein amino group, and its following rearrangement into the Amadori product (Fig. 2). The rate of this stage increases proportionally with the increase of monosaccharide concentration; formation of the Amadori products in the protein occurs for several hours to days [10, 18]. Galactose, fructose, ribose, trioses, and monosaccharide phosphates exhibit higher reactivity in glycation as compared to glucose [7, 10, 16]. The pivotal role of glucose in the glycation process is due to its higher concentration in blood and intercellular matrix.

The second stage involves the formation of carbonyl intermediates of glycation. These intermediates are more reactive in the reaction with amino groups, which significantly enhances the probability of protein modification. A number of pathways exist for formation of carbonyl compounds (see Fig. 2). The Wolff pathway comprises autooxidation of glucose and other monosaccharides (fructose, ribose, gyceraldehyde), forming the simplest dicarbonyl compound, glyoxal. The Namiki pathway includes decomposition of the Schiff base with the formation of glyoxal, as well as methylglyoxal, glyceraldehyde, and 3 deoxyglucosone. The Hodge pathway is connected with autooxidation of Amadori products catalyzed by metal ions

Table 1. Examples of end products of proteins, lipids, and DNA glycation

Advanced end products of protein glycation (*AGEs*)	
With participation of the amino group of one amino acid residue	*Cross links between two amino acid residues*
5-hydroxymethyl furfurol	Furoyl furanyl imidazole
N,ε-carboxymethyl lysine	Glyoxal-lysine dimer (*GOLD*)
N,ε-carboxyethyl lysine	Glyoxal dicarbonyl imidazolone crosslink (*GODIC*)
Imidazolones *A* and *B*	Methylglyoxal-lysine dimer (*MOLD*)
Argpyrimidine	Methylglyoxal dicarbonyl imidazoline crosslink (*MODIC*)
Azepinone	Glucosepane
Pyrraline	Vesperlysine
1-alkyl-2-formyl-3,4-glycosyl pyrrol	Pentosidine
Advanced end products of lipid glycation	
Carboxyethyl phosphatidylethanolamine	Carboxymethyl phosphatidylethanolamine
Advanced end products of DNA glycation	
Imidazopurinones	N_2-(1-carboxymethyl) guanine
5-glycolyl cytidine	N_2-(1-carboxyethyl) guanine
N_2-(1-carboxy-3-hydroxypropyl) guanine	$N_{2,7}$-bis(1-hydroxy-2-oxopropyl) guanine

with variable oxidation states, primarily by Fe^{2+}. As a result, the 2,3-dicarbonyl derivative of the Amadori product is formed, followed by its subsequent transformation into the *N*,ε-carboxymethyl lysine [37, 39, 44].

It must be mentioned that some carbonyl intermediates formed during in vivo glycation may have a different origin. For example, methylglyoxal is formed from the product of phosphoglyceraldehyde glycolysis in the course of threonine metabolism, as well as from ketone bodies in ketosis. It is significant that ROS—hydrogen peroxide and hydroxyl radical—are formed already at the stage of formation of glycation intermediates, which triggers oxidative stress [11, 46, 47, 70].

The third stage of glycation involves conversion of Amadori products and carbonyl compounds linked to the protein into the structurally various advanced glycation end products or *AGEs*. Formation of *AGEs* in proteins occur in weeks and months; hence, their accumulation is significant in the proteins with slow turnover. The *AGEs* accumulation is also determined by the protein amino-acid composition—amino groups of lysine and arginine form the greatest amount of *AGEs*. *AGEs* linked to one amino-acid residue, as well as those cross linking lysine and arginine in one or different protein molecules, have been recognized (Table 1). Some *AGEs* (argpyrimidine and pentosidine) absorb light in the UV region of the spectrum and are capable of fluorescence [4, 10, 16, 18, 38].

Carbonyl modifications of amino groups in phospholipids and nucleic acids occur in a similar way (see Table 1). Of the membrane phospholipids, the amino groups of polar fragments of phosphatidylethanolamine molecules are most susceptible to glycation [24, 57]. Free amino groups of purine bases of the adenine and guanine DNA nucleotides form the largest number of identified products of nucleic-acid glycation [46, 64].

THE EFFECT OF GLYCATION ON LIVE SYSTEMS. ENDOGENOUS PROTECTIVE MECHANISMS

Modification of the macromolecule structure during glycation results in several relatively independent consequences that are significant in the mechanisms of the glycation-related pathologies. It is well known that a change of structure results in loss of specific function of the glycated protein. For some proteins, this correlation is proportional to the number of modified amino-acid residues, but even modification of a single residue can cause the significant loss of functionality [54, 61]. A close correlation between the glycation and oxidative stress is realized via formation of ROS during the glycation reaction itself, inactivation of antioxidant enzymes during their glycation, and depletion of the reserves of the reduced glutathione and NADPH in antiglycation protective mechanisms [12, 23, 41, 55, 64, 69, 70]. The least investigated consequences of glycation are the emergence of antigenic properties of the glycated metabolites and induction of autoimmune reactions [10]. Finally, the advanced glycation end products are themselves an important part of signaling pathways in cells inducing reaction cascade via activation of the receptor for advanced glycation end products—*RAGE*.

Table 2. Antiglycating and deglycating enzymes

Enzyme	Nature of catalyzed reaction
Antiglycating enzymes	
Glyoxalase I and glyoxalase II	Glutathione-dependent inactivation of methylglyoxal with formation of *D*-lactoylglutathione and *D*-lactate
Aldehyde dehydrogenase	NAD(P)H-dependent oxidation of aldehydes to corresponding carboxylic acids
Aldose reductase	NADPH-dependent reduction of aldehydes to corresponding polyols
Deglycating enzymes	
Amadoriase (fructosamine-3-kinase, fructosamine-3-kinase-like proteins)	Phosphorylation of Amadori products followed by their cleavage from amino-acid residues and formation of 3-deoxyglucosone and other dicarbonyl compounds
Amadoriase II (fructosamine oxidase)*	Oxidation of Amadori products by oxygen with formation of hydrogen peroxide and following cleavage of glucosone from amino-acid residue
Fructosamine-6-kinase*	Phosphorylation of fructosamine to fructosamine-6-phosphate
Deglycase*	Hydrolysis of fructosamine-6-phosphate bond with amino-acid residue and formation of glucose-6-phosphate
Proteins *DJ*1(*PARK*7) and *HSP*30	Reduction of lysine, arginine, and cysteine adducts with glyoxal and methylglyoxal accompanied with cleavage of glycolate and *D*-lactate

* found only in prokaryotes.

The *RACE* receptor is a transmembrane glycoprotein type I, which belongs to the immunoglobulin superfamily and consists of three main domains—extracellular, transmembrane, and intracellular. The *RAGE* ectodomain consists of three immunoglobulin molecules with *V*, *C*1, and *C*2 domains responsible for interaction with different ligands. The *RAGE* receptor belongs to the pattern recognizing receptors binding *DAMP* (damage-associated molecular pattern)—molecules associated with damages. In addition to *AGEs* themselves, the proteins of *S*-100 family, β-amyloid, and nuclear nonhistone proteins *HMGB-1* are the ligands of the *RAGE*. The expression of *RAGE* in the membrane has been proven for endotheliocytes, monocytes, macrophages, and lymphoid cells, as well as for neurons and fibroblasts. This opens significant possibilities for modulation of the activity of various cells during their interaction with *AGEs* [19, 27].

The interaction of *RAGE* in a membrane with advanced glycation end products activated several cascades. Nuclear transcription factor *NF*-κB is activated via the *Ras* signaling pathway, while factors *STAT3* and *STAT1* are activated through activation of the *JAK* and *JAK2* protein kinases, respectively. This stimulated the expression of the signaling molecule genes (*IL*-6, *TNF*-α, intercellular adhesion molecules, *E*-selectin, and endothelin-1), which results in the development of inflammation, accelerated cell apoptosis, and endothelial dysfunction. The *NF*-κB transcription factor stimulates synthesis of new *RAGE* molecules and their incorporation into the membrane, which closes the fallacious cycle [10, 39, 42].

Partial *RAGE* proteolysis results in the release of its ectodomain into the intercellular matrix as a soluble *RAGE* (*sRAGE*). Furthermore, the possibility of incomplete splicing of the receptor with secretion of the *V*–*C*1–*C*2 domain as an endogenous secretory *RAGE* (*esRAGE*) into the intracellular matrix was demonstrated. Both variants of the soluble receptors have been observed in blood, where they can bind *AGEs*, thus playing a protective role [35].

Protective enzyme systems exist in cells of different taxonomic groups that prevent glycation or repair glycated proteins [22, 29, 32, 47, 59, 62, 70] (Table 2).

The first line of defense comprises antiglycating enzymes that metabolize the highly active carbonyl product to polyols or acids [47, 59, 70]. The glyoxalase system for inactivation of methylglyoxal and other dicarbonyl intermediates is the most active. The second line of defense is represented by deglycation enzymes [62]. It has been shown that the expression of glyoxalase 1, aldose reductase, and aldehyde dehydrogenase was activated by the *Nrf 2* transcription factor, which affected the antioxidant responsive element (*ARE*) and increased under carbonyl stress with a compensatory mechanism [47]. Deglycation activity was reported recently for the proteins of the *ptfl*/*DJ1*(*PARK7*)/*HSP30* family involved in the Parkinson disease pathogenesis. The role of genetic polymorphism of the enzymes in the development of complications in diabetes and neurodegenerative diseases has been discussed [22, 29]. Accelerated development of neurodegeneration has been observed in individuals carrying alleles with mutations for enzymes with decreased activity [48]. The deglycation enzymes

found only in prokaryotes and fungi are of significant importance for construction of biosensors for detection of glycated proteins in blood and tissues [32].

It is important to note that antiglycating and deglycating proteins are localized intracellularly and do not protect proteins in the intercellular matrix [17]. Moreover, these enzymes can affect only the products of the initial and intermediate stages of glycation. The end products of the process cannot be eliminated from the composition of protein, which, in this case, must be subjected to complete proteolysis in lysosomes or proteasomes. Proteolytic systems comprise the third line of defense of proteome against glycation. This process occurs actively in microphages. The products of proteolysis of glycated proteins—oligopeptides and individual amino acids carrying *AGEs*—circulate in blood and are removed from the body in urine [10, 46, 65].

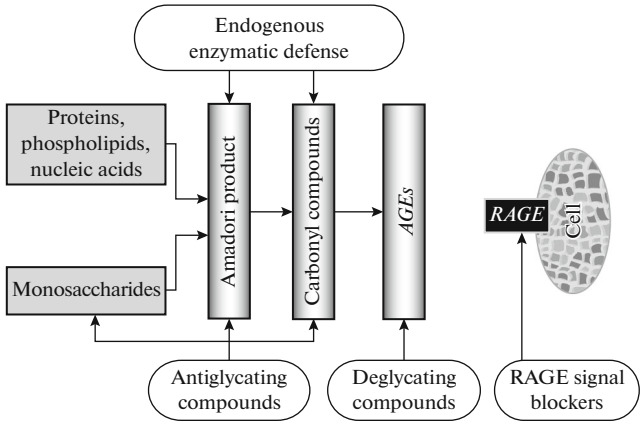

Fig. 3. Target points of endogenous and pharmacological antiglycating and deglycating functions (adapted from [9]).

PRODUCTS OF GLYCATION AS BIOMARKERS OF AGING. THE ROLE OF GLYCATION IN DEVELOPMENT OF AGE-RELATED DISEASES

The pathogenetic role played by glycation products in the development of cell dysfunction and apoptosis and disruption of the properties of intercellular matrix has been documented by multiple studies on their participation in pathogenesis of different diseases: diabetes, atherosclerosis, Parkinson's and Alzheimer's diseases, chronic kidney disorders, and inflammatory diseases [10, 18, 37, 47, 53, 54, 56, 57].

The products of the initial, intermediate, and final stages of glycation are used as biomarkers predominately in scientific studies and much more rarely in clinical practice. The use of glycated hemoglobin (HbA_{1c}) constituting the Amadori product in hemoglobin composition as a diagnostic criterion and therapeutic target for diabetes is well known. This is based on massive population studies demonstrating correlation between the level of HbA_{1c} and the risk of development of diabetic angiopathy and neuropathy, as well as the reduced risk of complications and mortality in patients with this indicator corrected [4, 10, 18, 56, 60].

Accumulation of *AGEs* in tissues increases with age [3, 51, 65]. However, it is difficult to differentiate sometimes whether this accumulation is due to aging as such or due to age-related diseases. For example, it was reported in the Baltimore longitudinal study of aging that the concentration of carboxymethyl lysine in blood correlated with the age and chronic kidney disease. The existence of a connection between the development of complications and adverse outcomes of heart surgery and the carboxymethyl lysine content in the pericardial fluid and the age of the patient has been demonstrated [53]. Accumulation of *AGEs* is common in the patients with diabetes as compared with the healthy individuals. The differences become more pronounced with deterioration of kidney functions and development of cardiovascular diseases [14].

Noninvasive detection of the *AGEs* in an organism may become possible thanks to investigation of skin autofluorescence, which is due to accumulation of fluorescent *AGEs*—pentosidine and argpyrimidine—in the dermis [6, 9, 14]. According to a number of clinical studies, autofluorescence can serve as a marker of cardiovascular diseases as well as predictor of cardiovascular and general mortality [14, 53]. Skin autofluorescence correlates with the *AGEs* content in blood and with the pulse wave velocity as an indicator of arterial stiffness [6].

PROSPECTS FOR PHARMACOLOGICAL CORRECTION OF GLYCATION

Despite the fact that the role of glycation in human pathology was proven, the results of the clinical testing of pharmaceutical intervention in this process revealed ambiguous results. Several targets for the potential protective compounds can be identified (Fig. 3). First, this is the antiglycation action itself—competition with molecular targets of glycation for binding with monosaccharides, binding of Amadori products and/or carbonyl compounds. Second, this can be binding of free radicals or metal ions initiating the development of oxidative stress. Third, this can be binding of *AGEs* and cleaving them from the protein molecule (deglycation action). Finally, protection from glycation can be realized by hindering of the *AGEs* interaction with the *RAGE* receptor or during the postreceptor stages [9, 37, 44]. It is often difficult to distinguish these mechanisms under experimental conditions and, in particular, during clinical studies. It is likely that compounds employing several mechanisms exhibit the best protective effect.

The chemical antagonism of antiglycating compounds to monosaccharides and glycation products is

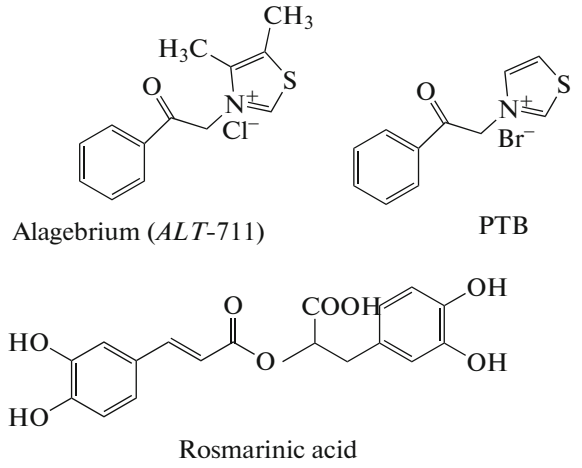

Fig. 4. Structures of compounds with deglycating activity.

based on the ability of the former to form covalent bonds with the carbonyl groups of the latter. The compounds exhibiting this type of action have nitrogen-containing group (amino-, hydrazine-, or guanidine-) or thiol group in their composition. Among the amino derivatives, preparations of the group B vitamins and their derivatives (thiamine, benfotiamine, pyridoxamine, carnitine, and folic acid), amino sulfonic acid taurine, endogenous polyamines (spermine, spermidine, and others), as well as oligopeptides (carnosine), exhibit antiglycating activity [22, 37, 50].

Aminoguanidine is most often used in experiments as a standard antiglycating agent [9, 10, 26, 40]. However, its low bioavailability and fast renal clearance do not allow creating a sufficiently high concentration of this compound in the organism fluids. No clinically significant improvement of kidney function in patients with type 2 diabetes was observed in the clinical study ACTION (1999), and the study ACTION2 (2004) was discontinued earlier than planned due to patient-safety concerns [26, 37, 40].

Biguanide metformin is one of the guanidine derivatives widely used for treatment of type 2 diabetes. In addition to the main antidiabetic action realized via the effect of this preparation on insulin resistance, metaformin also exhibits the ability to inhibit protein glycation [33]. A dose-dependent ability of the preparation to bind methylglyoxal in blood was observed, and adducts of metaformin with it were excreted in the urine [10]. Geroprotective activity of metformin was demonstrated, which manifested itself in an increase in maximum lifespan and suppression of spontaneous and chemical cancerogenesis in animals [2]. Nevertheless, the question of the role of inhibition of glycation in these effects of metformin remains open.

The prevention of glycation by pyridoxamine has been shown to be successful in experiments; however, its clinical efficiency in patients with diabetes was not so prominent: only an insignificant nephroprotective effect was observed (decrease of creatinine level and increase of glomerular filtration rate) [26, 40, 50].

Thiamine and its lipid-soluble derivative benfotiamine are used for treatment of diabetic neuropathy. The data available in the literature show that thiamine and benfotiamine exhibit antiglycation activity in experiments in vitro [36]. Benfotiamine is more effective than thiamine for protection from damage to nerve fibers during streptozotocin-induced diabetes in rats. Application of befotiamine for 6 months restored the rate of nerve-impulse propagation along the fiber to the level observed for intact animals. However, the clinical efficiency of befotiamine was shown only in one study (BENDIP) [58].

Among the thiol derivatives, the α-lipoic acid has attracted significant attention with its active intracellular form—dihydrolipoic acid—having several targets for antiglycation action: binding of carbonyl compounds and activation of enzymes involved into their intracellular metabolism [20]. Application of α-lipoic acid preparations for treatment of diabetic neuropathy and a number of other nervous-system diseases was reported [9]. However, the high antioxidant activity of the α-lipoic acid–dihydrolipoic acid pair does not allow considering the antiglycation action as a major or unique mechanism of the therapeutic effect. Contradicting data were obtained in an experiment on the geroprotective activity of α-lipoic acid: this compound increased the maximum lifespan of *Drosophila melanogaster*, but decreased the lifespan of the senescence accelerated mouse line SAMP8 [49].

Deglycating agents are termed in the English-language literature "AGE-breakers"—degraders of advanced glycation end products. Both natural and synthetic compounds belong to this group. Most of experimental data deal with the synthetic derivatives of phenylacetyl thiazolium (Fig. 4)—compounds *ALT*-711 (alagebrium) and *PTB* (phenylacetyl thiazolium bromide) [34, 49, 68]. The clinical efficiency of alagebrium was studied from 2000 to 2010. The use of alagebrium for 2–3 months for treating patients with artherial hypertension and chronic heart failure resulted in the decrease of puls pressure, normalization of echocardiography indicators, improved endothelial function, and overall quality of life [26, 40, 43, 49]. However, observations for 9–12 months in the longer study BENEFICIAL (2010) showed that the effects were not stable; moreover, there was no difference in the level of *AGEs* in blood when compared with the placebo group [28, 66].

The role of glycation processes in the development of cardiovascular pathology and diabetes served as a reason for searching for pleotropic effectors limiting glycation in an angiotensin-converting enzyme (ramipril), angiotensin II receptor antagonists (valsartan, irbesartan), statins (simvastatin, atorvastatin), and sugar-reducing preparations, thiazolidinediones (pioglitazone, rosiglitazone). The ability of statins to

decrease the *RAGE* expression in atherosclerotic plaques and the ability of pioglitazone to increase the level of soluble *sRAGE* receptor was reported in clinical studies, as well as the ability of rampiril and angiotensin II receptor antagonists to decrease the level of circulating *AGEs* [28, 33, 40].

Plant polyphenols (resveratrol, ferulic, isoferulic, and gallic acids, epigallocatechin and epigallocatechin gallate (*EGCG*), curcumin, as well as a number of other compounds of phenolic acids and flavonoids classes and their glycosides with natural monosaccharides), have been shown to be effective in protection from glycation [25, 49, 50]. Analysis of the *structure–function* relationship in polyphenols—which are inhibitors of glycation—showed that polyphenolic acids exhibited the highest activity, which was reduced in the cases when hydroxyl groups were methylated and glycosides with monosaccharided were formed [67]. Curcimun, quercetin, caffeic acid, and *EGCG* have demonstrated geroprotective activity in the experiments with mice, *Drosophila melanogaster*, and nematode *Caenorhabditis elegans* [50].

Various possible mechanisms of polyphenol intervention in the glycation process have been discussed in the literature. The leading role is assigned to their antioxidant activity and ability to chelate metal ions with variable oxidation states [49, 63, 67]. Their ability to bind carbonyl compounds, change protein conformation, and shield amino groups, making them less accessible to glycation, also has been discussed [63].

Rosmarinic acid—dimer of caffeic acid—is a plant polyphenol that presents particular interest. This compound exhibits numerous biological effects, including antioxidant, membranotropic, radioprotective, and anti-inflammatory ones [1, 5, 15]. The antioxidant activity of rosmarinic acid surpasses those displayed by standard antioxidants such as dihydroquercetin, trolox, and ascorbic acid [15]. The deglycation effect of rosmarinic acid in vitro was reported in [30, 31]. Rosmarinic acid outperformed *ALT-711* in its ability to disrupt cross links in bovine serum albumin incubated with ribose, while carnosine and aminoguanidine did not exhibit any deglycating activity. Of the other plant polyphenols derivatives of caffeic acid, rosmarinic acid exhibits the highest deglycating activity, which is protected by the patent [30]. The geroprotective effect of rosmarinic acid has been demonstrated, which manifested itself as an increased lifespan of the *Caenorhabditis elegans* nematode [45, 50] and mice during modeling of amyotrophic lateral sclerosis [52].

Hence, investigation of the role of glycation in the aging processes remains a hot topic in biogerontology. Further studies may deal with evaluation of the clinical significance of glycation biomarkers and the search for polymorphism in genes of antiglycating and deglycating enzymes participating in the aging process and age-related pathologies, as well as being devoted to the investigation of the geroprotective potential of natural and synthetic inhibitors of glycation.

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