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Oxidative Stress in Diabetes and Alzheimer's Disease

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Abstract

Oxidative stress plays a major role in diabetes as well as in Alzheimer's disease and other related neurological diseases. Intracellular oxidative stress arises due to the imbalance in the production of reactive oxygen/reactive nitrogen species and cellular antioxidant defense mechanisms. In turn, the excess reactive oxygen/reactive nitrogen species mediate the damage of proteins and nucleic acids, which have been shown to have direct and deleterious consequences in diabetes and Alzheimer's disease. Oxidative stress also contributes to the production of advanced glycation end products through glycoxidation and lipid peroxidation. The advanced glycation end products and lipid peroxidation products are ubiquitous to diabetes and Alzheimer's disease and serve as markers of disease progression in both disorders. Antioxidants and advanced glycation end products inhibitors, either induced endogenously or exogenously introduced, may counteract with the deleterious effects of the reactive oxygen/reactive nitrogen species and thereby, in prevention or treatment paradigms, attenuate or substantially delay the onset of these devastating pathologies.

Keywords

advanced glycation end products; AGE inhibitors; Alzheimer's disease; diabetes; glycation; Maillard reaction; oxidative stress; protein crosslinks

INTRODUCTION

Oxidative stress, the direct result of the imbalance between the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), and intracellular antioxidant defenses, is invariably involved in the onset of diabetes and neurological pathologies such as Alzheimer's disease (AD), Parkinson's disease, and amyotrophic lateral sclerosis [1]. Diabetes, in many cases, usually results in further complications such as cardiovascular disease, atherosclerosis, and diabetic nephropathy. Thus, the hypothesis of diabetes leading, in part, to the onset of AD is an appealing topic and is hotly debated in the current literature.

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In addition to oxidative stress[2,3], cell cycle abnormalities also play a vital role in the pathogenesis of AD[4–6], as highlighted in the two-hit hypothesis that encompasses both oxidative stressors and mitotic insults for the onset of AD [7–9]. By analyzing the presence of both oxidative stress responses and abnormalities in mitotic signaling in the same neurons in many cases of AD, it was found that while each stressor can independently initiate cellular dysfunction, both are necessary to propagate disease pathogenesis. Similar hypotheses encompassing multiple sites of action, including genetic and receptors for advanced glycation end products (RAGEs), have also been proposed for the development of diabetes [10]. Interestingly, although AD and diabetes are among the most prevalent diseases in developed countries, a complete cure has, to date, evaded pharmaceutical intervention. At best, disease progression can be delayed or controlled with available treatments. Especially in AD, the causative factors are still not entirely clear. However, both diabetes and AD have common pathogenic factors and evidence suggests oxidative stress as a major factor causing these pathologies[11].

The major species responsible for oxidative stress is the overproduction of ROS and RNS, a major source of which is mitochondrial dysfunction [12]. ROS, which include superoxide radical anion and hydroxyl radicals are involved in the damage of lipids, DNA, and protein modifications. Minor modifications of the nucleic acid bases are repaired through base excision repair involving DNA glycosylase and AP endonuclease, which are located in nuclei and mitochondria. The progression of AD is associated with the diminished expression of these DNA repair enzymes[13,14]. The accumulation of the oxidatively damaged nucleic acids and proteins likely exceed the limit of cellular repair and detoxification mechanisms and leads to the onset or progression of diabetic and neurological pathologies. In general, accumulation of oxidatively damaged proteins, lipids, and nucleic acids correlate with the onset of age-related diseases, especially in diabetes and AD [15], indicative of one and the same common pathological mechanisms.

Glycooxidation and lipid peroxidation, which are mediated by ROS, generate a variety of reactive carbonyl compounds. These electrophilically-activated carbonyl compounds further react with cellular proteins, lipids, and nucleic acids resulting in protein crosslinking and DNA damage. A variety of advanced glycation and advanced lipid peroxidation products (AGEs and ALEs), some of which are intensely fluorescent, are produced during these slow and complex reactions [16]. AGEs and ALEs, through their interaction with receptors for advanced glycation end products (RAGEs), further activate signal transduction, inducing formation of proinflammatory cytokines such as interleukin-6 (IL-6) [17]. The AGE-RAGE interactions are partially responsible for diabetic neuropathy and nephropathy [18]. RAGEs are multi-ligand receptors, and their interaction with amyloid- β peptides exaggerates neuronal stress and neuroinflammation, resulting in impaired learning [19]. Therefore, blocking RAGEs as well as AGE/ALE-inhibitors may provide an attractive strategy for the treatment of diabetes as well as AD [20].

REACTIVE OXYGEN AND NITROGEN SPECIES

A variety of ROS and RNS are produced *in vivo* through both enzymatic and nonenzymatic routes. ROS include superoxide radical anion, hydroxyl radical, alkoxy radicals, and singlet oxygen. The hydroxyl radical is an especially highly reactive species and has a relatively short life time. It is abundantly produced in the mitochondria during respiration cycles and reacts with the proteins, lipids, and nucleic acids in the vicinity of its production. Peroxynitrous acid is one of the major RNS found intracellularly and is involved in the rapid nitration of aromatic residues of proteins, such as tyrosine to give 3-nitrotyrosine, which may alter the protein structure, and is also a marker of oxidative stress [3,21]. Apolipoprotein E (ApoE)-deficient mice show significantly elevated concentrations of 3-nitrotyrosine, indicating ApoE may

modulate the oxidative stress produced by peroxynitrite [22]. Peroxynitrous acid is an additional source of hydroxyl radicals and may in fact be a dominant pathway in diabetes [23].

Transition metal ions, typically Cu(I) and Fe(II), are capable of reducing molecular oxygen to superoxide radical ion via single electron transfer and are involved in the pathogenesis of AD [24,25]. Other sources of superoxide radical anions are the mitochondrial respiration and NADPH oxidases in AD and diabetes. The superoxide radical anion is a source of hydrogen peroxide through either metal ion reduction followed by protonolysis or via superoxide dismutase. Superoxide radical anion, as well as hydrogen peroxide, is a significantly less reactive species than the hydroxyl radical, which is formed by the transition metal-mediated Fenton reaction of hydrogen peroxide.

Superoxide radical anion forms peroxynitrous acid through its reaction with intracellularly available nitric oxide. Inducible nitric oxide synthase (iNOS) was shown as a significant source of ROS in the streptozotocin-induced diabetic rats [23]. Nitrous acid is also effective in the formation of DNA-protein crosslinks through oxidative modification of guanine residues [26–29].

GLYCOXIDATION AND AGEs

Maillard reaction of reducing sugars (e.g., glucose, ribose, ascorbate) with amino groups of lysine or arginine residues of proteins, followed by Amadori rearrangement, and further ROS-mediated glycoxidations, give a complex product mixture, collectively called AGEs [30–33]. AGEs may exist as protein cross-links or as modification of the side chains of a single protein, and significantly alter the protein conformations leading to protein inactivation. Numerous AGEs have been isolated and characterized after cleavage from the protein backbones, by spectroscopic analysis. AGEs involving protein cross-links include pentosidine, a dimer of arginine and lysine; MOLD, a dimer of two lysine residues; and MODIC and GODIC, dimers of arginine and lysine residues. Examples of AGEs resulting from the single protein modification are pyrraline and N^ε-(carboxymethyl)lysine (CML), the lysine-residue modified products, and argpyrimidine, an arginine-residue modified protein. Although many other AGEs, including the hydroimidazolone adduct MG-H1, have been characterized in diabetes, this review focuses on those AGEs which have common occurrence in AD and diabetes [34]. It must, however, be pointed out that glycoxidation and oxidative stress are mutually dependent and reinforce each other. Thus, while the sources of oxidative stress may widely differ in diabetes and AD, and while a number of AGEs accumulate in both conditions, other AGEs found in diabetes have yet to be characterized in AD.

Methylglyoxal, an intermediary degradation product of Maillard reactions, is derived from polyol pathways and forms adducts with DNA nucleic acid bases, giving N²-(1-carboxyethyl)-2'-deoxyguanosine as one of the major AGEs [35]. Similarly, methylglyoxal adducts of lysine residues of proteins have been characterized as N²-(carboxyethyl)lysine (CEL) [36,37]. CEL-modified proteins are detected in the distal tubule epithelial cells in diabetic rats [38].

Pentosidine and CML are shown to be common to both diabetes and AD pathologies and may serve as markers of the disease progression [2,39–44]. The question of whether AGEs are the cause or consequence of the pathology is not clear, although there is likely a primary role of oxidative stress in AD [45]. However, their interactions with RAGEs would lead to deleterious signal transduction resulting in cellular degeneration or apoptosis, or the generation of other inflammatory compounds [46–50].

To alleviate the deleterious effects of AGE in diabetes, a variety of AGE inhibitors were developed, whose mechanisms rely on transition metal ion chelating properties, high reactivity with the carbonyl groups, or breaking of the cross-links(*vide infra*).

ADVANCED LIPID PEROXIDATION PRODUCTS

Polyunsaturated fatty acids, arachidonic acid, and docosahexaenoic acid are abundant in the cerebral cortex and visual system, and are uniformly distributed in all cell types in brain [51, 52]. ROS-mediated lipid peroxidation of polyunsaturated fatty acids gives rise to several reactive α,β -unsaturated aldehydes, among which 4-hydroxy-*trans*-2-nonenal (HNE), 4-oxo-*trans*-2-nonenal (4-ONE), acrolein, and 4-oxo-*trans*-2-hexenal, all of which are well recognized neurotoxic agents. These compounds are prone to undergo reactions with amino groups of proteins at the carbonyl group to form Schiff bases as well as Michael additions (conjugate additions) on the olefinic moiety adjacent to the carbonyl group, resulting in protein crosslinks and thereby protein inactivation. They also readily undergo Michael reactions with sulfhydryl group of protein cysteines and nucleic acid bases, the latter also resulting in DNA damage through crosslinking [53].

HNE is a widely recognized lipid peroxidation end product and its involvement in neuronal loss in AD is demonstrated[53–58]. Although the exact mechanism of the neurotoxicity due to HNE is still in debate, one idea is that its reaction with microtubule protein-cysteine sulfhydryl groups would disrupt microtubule network [53]. 4-ONE is especially significantly more reactive than HNE and is substantially more toxic [59,60]. HNE and 4-ONE modify the structure of the protein disulfide isomerase, which is critical for maintaining correct disulfide bonds in the protein, by reacting with protein sulfhydryl groups[61]. Glutathione is capable of attenuating the damage caused by HNE and 4-ONE, as the sulfhydryl groups of glutathione effectively compete with those of the proteins. However, glutathione levels are usually depleted in chronic diabetes or AD cases. Similarly, other cellular antioxidant mechanisms, e.g., those involving superoxide dismutase and glyoxalase are also downregulated in cases of AD[62, 63]. Alternatively, increased concentrations of HNE are countered by the cellular expressions of antioxidant heat shock proteins, heme oxygenase-1 (HO-1), and thioredoxin reductase-1 (Trx-R1) in cases of diabetic nephropathy[61] and AD [56,64,65]. Low density lipoproteins may act as quenching agents for HNE as it has been shown that as many as 486 molecules of HNE are bound to a single particle of low density lipoprotein[66]. Additionally, lipid peroxidation products may be quenched by neurofilaments [67]and/or microtubules [68–70].

Sayre and coworkers have characterized the lysine adducts of HNE and 4-ONE by using mass spectroscopy [71]. The Michael adducts of HNE with lysine, histidine, and cysteine residues of proteins may form cyclic hemiacetals, which can further form Schiff bases by reaction with other histidine (through imidazole nitrogen) or lysine (through ϵ -amino group) residues of proteins, resulting in intra- or inter-molecular protein crosslinks. The resulting altered protein conformations can lead to enzyme inactivation and induce cellular signal transduction [72]. In the latter, elevated concentrations are correlated with an upregulation of receptor tyrosine kinases and a downregulation of nuclear factor kappa B [72]. Amyloid- β -induced oxidative stress, in part, may be due to HNE and related pro-oxidant molecules, and it has been demonstrated that HNE-mediated activation of mitogen activated protein kinases known to be upregulated in AD [73,74] is an early event prior the amyloid- β -induced neuronal apoptosis [75]. Mitochondria are also important in the oxidative damage in AD and, perhaps, diabetic complications [76–79]. AD-type changes can be induced in control fibroblasts using N-methylprotoporphyrin, which inhibits cytochrome oxidase assembly, an effect attenuated by antioxidants, N-acetylcysteine and lipoic acid [80]. In models of diabetes, controlling increased levels of mitochondrial-derived ROS by normalizing superoxide mitigated glucose-induced formation of AGEs [81–83]. A major limitation in the study of oxidative stress in AD is the

paucity of cellular models homologous to AD. In this regard, olfactory neurons may be used as a reliable model since cultured olfactory neurons from patients with AD show elevated levels of lipid peroxidation products such as CML and HNE, as well as upregulation of HO-1, strikingly similar to the findings in vulnerable neurons in the brain [84,85].

ANTIOXIDANT THERAPY IN ALZHEIMER'S DISEASE AND DIABETES

Oxidative stress is one of the earliest events in the neurological and pathological changes of AD [45], while the effects of oxidative stress are manifested in the slow accumulation of AGEs and ALEs in diabetes. Oxidative stress leads to the irreversible protein aggregation and consequent neuronal degeneration in AD [86–88]. Advanced lipoxidation products, such as HNE, bind to phosphorylated tau protein to form paired helical filaments, accelerating the formation of neurofibrillary tangles. Thus, antioxidant therapy in combination with AGE inhibitor therapy may be effective approaches for AD and diabetes-related complications.

Oxidative stress also results in the covalent crosslinking of tau filaments to form large aggregates that are resistant to proteolytic cleavage. Larbig and coworkers reported a series of inhibitors for the tau protein aggregation [89]. Remarkably, thiazolium-based compounds, which are also AGE inhibitors and potentially useful for diabetic therapy, are effective inhibitors of tau aggregation. 4-(4-bromophenyl)-2-(4-pyridoylhydrazino)-1,3-thiazole shows an IC_{50} value of 18 μ M.

4-(4-bromophenyl)-2-(4-pyridoylhydrazino)-1,3-thiazole

AGE inhibitors and AGE crosslink breakers

Much of the initial attention towards AGE inhibitors was focused on aminoguanidine, which traps electrophilically activated 1,3-dicarbonyl compounds, the precursors of AGEs [90–93]. This compound was not approved by the US Food and Drug Administration due to adverse side effects in diabetic patients during Phase III clinical trials, and the search for safer alternatives continues. Pyridoxamine (Vitamin B6, Pyridorin) and thiamin pyrophosphate are potential alternatives to aminoguanidine, as the former suppresses the formation CML [94–96]. Furthermore, these compounds are also good metal ion chelators and attenuate oxidative stress. N-Acetylcysteine and lipoic acid act as inhibitors of ALEs through attenuation of oxidative stress. While the AGE-inhibitory effect of these compounds is not clearly understood, similar mechanism may operate in case of AGEs.

Carnosine, homocarnosine, and related compounds are potentially suitable as AGE inhibitors although further studies are needed to prove their efficacy in diabetes and AD [97]. Carnosine protects superoxide dismutase, catalase, and α -crystallin from nonenzymatic glycation and protein crosslinking [98]. OPB-9195 inhibits AGE formation, especially pentosidine and CML, apparently through carbonyl trapping and metal ion chelation [99,100]. Thiazolium-based compounds such as Alagebrium chloride (ALT-711) and N-phenylacetyl-1,3-thiazolium bromide (PTB) are effective AGE crosslink breakers, and are potentially useful drugs for diabetes and AD [101–103]. It should, however, be pointed out that the mechanisms of the action of the latter compounds is not clearly demonstrated. In addition to their action as crosslink breakers

of AGEs derived from 1,2-dicarbonyl compounds, they may also act as antioxidants through chelation of transition metal ions. The development of these drugs as therapeutics thus depends on the detailed understanding of their mechanisms of action.

An alternative strategy involves removal of AGEs through the soluble receptors for AGEs (sRAGEs) [104]. Poor glycemic control in diabetes results in decreased concentrations of sRAGEs, and upon insulin treatment, significant improvements in the levels of sRAGEs were observed, with concomitant decrease in AGEs [105]. Plasma levels of sRAGEs in healthy humans is in the range of 1500 pg/mL [106]. Treatment of diabetic patients with Rosiglitazone, a 2,4-thiazolidine dione derivative, results in increase of plasma sRAGEs, comparable to controls [107]. Significant amounts of plasma sRAGEs are also produced when angiotensin converting enzyme inhibitors (ACEi; e.g., perindopril) were used for the treatment of diabetes [108]. Therapeutic approaches which attenuate AGEs and insulin resistance are thus better suited for delaying the onset of AD or diabetes related complications. Protective effects of sRAGEs has been questioned recently as they are much higher in experimental animal models than those found *in vivo*, suggesting they may be only markers of inflammation [109].

Fe(III) and Cu(II) ions are localized in amyloid plaques and neurofibrillary tangles, in cases of AD [24]. Metal ion chelators such as desferrioxamine (Fe(III) chelator), tetrathiomolybdate (Cu(II) chelator), and mercaptopropanol (Pb(II) and Hg(II) chelator) attenuate the expression of the amyloid- β protein precursor, and thereby decrease secretion of the amyloid- β peptide as well as reduce amyloid- β toxicity [110]. As such, desferrioxamine and clioquinol, a Cu(II) chelator, may be potentially useful therapeutic in AD [111].

CONCLUSION

Oxidative stress plays a vital role in the pathogenesis of diabetes and AD, as well as related diseases. Oxidative modification of proteins, lipids, and nucleic acids, through glycoxidations and lipid peroxidations generate a complex array of AGEs and ALEs which are increasingly shown to be prevalent in AD, diabetic neuropathy, and diabetic nephropathy. AGEs, through reaction with RAGEs, further generate inflammatory cytokines and induce signal transduction which may result in cell apoptosis. Specifically, to counter the effects of oxidative stress in these pathologies, therapeutic strategies involving AGE inhibitors and anti-inflammatory antioxidants appear to be most promising. By comparing the stressors and responses that are common between the two conditions, understanding the mechanisms and possible therapeutic avenues may provide alternate treatment modalities for both diabetes and AD.

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Scheme 1.

Cellular generation of ROS and RNS. Superoxide radical anions generated from the transition metal ion mediated reduction of molecular oxygen is transformed into hydrogen peroxide either through superoxide dismutase catalyzed reaction or by further reduction by metal ions. The superoxide radical anions also react with intracellularly available nitric oxide giving peroxy nitrite anion which upon further protonation forms the peroxynitrous acid, one of the significant RNS, and also a source of hydroxyl radicals

Scheme 2.

Structures of representative AGEs. AGEs are the end products of complex series of glycoxidation reactions involving proteins and reducing sugars. Some of the AGEs are protein crosslinks (e.g., pentosidine, MOLD, GOLD, MODIC, GODIC), while others are single protein modifications (e.g., CML, pyrraline, argpyrimidine). AGEs not only serve as the markers of the progress of the pathology of diabetes and AD, but may be involved in the pathogenesis through release of antiinflammatory agents upon binding with RAGEs.

Scheme 3.

Lipid peroxidation. Polyunsaturated fatty acids undergo oxidative degradations mediated by ROS and RNS. A variety of deleterious and neurotoxic γ -hydroxy and γ -keto aldehydes, such as HNE, 4-ONE, and acrolein are formed through lipid peroxidation. HNE and ONE undergo Michael additions to sulfhydryl or amino residues of proteins causing their structural modifications.

Scheme 4.

Reactions of HNE and 4-ONE. HNE and 4-ONE are highly reactive with ϵ -amino group of lysine, imidazole nitrogen of the histidine, and sulfhydryl groups of cysteine moieties. 4-ONE is much more reactive than HNE and substantially neurotoxic. HNE and 4-ONE through Michael additions and through reaction at their carbonyl groups result in protein modifications.

Scheme 5.

Structures of and AGE-inhibitors. There is an active interest in the development of AGE inhibitors that show therapeutic promise in diabetes, and AD. AGE inhibitors may have varied mechanisms of their action, which involve carbonyl trapping, metal ion chelation, or AGE-breaking.

Scheme 6.

Structures of metal ion chelators. Clioquinol and desferrioxamine are chelators of transition metal ions, Cu(II) and Fe(III), respectively. Particularly, in AD, the metal ion concentration is elevated at the sites of amyloid- β and neurofibrillary tangles, resulting in the generation of inflammatory agents through oxidative stress. Therefore, metal ion chelation therapy may be promising for AD.