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Carbonyl Stress Chemistry

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Abstract: Exogenous and endogenous factors can induce an increase in oxidative stress, which causes a change in the cell's redox status and is accompanied by the formation of reactive oxygen species (ROS). ROS are triggers of several non-enzymatic processes, such as lipid peroxidation, glycation of protein molecules, and auto-oxidation of amino acids and monosaccharides. At the same time, some metabolic processes, for example, glycolysis and its switching to the polyol pathway, increased metabolism of ketone bodies, induce the formation of another kind of unstable substance – reactive carbonyl species (RCS), which can exhibit cytotoxic and mutagenic effects. Excessive formation and/or improper detoxification of RCS leads to the development of a specific form of oxidative stress, carbonyl stress, which is accompanied by irreversible structural and functional changes in biomolecules. As a result, abnormal products are formed – Advanced glycation and lipoxidation end products (AGEs/ALEs) and Advanced oxidation protein products. ROS, RCS, and AGEs/ALEs trigger signaling transduction pathways that alter cell metabolism and behavior. In addition, activation of receptors for AGEs (RAGE) provokes the formation of ROS. AGE- induced oxidative stress causes endoplasmic reticulum stress and triggers apoptosis of target cells. The intensity of these processes depends on the effectiveness of the antioxidant protection system, the functioning of the glyoxalase system, aldehyde dehydrogenases, carbonyl reductases (aldo-keto reductases), the presence of transition metal ions chelators, natural or synthetic ROS and RCS scavengers. The number of studies on carbonyl stress is growing rapidly, and a significant amount of information is accumulated on the mechanisms of stress reactions underlying pathological changes in various diseases. The purpose of this review is to summarize current data on the mechanisms of implementation of carbonyl stress reactions and neutralization of highly reactogenic carbonyl compounds.

Keywords: ROS; RCS; ALEs; AGEs; RAGE, AGE-R, detoxification.

1. Introduction

The development of any disease is always accompanied by numerous biochemical changes manifested by a violation of certain physiological processes and triggering stress reactions. The concept of "stress" is rather vague and consists equally of the influence of some factors on the body and the implementation of an adequate response to it. Modern ideas about the etiology of many diseases consider oxidative stress as one of the most important links in violating homeostasis in the body. Even though redox reactions occur under normal conditions and are an integral part of the body's functioning, they are mainly associated with pathological conditions [1]. The damaging effect of many exogenous (toxic substances, ionizing radiation, heavy metals, xenobiotics, etc.) and endogenous factors (activation of cells of the immune system, inflammation, ischemia, aging, etc.) provokes a disruption of the dynamic balance

between pro- and antioxidants, disturbances of oxidative processes, resulting in the formation of highly reactogenic free radicals [2]. They play the role of triggers of various harmful effects, including damage to proteins, lipids, carbohydrates, and nucleic acids, which either distorts the functions of these macromolecules, or even leads to their complete loss [3-5]. Although active oxygen species are the main initiators and mediators of oxidative stress, modern studies prove the equally important role of carbonyl compounds in the unfolding of pathogenetic changes [6].

2. Reactive Oxygen Species

Molecular Oxygen in the triplet state is a stable biradical. It has two unpaired electrons with parallel spins in the outer orbit. [7]. Oxygen withdrawal from such an inert state under aerobic conditions can be carried out both during its spontaneous activation and with the participation of enzymes. The transfer of an additional electron to Oxygen converts it into an unstable reactive superoxide radical. Simultaneous one-electron reduction and protonation of a superoxide radical leads to the formation of hydrogen peroxide [8,9]. $O_2^{\bullet-}$ and H_2O_2 are powerful reactants that, in the presence of metal ions with transient valence (Fe^{3+}, Cu^{2+}), are converted intoan extremely reactive hydroxyl radical $^{\bullet}OH$ (Fenton reaction), which reacts instantly and nonspecifically with surrounding biomolecules [10]. All these intermediates with high reactivity are combined into a group of reactive oxygen species (ROS), which, in addition to those listed, include other free radicals (peroxyl, alkoxyl, etc.) and non-free radical compounds (singlet oxygen,hydrogen peroxide, hypochlorite, nitrite, peroxynitrite, etc.), which cause chain reactions of free radical oxidation [4].

ROS are generated in almost all organelles of living cells. This process is mainly related toelectron transfer circuits in mitochondria, lysosomes, and endoplasmicreticulum (Figure 1).

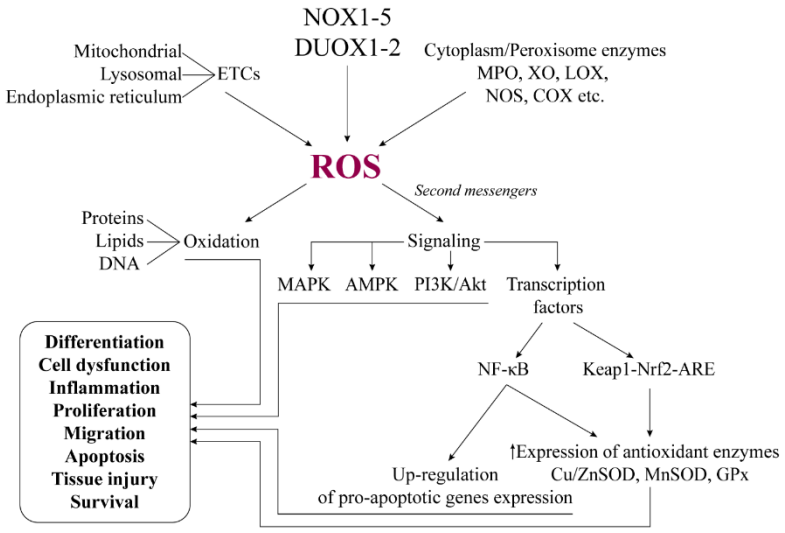

Figure 1. Main sources of ROS and cell response.

ROS are by-products of the functioning of electron transfer chains (ETCs) in mitochondria, lysosomes, endoplasmicreticulum, and catalyzing reactions of myeloperoxidase (MPO), xanthine oxidase (XO), NO synthase (NOS), lipoxygenase (LOX), cyclooxygenase (COX) X), NADPH-oxidase (NOX) and dual oxidases (DUOX1-2). ROS provoke biomolecular damage and/or trigger mitogen-activated protein kinases (MAPK), 5'-adenosine monophosphate-activated protein kinase (AMPK), phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) intracellular signal causing a corresponding cellular response.

An ordered ensemble of carriers of the inner membrane of mitochondria (electron transferchain) directs the electron transfer energy to generate ATP. However, a small number of electrons are transferred not to the substrate but directly to oxygen, which leads to the formation of ROS. This leakage of electrons from the chain mostly occurs in areas of I, III, and IV complexes(NADH dehydrogenase, $CoQH_2$: cytochrome c-oxidoreductase and cytochrome oxidase, respectively) and is enhanced by blocking any of them or at low ADP content [7,11,12]. The main thing is the transfer of one electron to form a superoxide radical, which spontaneously or under the action of superoxide dismutases (Cu/ZnSOD, MnSOD) is converted to hydrogen peroxide [13]. However, there may be a direct reduction of molecular Oxygen to hydrogen peroxide due to the transfer of two electrons at once [7]. It is believed that under physiological conditions in the electron transfer chain, about 2% of the total amount of oxygen consumed turns into ROS, whereas in pathological conditions, this indicator depends on the animal species' respiratory rate and is within 0.25-11% [14].

Consequently, the functioning of mitochondrial electron transfer chains is largely unrelated to the formation of ROS. Instead, lysosomal ETC, although they operate on a similar principle, is considered a stable source of them. Lysosomal FAD-containing NADH dehydrogenase oxidizes cytoplasmic NADH, accompanied by electron transfer first to cytochrome(Cyt) b, then to ubiquinone (Q), which is reduced to ubisemiquinone ($Q^{\bullet-}$) [15]. The final acceptor of the electron inside the lysosome is molecular oxygen. The process is accompanied by the movement of the proton into the lysosomal matrix. Acidic pH contributes to the formation of $O_2^{\bullet-}$,H_2O_2, $^{\bullet}OH$ [16].

Another source of ROS is the microsomal oxidation system (MOS), which is involved inthe oxidation of endogenous and exogenous substances, including fatty acids, cholesterol, steroids,polycyclic hydrocarbons, drugs, and xenobiotics. MOS components are localized in the membrane ofthe endoplasmic reticulum. These include redox partners cytochrome P_{450} (CYP)/NADPH: Cyt P_{450}-reductase (CPR) and Cyt b_5/NADH: Cyt b_5-reductase [17]. The main function of MOS is to transfer electrons from NADPH to CYP through CPR, which ultimately leads to the hydroxylation of substrates. Electron leakage may be accompanied by ROS formation, especially $O_2^{\bullet-}$ and H_2O_2. Itis believed that in the catalytic cycle of CYP there are two "shunts" that are capable of generatingROS without completing the oxidation of the substrate, known as the "separation reaction". The reduction of the Fe^{3+} to Fe^{2+} CYP under the action of CPR facilitates the addition of molecular.

Oxygen and the formation of the $Fe^{2+}O_2$ complex, which accepts one extra electron from Cyt b_5 and converts to $Fe^{2+}O_2^{\bullet-}$. This complex decomposes with the release of a superoxide radical [18,19]. If two electrons arrive (one from Cyt b_5, the second one from CPR), then protonation also occurs, and H_2O_2 is formed. The degree of electron leakage is usually less than 50%, and CYP oxidizes NADPH and produces ROS even in the absence of substrates [18-20].

Part of ROS is synthesized in the endoplasmic reticulum due to the functioning of protein disulfide isomerase, which is involved in the post-translational oxidative folding of proteins due to the formation of disulfide bonds between cysteine radicals. Endoplasmic reticulum oxidoreductase 1 (ERO1) transfers part of electrons from reduced protein disulfide isomerase to molecular Oxygen [21,22]. It is estimated that the amount of ROS generated during oxidative folding is proportionalto the amount of disulfide bonds in the protein molecule [23,24].

ROS generated in the aforementioned electron transport systems andas a result of the activity of certain enzymes, such as myeloperoxidase, xanthine oxidase, NO synthase, lipoxygenase, etc., are actually metabolic by-products [25-28]. The only specific enzymesystem in which synthesized ROS are final products is NADPH oxidase (NOX) [29]. All currently known 7 NOX isoforms (NOX1-5, DUOX1-2) have a similar structure. NOX is a multicomponentelectron transport complex that is localized on the cytoplasmic membrane, mitochondrial membrane, endoplasmic reticulum, and cell nucleus of many types of tissues. The composition of NOX includes the transmembrane flavocytochrome b_{558}, which is the heterodimeric assembly of $gp91^{phox}$ (NOX2) and $p22^{phox}$, supported by cytosolic protein factors $p47^{phox}$, $p67^{phox}$ and $p40^{phox}$ and small GTP-binding proteins (Rac1 or Rac2), accompanied by translocation of cytosolic subunits during activation. The prerequisite for NOX activation is binding membrane phospholipids to phox homology domains of $p47^{phox}$ and $p40^{phox}$ [30,31]. Eventually, the ROS formed by the NOX cell membrane are routed into the extracellular space, and those generated byNOX organelles form the intracellular pool of ROS, with NOX1-3, NOX5 predominantly producing $O_2^{\bullet -}$, while NOX4, DUOX1-2 – H_2O_2 [32].

ROS synthesized by NOX act as secondary messengers and therefore NOX hyperactivation causes genetic instability, DNA, and protein damage. That is why NOX-dependent synthesis of ROS is a strictly regulated process. All NOX, except NOX4, are inducible systems. NOX4 activityis regulated only at the expression level, but the consistent activity may be regulated by the cellular localization of NOX4, the involvement of protein disulfide isomerase, or polymerase-δ interactingprotein 2 [33]. The main activator of NOX is protein kinase C (PKC) [29].

As secondary messengers, ROS can trigger signal transduction pathways mitogen-activated protein kinase (MAPK), AMP-activate protein kinase (AMPK), phosphatidylinositol 3-kinase (PI3K)/Akt, Keap1-NRF2-ARE, etc., affecting on the functioning of ion channels and ubiquitin-proteasome system. ROS can inhibit the activity of IκB-kinase (IKK) β and thus preventphosphorylation of the inhibitor of the nuclear transcription factor NF-κB – IκB, which leads to the destruction of the NF-κB-IκB complex and the translocation of NF-κB into the nucleus, whereit, by binding to the promotors, induces the transcription of certain genes [12,34].

Dysregulation between the production of ROS and the endogenous antioxidant defense mechanisms is defined as oxidative stress. When present in low concentrations, ROS plays a critical function in cell homeostasis. However, excess ROS causes cellular dysfunction, protein and lipid peroxidation, DNA damage and eventually leads to irreversible cell damage and death.

3. Active Carbonyl Compounds Formation and their Biological Effects. Carbonyl Stress

Changing the redox status of a cell can cause the formation of unstable substances other than ROS. In this case, due to metabolic transformations in cells, active carbonyl species/compounds (RCS) can be formed, which in their structure contain one or more carbonyl groups (aldehydes, carboxylic acids, ketones, ozone) [35,36]. Most RCS are short-chain (C3-9) highly reactogenic stable compounds with a long half-life (from minutes to days), which determines their ability to both be inside and diffuse outside the cell. These features are the root cause of the distinct cytotoxic and mutagenic effects of RCS [36]. Consequently, excessive formation and/or improper detoxification of RCS in the body causes the development of a

specificform of oxidative stress, carbonyl stress. As a rule, carbonyl stress is associated with the intensification of non-enzymatic (spontaneous) lipid peroxide oxidation, glycation of protein molecules, and auto-oxidation of amino acids and monosaccharides, but enzymatic processes will warm up an equally important role and take place during glycolysis, when switching glucose oxidation from glycolytic to polyol pathway and enhancing metabolism ketone bodies [37-39]. Additionally, RCS can enter the body with heat-treated food, chlorinated or ozonized drinking water, and polluted air, but they act equally regardless of origin [40-42].

Typical RCS synthesized as a result of metabolic transformations of various biomoleculesin the body are compounds whose high reactivity is due to the presence of a highly polarized α,β-unsaturated bond (nonenal, 4-hydroxy-2-nonenal, 4-hydroxyhexenal, acrolein), dialdehydes (malondialdehyde, glyoxal), ketoaldehydes (4-oxo-2-nonenal, methylglyoxal), γ-ketoaldehydes (isolevuglandins) (Figure 2). Sometimes a group of electrophilic metabolites of prostaglandins, which remain covalently bound with phospholipids is isolated [43-45].

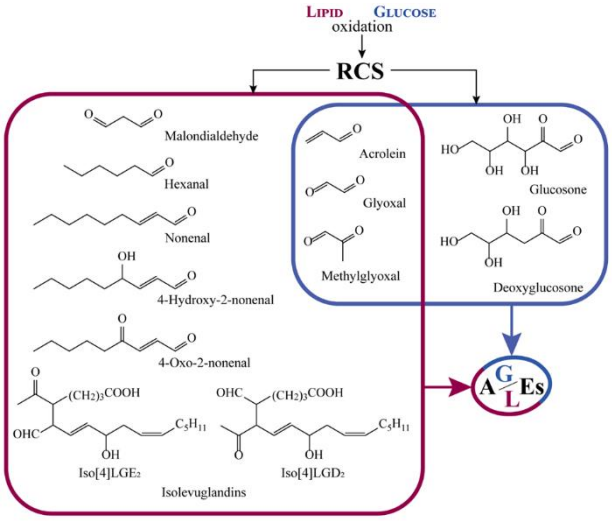

Figure 2. The common RCS structures.

Reactive carbonyl species (RCS) are generated during lipoxidation or non-enzymatic glycoxidation, some of which(acrolein, glyoxal, and methylglyoxal etc.) can be formed as a result of both processes. The ability to interact with proteins and DNA causes the formation of Advanced lipoxidation and glycation end products (ALEs and AGEs).

3.1. Lipoxidation.

The physical and chemical properties of membrane lipids determine their susceptibility to damage. Most reactive substances, including free radicals, are perfectly soluble in the lipid bilayerand can effectively attack surrounding membrane phospholipids. Polyunsaturated fatty acids are the most susceptible substrates of peroxidation reactions, so many carbonyl compounds are formedduring their oxidation [46]. In the structure of polyunsaturated fatty acids exposed to free radicals,hypersensitive sites are hydrogen atoms of methylene groups that separate double bonds in the carbon chain. Therefore, the more double bonds in the structure of a fatty acid, the higher its oxidation ability is. As a result of ROS attack, for example, $^{\bullet}OH$, lipid radicals ($L^{\bullet}$) (initiation phase of reaction of lipid peroxidation, or lipoxidation) are formed, which interact with molecularoxygen and turn into primary products, lipid peroxides (LOOH) (propagation phase). They are extremely unstable and, in the presence of transition metal ions (Fe^{3+}, Cu^{2+}), are immediatelytransformed into peroxyl ($LOO^{\bullet}$) or alkoxyl ($LO^{\bullet}$) radicals. The latter can

attack new molecules of polyunsaturated fatty acids, which subsequently leads to the accumulation of a wide range of secondary products – RCS [44-47].

3.1.1. Malondialdehyde .

Malondialdehyde (MDA) is considered the main product of the oxidation of polyunsaturated fatty acids, which is the lion's share of the total RCS, and is almost 70% [48]. Increasing the reactogenicity of this compound contributes to a decrease in the pH level in the organism. Even though under such conditions, MDA acquires the ability to interact with histidine, tyrosine, arginine, and methionine to a certain extent, the main target is the ε-amino group of lysine of proteins. As a result, stable advanced lipoxidation end products (ALEs), MDA-lysine adducts, and lysine-MDA-lysine cross-linkages are generated, which are markers of endogenous cell damage [46]. Interactionof MDA with protein predominantly occurs through an ε-amino group of lysine with the formation of N^{ε}-(2-propenal)lysine, which can further react with another molecule of MDA and a molecule of acetaldehyde to form a stable product dihydropyridyl lysine (DHP-lysine). MDA can also reactwith arginine, forming the stable N^{δ}-(2-pirimidyl)-L-ornithine (Figure 3, a) [49].

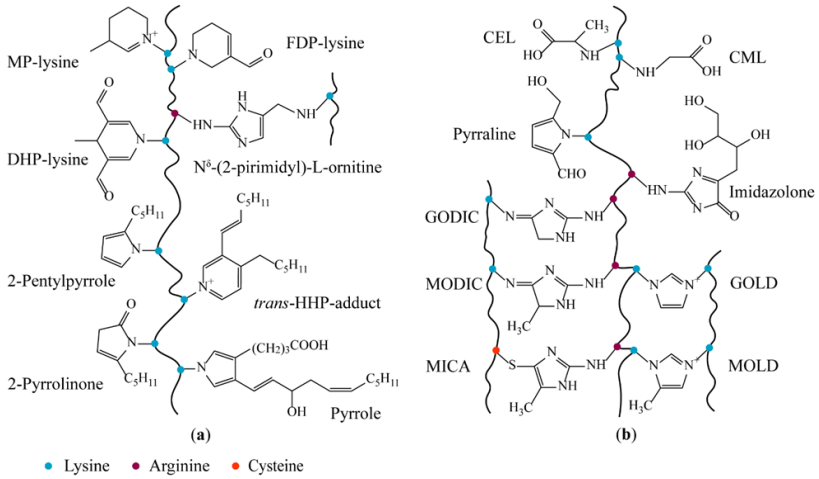

Figure 3. ALEs and AGEs formed by binding of reactive carbonyl species to proteins. (**a**) ALEs: N^{ε}-(3-methylpyridinium)lysine (MP-lysine) and N^{ε}-(3-formyl-3,4-dehydropiperidine)lysine (FDP-lysine) are formed as a result of acroleic binding with lysine, Dihydropyridyl lysine (DHP-lysine) – Malondialdehyde, *trans*-N^{ε}-3-[(hept-1-enyl)-4-hexylpyridinium]lysine (*trans*-HHP-adduct) – 2-Nonenal, 2-Pentylpyrrole – 4-hydroxy-2-nonenal, 2- Pyrrolinone – 4-Oxo-2-Nonenal; (**b**) AGEs: Glyoxal and methylglyoxal, interact with lysine, forming N^{ε}- (carboxyethyl)lysine (CEL) or N^{ε}-(carboxymethyl)lysine (CML), respectively, GODIC – imidazolium cross-linkderived from glyoxal, MODIC – lysine-arginine; imidazolium cross-link derived from methylglyoxal and lysine-lysine, MICA – methylimidazole cross-link derived from methylglyoxal and cysteine and arginine, GOLD – glyoxal-lysine dimer, MOLD – methylglyoxal-lysine dimer.

The direct interaction of both carbonyl groups of malondialdehyde with a nitrogen of any ofthe nitrate bases that are part of DNA leads to the formation of exocyclic adducts, mainly deoxyguanosine adduct – pyrimidopurinone (M_1dG). Spatially located opposite deoxycytidine, itis quite unstable and is able to arbitrarily change the conformation due to the opening of the ring to form N^2-(3-oxo-1-propenyl)-deoxyguanosine (OPdG) [50]. The same properties are inherent in4-hydroxy-2-nonenal, which forms DNA adducts, mainly γ-hydroxy-1,N^2-propano-2'- deoxyguanosine (γ-OH-PdG), in a similar way [50].

3.1.2. 4-Hydroxy-2-nonenal.

In the quantitative ratio of 4-hydroxy-2-nonenal, much less than malonic dialdehyde is formed (about 5% of the total RCS). The structural triad, carbonyl, and hydroxyl groups in addition to α, β-unsaturated bonds – cause its unique reactogenicity [43,51]. In general, 4-hydroxy-2-nonenal targets primary amino groups of cysteine, histidine, and lysine proteins and can form Schiff bases with them, but for the most part, generates Michael adducts through the addition of thiol or amino compounds at the C3 carbon [52,53].

The role of 4-hydroxy-2-nonenal is not only due to structural features but also depends on its concentration and environmental characteristics. 4-Hydroxy-2-Nonenal can induce premature apoptosis while simultaneously triggering several different processes: blocking ATP Synthase activity accompanied by impaired oxygen consumption, formation of adducts with c-Jun NH_2- kinase (JNK), inhibition of protein kinases B/Akt and C, increased regulation of the activator protein AP1 and activation of NF-κB-dependent gene expression [43,46,54,55]. In addition, 4- hydroxy-2-nonenal dose-dependent modifies Cys424 and His439 pyruvate kinase M2 isoform, reducing its activity at moderate concentration and completely inactivating at high, instead provoking a rapid increase in intracellular cAMP levels, a corresponding increase in protein kinaseA (PKA) activity and hormone-sensitive lipase [56,57].

3.1.3. Hexanal.

Another product of oxidation of polyunsaturated fatty acids is hexanal, which accounts for almost 15% [48]. The presence of only one carbonyl group in the structure causes itslow reactogenicity, but despite this, hexanal is able to attack amino groups of amino acids of protein molecules like lysine and form a stable adduct of the amide type N^{ε}-(hexanoyl)lysine [58,59]. It is assumed that N^{ε}-(hexanoyl)lysine 3 is involved in the conversion of cholesterol hydroperoxides to other highly active aldehydes 3β-hydroxy-5-oxo-5,6-secocholestan-6-al (secosterol A) and its aldolization product 3β-hydroxy-5β-hydroxy-B-norcholestane-6β-carboxyaldehyde (secosterol B) [60].

3.1.4. Acrolein.

Acrolein (propenal) is the simplest of all by-products of the oxidation of lipids, carbohydrates, and amino acids, which can additionally be formed in the intestinal cavity during the metabolism of glycerol by microflora [61]. This aldehyde is the strongest electrophile, which causes rapid interaction with amino and thiol groups of nucleophiles by covalent addition (Michael reaction) [62]. Compared to the same 4-hydroxy-2-nonenal, acrolein reacts on average 130 times faster, although the formation of adducts occurs almost the same. The only difference is that mostly adducts do not cycle and, with the rest, are able to transform into secondary Schiff bases [63] slowly. However, under the influence of Fe^{3+}-nitrilotriacetate during the interaction of acrolein and DNA, minor cyclic DNA adducts are still generated – 1,N^2-α-hydroxypropanoadenine and 3,N^4- α-hydroxypropanocytosine [64].

The undesirable effects of acrolein are not only the formation of DNA adducts. In particular, the effect of acrolein on the activity of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and pyruvate kinase was demonstrated. Even with physiological content, acrolein can attack the remains of Cys152, Cys150, and Cys358, but when the concentration increases in enzymes, other sensitive areas (Cys156, Cys282) that are attacked are identified [65,66]. Compared with 4-hydroxyhexenal, malondialdehyde, 4-hydroxy-2-nonenal, and 4-oxo-2-

nonenal,acrolein is the most potent enzyme inhibitor. However, it is proved that the effect of these compounds is dose-dependent and eventually leads to the destabilization of the tetramer and the complete inactivation of enzymes [56,66].

However, acrolein modifies not only enzymes but also structural proteins. Interaction of acrolein with lysine and histidine residues of antiatherogenic apolipoprotein E of low-density lipoproteins provokes its dysfunction due to the formation of N^{α}-acetyl-N^{ε}-(3-formyl-3,4- dihydropyridine)lysine and Nα-acetyl-Nim-propanalhistidine adducts [61]. Besides, acrolein causes a decrease in the regulation and redistribution of dense compound proteins (Zonula occludens 1, Occludin, Claudin 1) which regulate intercellular interaction [67].

3.1.5. Isolevuglandins.

The significance of lipid peroxide oxidation in the formation of RCS is undeniable, but it is known that arachidonic, γ-linoleic, eicosapentaenoic, docosahexaenoic, and others, longer polyunsaturated fatty acids can also be oxidized by isoprostane pathway. It is a cascade of spontaneous, ROS-initiated reactions (free radical-induced cyclooxygenation), accompanied by the formation of oxidatively truncated intermediates γ-hydroxy-α,β-unsaturated aldehyde phospholipid, γ-keto-α,β-unsaturated aldehyde phospholipid, and γ-keto-α,β-unsaturated carboxylic phospholipid generated inside the membrane. That is, the electrophilic part of such intermediates remains covalently bound to phospholipids and is eventually released from the membranes by phospholipase A_2 [47,68]. The central metabolites of the isoprostane pathway areprostaglandin-like compounds, F_2-IsoPs and H_2-IsoPs. F_2-IsoPs is considered stable and, at the same time, sensitive markers of oxidative stress, although they, like H_2-IsoPs, are capable of quickly regrouping into endoperoxide intermediates E_2/D_2-IsoPs [69]. The latter are dehydrated and converted into reactive isolevuglandins, IsoLGE_2 and IsoLGD_2, which differ in the position of the keto- and aldehyde groups, the length of the carboxylic side chain (in square brackets indicate the number of carbon atoms in the chain – Iso[n]LGs) and the position in it of the double bonds and hydroxyl groups [70]. In contrast to F_2-IsoPs, oxidation of H_2-IsoPs leads to the irreversible formation of IsoLGs through a carbinolamine intermediate, which is in equilibrium with the corresponding Schiff base [49,71].

Isolevuglandins can also be formed during the metabolism of arachidonic acid by cyclooxygenase pathway [72,73]. Initially, it was considered impossible to establish the path by which certain IsoLGs are produced. However, it was subsequently proved that structural isomers and their protein adducts, in which carboxylic side chains are in the *cis*-position relative to the prostane ring, are formed only during free radical-induced cyclooxygenation, while the cyclooxygenase-derived IsoLGs have a lateral chain in the *trans*-position [74].

The biological effect of IsoLGs is due to their ability to react lightning-fast while still being associated with phospholipids [45,75]. Initially, IsoLGs react with primary amines (lysine,phosphatidylethanolamine) to form Schiff bases, which subsequently interact with the second carbonyl and form sustainable Michael adducts [70,76]. With cysteine residues of proteins, Iso[4]LGE_2 reacts similarly because of the formation of pyrrole-cysteine adducts, which are capable of oxidizing to lactams and hydroxy lactams [77]. The accumulation of IsoLG-adducts can occur when the functioning of transcription factors, such as nuclear factor erythroid 2-related factor 2 (Nrf2), promotes antioxidant gene expression and is essential for maintaining ROS homeostasis [78].

3.2. Non-enzymatic glycoxidation/glycation.

It is not only lipid peroxidation processes that serve as RCS suppliers. Carbonyl compounds are also formed during the process of non-enzymatic glycation, which consists of thecovalent interaction of reductive monosaccharides (glucose, deoxyglucose, fructose, ribose, triosephosphates) with NH_2- and SH-groups of various biomolecules, mostly lateral radicals of amino acids of proteins (Maillard reaction). Initially, there is a spontaneous condensation of sugar with amino acids of proteins, which leads to the formation of unstable Schiff bases, which predominantly exist in cyclic form and are prone to instantaneous oxidation with the formation ofoxoaldehydes, glyoxal and methylglyoxal ("glycoxidation", glucose retro-aldol cleavage, or the Namiki pathway of the Maillard chemistry) [79]. Direct oxidation of glucose through the formationof an intermediate product of glycoaldehyde followed by oxidation in the presence of Fe^{3+} and Cu^{2+} and autooxidation of ascorbic acid serve as additional sources of glyoxal, while in the oxidation of glycolysis intermediates – glyceraldehyde 3-phosphate and dihydroxyacetone phosphate – methylglyoxal is mainly formed [80,81]. Acrolein, glyoxal, methylglyoxal, etc., are joint products that can be formed not only during glycoxidation but also because of lipoxidation,indicating a close relationship between these processes.

The Schiff bases existing in acyclic form are isomerized by regrouping the aldimine bond into more stable ketoamines (Amadori intermediates) [82]. Of the total content of Amadori products, only a small amount is subjected to further chemical transformations, such as oxidative degradation or rearrangement, dehydration, cyclization, and fragmentation, which leads to the formation of stable conjugants, advanced glycation end products (AGEs) [83]. All known AGEs are divided into four groups. The first group includes monolysine adducts, which are formed during the interaction of glyoxal/methylglyoxal with the primary ε-amino group of lysine to form N^{ε}-(carboxymethyl)lysine, N^{ε}-(carboxyethyl)lysine, pyrraline, and imidazolones. To the second –imidazolium dilysine cross-links (glyoxal-lysine dimer, GOLD, or methylglyoxal-lysine dimer, MOLD) cross-links which derive from the reaction between two lysine sidechains and two molecules of glyoxal and methylglyoxal, respectively. Lysine residues may undergo two-stage glycation. In the first stage, monolysine adducts are formed. In the second stage, glycation by reductive mono- or disaccharides of the secondary amino group occurs. This is how the Amadori pathway cross-links single ribose or glucose with lysine and arginine to form a pentosidine [84]. Maillard reaction is considered a highly selective process, the direction of which, most likely, depends on the type of protein. In particular, the glycation of collagen argnineresidues with glyoxal/methylglyoxal may be similar to lysine glycation with the generation of N^{ω}- (carboxymethyl)arginine, whereas bovine RNase в modification occurs near the active center in the Arg39 and Arg85 region with the formation of glyoxal-derived dihydroxyimidazolidine and hydroimidazolone adducts [85-87]. These imidazolium cross-links derived from glyoxal and lysine-arginine (GODIC) and imidazolium cross-links derived from methylglyoxal and lysine-lysine (MODIC) get into the third group [36,88]. The fourth is cysteine derivatives formed by glycation of the sulfhydryl group, mainly S(carboxymethyl)cysteine, although a new methylimidazole cross-link derived from methylglyoxal and cysteine and arginine (MICA) has recently been discovered [36,89,90]. The structure of the above AGEs is shown in Figure 3, b.

3.2.1. Mechanisms of action of AGEs.

The important role of AGEs is determined by their ability to interact with receptors andtrigger intracellular signaling. The receptor for advanced glycation end products (RAGE) is a 50-55 kDa transmembrane glycoprotein synthesized by many normal and transformed mammalian cells and belongs to the immunoglobulin superfamily cell adhesion molecules [91]. The RAGE possesses the extracellular domain (ectodomain), a hydrophobic helical transmembrane domain, and a short cytoplasmic domain and is called full-length RAGE (Figure4). In the structure of the ectodomain of RAGE, distinguish three immunoglobulin-like domains: avariable V (residues 23-116) and two constant C1 and C2 (residues 124-221 and residues 227-317,respectively) domains. C1 and C2 are interconnected flexible seven amino acid linkers [92]. V andC1 domains are in hydrophobic, positively charged pockets rich in arginine and lysine residues[93]. Due to hydrogen bonds and hydrophobic interactions between the V and C1, it can form anintegrated domain (VC1), which has two glycosylation sites in Asn25 Asn81 sites, which contributes to the stability of the protein molecule.

Each of the extracellular domain of full-length RAGE contains two cysteines, between which a disulfide bond is formed within the domain, which helps stabilize the receptor, while cysteines of the C2 domain may also form intermolecular linkage, stabilizing a RAGE dimer. Furthermore, V and VC1 domains are involved in forming dimeric and oligomeric forms due to the formation of intramolecular disulfide linkages, which facilitate interaction and extend the range of ligands they can bind [94,95]. In the transmembrane domain of RAGE structure, a conservated GxxxG motif can also be involved in forming dimers or oligomers [94,96].

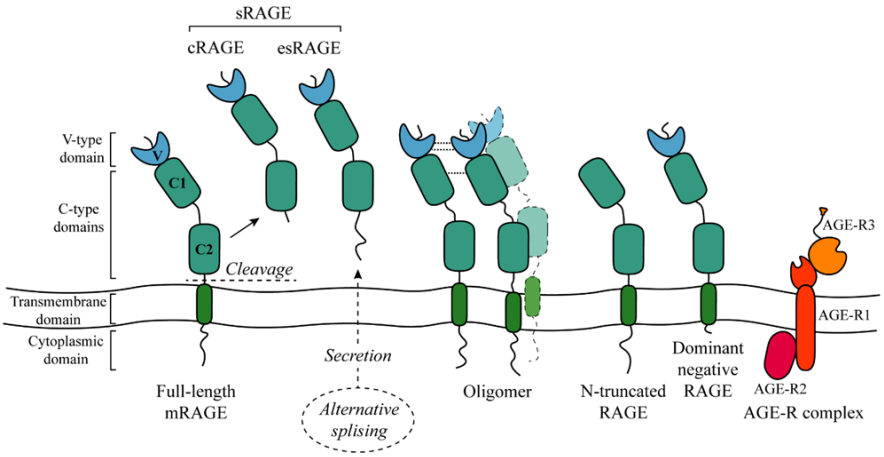

Figure 4. Schematic representation of RAGE.

Most currently known RAGE isoforms are exposed on the cytoplasmic membrane (full-length mRAGE), but there are also two soluble isoforms (sRAGE). One of them, cleaved RAGE (cRAGE, ~48kDa), is formed by splitting off from the full membrane receptor of the ectodomainat the extracellular juxtamembrane region [97]. Ectodomain shedding is carried out by various proteinases – matrix metalloproteinases, metalloprotease domain-containing protein ADAM10, etc. Another endogenous secretory form of esRAGE, also termed RAGEv1, is a product of alternative splicing pre-mRNA [98].

Proteolytic cleavage of the V-domain or cytoplasmic domain leads to the formation of N- truncated RAGE and a dominant negative RAGE, respectively, which have a low ability to bind to ligands, which impairs signal transduction [99].

Full-length mRAGE can bind not only AGE, but also the S100/calgranulin family, high mobility group box HMGB1 protein, nucleic acids, lysophosphatidic acid, amyloid β, FH1

(forminhomology 1) domain of Diaphanous 1 (Diaph1), etc. [95, 100-102]. In general, RAGE monomers have low affinity to ligands and need oligomerization to implement RAGE signaling after ligand binding [93]. The interaction of AGE with mRAGE is not accompanied by ligand endocytosis butleads to the switching on signal transduction pathways, such as the MAPK, PI3K/Akt, and Toll-interleukin 1 receptor domain-containing adaptor protein pathways, etc. As a result, NF-κB is activated and up-regulation of pro-inflammatory modulators (e.g., IL1, IL1β, IL6, ICAM1,VCAM1, TNFα, MCP1, PAI1, and mRAGE itself) [93].

Attention is drawn to the fact that the activation of RAGE provokes the formation of ROS.AGEs increase NOX $p47^{phox}$ at the protein level by stimulating mRNA synthesis. AGE-induced oxidative stress causes endoplasmic reticulum stress and triggers apoptotic mechanisms of destruction of target cells C/EBP homologous protein and caspase-12 by pathways [103].

Unlike mRAGE, sRAGE exhibits conflicting properties. The peculiarity of sRAGE is that it can exhibit antioxidant qualities, acts as a decoy receptor, and binds RAGE ligand, inhibiting the mRAGE activation. This leads to the inhibition of the main signal transmission routes and a decrease in the main indicators of oxidative stress [104-106]. However, sRAGE can also act as a ligand of Mac-1/β2 integrin and, conversely, stimulate pro-inflammatory signals [104].

V domain plays a key role in ligand binding, so N-truncated RAGE is unable to bind ligands, and a dominant negative RAGE has a low binding ability, which impairs signal transduction [92].

There are other receptors for AGEs (AGE-R), which include the oligosaccharyltransferase48 (OST48, AGE-R1), 80 K-H phosphoprotein (AGE-R2), galectin-3 (AGE-R3). AGE-R1-R3 only recognizes and binds AGE without signal transduction. AGE-Rs can inhibit AGE-mediated signal transmission and oxidative stress, competing with RAGE for binding to AGE. AGE-R3 is capable of binding to AGE-R1 and AGE-R2 to form a complex [107].

In addition to these, there is also a separate group of scavenger receptors with which AGEsinteract. These include macrophage scavenger receptors SR-A (I/II), SR-B/CD36, SR-BI, lectin-like oxidized low-density lipoprotein receptor 1 SR-E/LOX-1, fasciclin, EGF-like, laminin-type EGF-like, and link domain-containing scavenger receptor-1/2 (FEEL1/2 or Stab1/2) [84,108,109].

3.3. Metabolic pathways.

The proper functioning of the cell depends on the intracellular ratio of $NADH/NAD^+$. The prevalence of NAD^+ causes the breakdown of glucose during glycolysis, while in hyperglycemia,an increase in NADH content, as well as an increase in the affinity of aldo-keto reductase (EC 1.1.1.21) to glucose, stimulates the activation of an alternative polyol pathway. Initially, glucose is reduced by NADP-dependent aldose reductase to sorbitol, which, under the influence of NADH-dependent sorbitol dehydrogenase (EC 1.1.1.14) is oxidized to fructose (Figure 5).

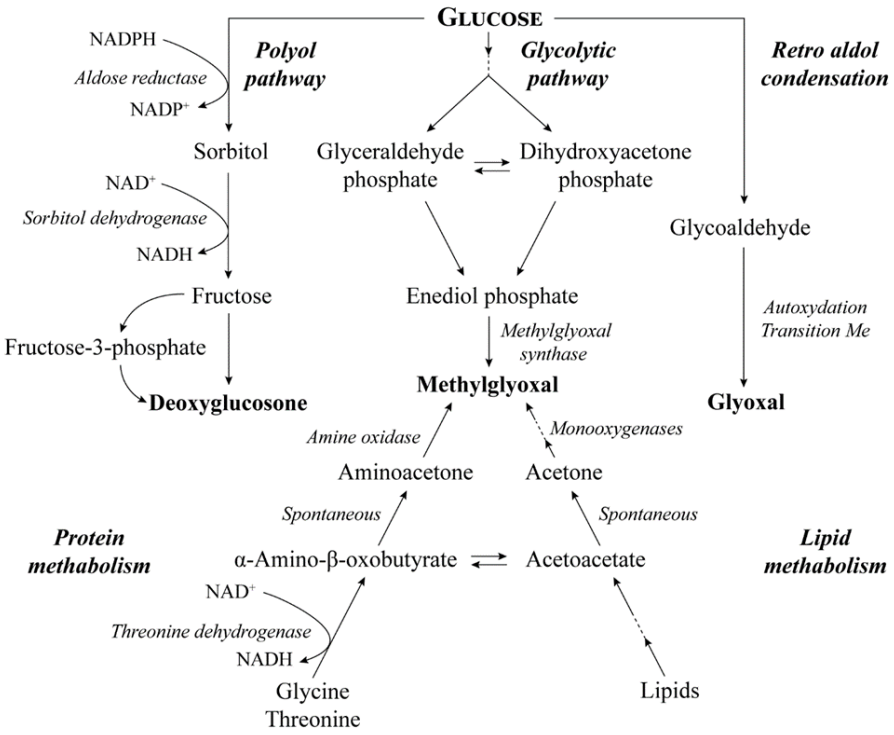

Figure 5. Metabolic pathways RCS generation.

Most studies focus on glycation processes in which glucose is the main glycation agent but is less reactive than fructose. The total fructose content in the blood plasma is about 1% of the glucose concentration, making it difficult to measureI ts adducts [110]. Excess of fructose and its metabolites 3-deoxyglucosone, fructose-3-phosphate, which are also powerful glycation agents, provoke the formation of Heyns compounds, the first stable intermediates of the Maillard reaction [111]. This causes protein dysfunction, which is aggravated by a decrease in the antioxidant defense of cells. Glutathione reductase, aldosereductase, and other enzymes involved in various anabolic processes compete for NADPH, which leads to the depletion of its pool and, as a result, makes it impossible to recover glutathione [112-114]. Additionally, the increase in NADH due to the high activity of the polyol pathway can contribute to the formation of diacylglycerol, an activator of PKC, which in turn activates NOX, which promotes oxidative stress. This is confirmed by the fact that in the absence of PKC there is a decrease in oxidative stress indicators,8-hydroxydeoxyguanosine and isoprostane [115].

On the other hand, the slowdown of glycolysis causes the accumulation and subsequent non-enzymatic deprotonation of glyceraldehyde-3-phosphate and dihydroxyacetone phosphate, which are spontaneously converted to methylglyoxal through intermediate enediol phosphate [116].

4. ROS and RCS Detoxification Pathways

Knowing that highly reactogenic compounds are formed constantly in the body, their action is limited to the processes of utilization of these compounds, that is, the intensity of oxidative processes depends on the effectiveness of the antioxidant defense system. In general, antioxidant reactions are realized in non-enzymatic and enzymatic pathways (Figure 6). Non-enzymatic antioxidants can be exogenous (vitamins C, E, A, carotenoids, polyphenols, flavonoids,hydroxycinnamic acids, allyl sulfides, and curcumin) and of endogenous origins

(glutathione, melatonin, bilirubin, albumin, polyamines, uric acid, and coenzyme Q) [117]. They can weaken or neutralize the oxidative effect by engaging antioxidant defense mechanisms or directly inhibitingthe oxidative chain reaction [118]. The main enzymes of antioxidant systems are superoxide dismutase, represented by cytosolic Cu/ZnSOD, mitochondrial MnSOD, and extracellular SOD, catalase, glutathione peroxidase, thioredoxin reductase.

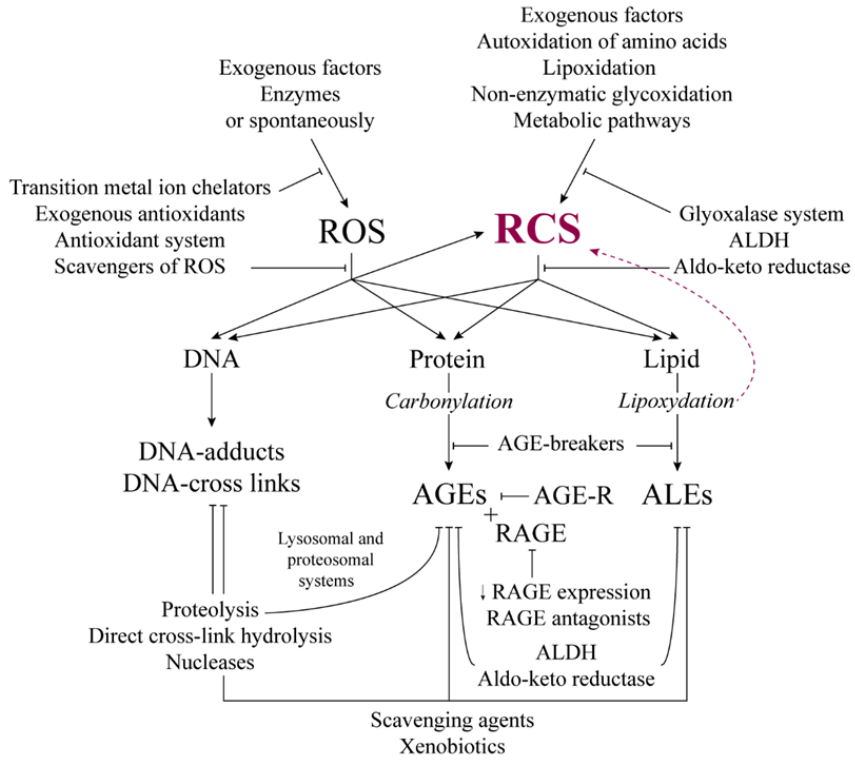

Figure 6. Exogenous and endogenous factors that reduce the formation ROS, RCS, and AGEs/ALEs and providedetoxification of toxic metabolites. ALDH – aldehyde dehydrogenase, AGE-R – receptors for AGEs, RAGE – receptor for advanced glycation end products.

Therefore, antioxidants and antioxidant defense enzymes lead to a decrease in ROS, and, since ROS are triggers of carbonyl stress reactions, to a corresponding decrease in RCS content. However, the formation of RCS depends not only on the indirect impact of ROS. It is known that in response to increased production and accumulation of RCS, the expression of enzymes involved in neutralizing these compounds, mainly due to their conversion to less toxic ones, which can be metabolized and eliminated from the body, is enhanced. The redox-sensitive glyoxalase system plays a significant role in suppressing carbonyl stress. It consists of two cytoplasmic enzymes, glyoxalase 1 (Glo1, S-D-lactoylglutathione lyase, EC 4.4.1.5) and glyoxalase 2 (Glo2, hydroxyacylglutathione hydrolase, EC 3.1.2.6), and reduced glutathione (GSH) [119]. The glyoxalases in the presence of GSH consistently convert methylglyoxal to lactate via the intermediate S-d-lactoylglutathione [120]. In addition to glyoxalases, other enzymesare involved in the detoxication of RCS: aldehyde dehydrogenases catalyze the conversion of aldehydes into carboxylic acids, carbonyl reductases (aldo-keto reductases) – to alcohols (the firststage of the polyol pathway) [121,122].

4.1. Antiglycation.

4.1.1. Amadoriases.

In mammals, there is a specific group of deglycating enzymes – Amadoriases(Fructosyl Amine Oxidases). The principle of action of Amadoriases is quite different from the above-mentioned enzymes [123,124]. They mostly hydrolyze or oxidize ketoamines but are alsoable to exhibit kinase activity. In this case, phosphorylation of ketoamine leads to destabilization of the bond between the amino acid and sugar and provokes spontaneous cleavage of the latter [125]. However, since its discovery, Amadoriases remain among potential deglycating agents because they are unable to exhibit more-or-less significant activity against intact proteins. A special tunnel conformation of the catalytic center, which allows splitting only low molecular weight substrates, is believed to be a hindrance [126].

In addition to mammals, identical in structure, Amadoriases synthesize microorganisms andfungi, the genome of which is quite easy to manipulate [125,127]. Therefore, the study of these enzymes gradually transferred to the plane of experimental studies. Due to specific and randommutations, certain areas of the active center were identified and, most importantly, successfully modified, which prevented the destruction of large substrates. This changed the substrate specificity for certain, and the enzyme acquired the ability to recognize the glycated area and the whole protein [127,128]. Some achievements in obtaining recombinant Amadoriases I and II with expanded substrate specificity allow partial deglycation of individual proteins and peptides [125,129]. Thus, Amadoriases still predict the role of important therapeutic tools.

4.1.2. Scavenger receptors AGE-Rs.

Scavenger receptors AGE-R1, AGE-R3 are also involved in AGE detoxification. Binding AGE to the receptor leads to activation of the latter by phosphorylation or ubiquitinylation of the cytoplasmic domain, which provokes clathrin-dependent or -independent internalization of AGE-AGER complex. This complex is in the formof a vesicle is transported to endosomes. Low pH in endosomes causes the AGE-AGER complexto dissociate, after which AGE remains, and the receptor can return back to the cell surface [108].

4.1.3. Inhibitors.

AGEs/ALEs, and RAGE can serve as targets for the action of inhibitors, whichare a heterogeneous group of natural and synthetic substances characterized by specific mechanisms of action. Some of them, like transition metal ions chelators, ROS, and RCS scavengers, stop triggers, while others prevent the conversion of Amadori products to AGEs or destroy Amadori products or AGE cross-links. But most often, inhibitors can block glycation processes in several ways, so it is difficult to determine their belonging to a particular group.

Natural inhibitors of glycation processes are carnosine (β-alanyl-L-histidine) and its analogs and α-Lipoic acid. They are imidazole-based and thiol-based compounds, respectively, belonging to the RCS scavengers group interacting with functional groups of primary nucleophiles. The free amino group β-alanine of carnosine competes with proteins for binding to RCS, mainly methylglyoxal and MDA, and selectively α,β-unsaturated carbonyl species, in particular 4-hydroxy-2-nonenal, to form adducts [48,130]. α-Lipoic acid acts on the following

the same principle, but it can block not only amino but also carbonyl groups of reductive sugars, preventing the formation of the Amadori products and dicarbonyl intermediates [131].

Among carbonyl product scavengers, the hydrazine compound aminoguanidine (AG) deserves special attention. In early studies, powerful antiglycation properties of AG were discovered due to its ability to prevent the formation of glucose-derived collagen cross-linking, AGE formation, and trapping RCS [132]. For the use of AG to have an effect, it must be used inhigh concentrations. Since it turned out that AG can exhibit side effects at a concentration of >10 mmol/L, for some time, the scientific interest in it subsided [133]. Later, after the anti-glycationeffect of gold nanoparticles (Gnp) was demonstrated, the work resumed [134]. In the end, thanks to modern technology, AG bioconjugated with gold nanoparticles (AG-Gnp) with minimal toxic effects was obtained. Moreover, AG-Gnp has been proven to be more effective than AG itself: it competes with RCS for protein binding and contributes to increased catalase activityand glutathione concentration [135].

Immediately after determining the antiglycation properties of Pyridoxamine (vitamin B_6, pyridorin, 2-aminomethylphenol-based scavenger), it was referred to amadorins, inhibitors that prevent the transformation of Amadori products to AGEs [136]. Surprisingly, no Pyridoxamine reaction product with some of the intermediates was detected. Given the sensitivity of modern methods, this can hardly be considered a consequence of technical limitations [137]. However, subsequent studies have found that the basis of the inhibitory activity of Pyridoxamine is not the inhibition of AGE formation but its potent chelating properties with respect to transition metal ions [138]. Because heavy metal ions can trigger free radical oxidation and are the main triggers of ROS and RCS formation, using metal cations chelators is an important mechanism to prevent the spread of oxidative stress. For example, individual iron chelators diethylenetriaminepentaacetic acid, desferrioxamine/deferoxamine, and copper chelator triethylenetetramine, etc., inhibit glycoxidation and block the propagation of oxidative stress [139].

Compared to Pyridoxamine and aminoguanidine, Lalezari-Rahbar compounds, named after the developers, are more effective chelators. These include aromatic organic acids with ureido- and carboxamide functional groups [137].

In addition to the corresponding ligands, low molecular weight inhibitors of RAGE, or RAGE antagonists can bind to RAGE domains. These include many different synthetic (FPS-ZM1and its analogs, Azeliragon, Tranilast, and Papaverine (a benzylisoquinoline alkaloid), etc.) and natural compounds (emetine), which react with extracellular V- or VC1-domains, mainly blocking interaction with S100B, HMGB1, and AGEs [99]. Another group of antagonists binds to the cytoplasmic domain, interfering with interactions between RAGE and Diaph1 [99, 140]. But in any case, RAGE-signaling is blocked.

4.1.4. AGE-breakers.

Cross-links, which are formed due to non-enzymatic processes, are very durable and do not lend themselves to proteolytic cleavage. However, some compounds candestroy cross-links in AGE and thus restore the native structure of the protein [141]. They are termed AGE-breakers. The prototype was N-phenacyl-thiazolium bromide, which effectively destroyed dicarbonyl intermediates [142]. Although AGE-breakers were developed for dicarbonylAGEs (thiazolium-based (Alagebrium, ALT-711) and pyridinium-based (TRC4186, TRC4149) AGEs breakers – effectively destroy cross-linkages formed by methylglyoxal), but the mechanismof their action in relation to other types of AGEs and still completely unclear

[139,141]. It is known that AGE-breakers do not always show their AGE-breaking activity. Therefore, it is assumed that the beneficial effects of AGE-breakers are not due to the splitting of existing AGE cross-links but their powerful chelating ability [137].

4.2. ROS- and RCS-mediated modified proteins removal.

Much of the waste or defective molecules of intracellular and extracellular proteins, including ROS- and RCS-mediated modified proteins, are removed using the ubiquitin-proteasome system. But, carbonylated proteins can form high-molecular aggregates, which are characterized by significant resistance to degradation [143]. Accumulation and growth of areas of such protein aggregates may reduce proteasome activity in cells. For example, docosahexaenoic acid-mediated tau protein aggregates provoke a weakening of proteasome activity and, accordingly, a slowdown of proteasomal degradation of proteins, which causes an additional outbreak of oxidative stress [144]. A similar effect is mediated by the influence of ROS. With an increase in the level of H_2O_2, there is an increase in MDA, 8-hydroxydeoxyguanosine. Under suchconditions, the total activity of the proteasome decreases, instead, there is an increase in carbonylation and accumulation of proteins. This effect is dose-dependent and is completely canceled due to excessive expression of β5 subunits of the proteasome [145].

The functional activity of proteasomes, like any other proteins, also depends on the intensity of glycoxidation. It was found that methylglyoxal covalently modifies the 20S-β2 subunit and reduces the level of 19S proteasome subunits and the number of ubiquitin receptors 19S Rpn10, which leads to the accumulation of polyubiquitinated substrates [146,147]. 4-Hydroxy-2- nonenal post-translational modifications of proteasomes are somewhat different from the effects of methylglyoxal. 4-hydroxy-2-nonenal mainly modifies cardiac 20S proteasome α1, α2, α4-6, andβ6 subunits, whereas liver 20S proteasome α2-5 and β4 subunits, while increasing the concentration additionally β3 and $\beta1_i$ subunits [148].

5. Conclusions

The combined influence of adverse exogenous and endogenous factors on the body can increase oxidative processes, at least accompanied by adaptive hyperproduction of several active intermediates such as reactive oxygen and carbonyl species. These reactive compounds are mostly generated as a result of free radical reactions and are common by-products of catabolism, which have a strong cumulative effect. ROS and RCS formation can be carriedout in various competing ways, contributing to the development and spread of carbonyl stress, accompanied by irreversible structural and functional changes in biomolecules. As a result, abnormal products are formed. Advanced glycation and lipoxidation end products and Advanced oxidation protein products. ROS, RCS, ALE_S/AGE_S trigger signaling transduction pathways, which ultimately change the metabolism and behavior of the cell. Natural and synthetic inhibitors are sometimes limited to the need for their considerable concentration in tissuesto achieve a certain effect. In this context, finding ways to prevent the spread of carbonyl stress orleveling of undesirable consequences is a very promising direction.

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Conflicts of Interest

The author declares no conflict of interest.

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