Advanced glycation end products and human diseases

Hamad Abu Zahra

Department of Biological Sciences, College of Science, King Faisal University, Al-Ahsa, Saudi Arabia

Abstract

Proteins, lipids, and nucleic acids can undergo non-enzymatic glycation and oxidation, leading to the formation of Advanced Glycation End products (AGEs). These chemically stable compounds accumulate in various tissues over time and are strongly implicated in the pathogenesis of several chronic human diseases, including cognitive impairment, diabetes, kidney failure, stroke, cardiac disease, and neurodegenerative disorders. AGEs contribute to the development of these conditions by forming cross-links between proteins, modifying cellular receptors, and inducing oxidative stress, which results in the functional compromise of biological molecules. As such, they are considered a hallmark of metabolic diseases, particularly those associated with aging and poor glycemic control. This review provides a comprehensive analysis of the role of AGEs in the etiology of vascular dysfunction, cognitive decline, renal impairment, cerebrovascular accidents, and cardiovascular disease. Additionally, the underlying cellular mechanisms by which AGEs exert their deleterious effects, including receptor-mediated signaling pathways, inflammation, and oxidative damage, are explored. Finally, the potential therapeutic strategies aimed at inhibiting AGE formation, breaking AGE cross-links, or blocking AGE receptors, highlighting their promise in mitigating AGE-associated pathologies, are discussed.

Correspondence: Hamad Abu Zahra, Department of Biological Sciences, College of Science, King Faisal University, P.O. Box 420, Al-Ahsa 31982, Saudi Arabia.
Tel.: +966 135897434
E-mail: habuzahra@kfu.edu.sa

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Introduction

The reduction of sugar involves a series of complex biochemical reactions including oxidative and non-oxidative molecular rearrangements and a series of stable covalent adducts referred to as Advanced Glycation End products (AGEs). These compounds result from non-enzymatic reactions with amino groups in proteins or lipids.[1–3] A slow reaction can alter a protein's structure and modify its molecular surface topology, which in turn affects its biochemical properties. AGEs have been detected in human tissues under AGE-specific epitope antibodies, thereby revealing that AGEs are associated with protein degeneration and biological aging over time.[4]

The formation of AGEs is accomplished in two primary steps.[5] First, carbonyl groups in reducing sugars react reversibly with amino groups in proteins and nucleic acids to form unstable Schiff bases within a few hours. The concentration of glucose drives this reaction. The driving force of this reaction depends on the glucose concentration. Within a few weeks, Schiff base adducts undergo spontaneous intramolecular rearrangements that convert them to relatively stable, covalently bound early glycation products. Second, a small fraction of early glycation products (Amadori products) can be transformed directly into AGEs via irreversible oxidation or hydrolysis. The AGE compounds are formed by the covalent attachment of active dicarbonyl compounds to long-lived proteins and the basement membrane or connective tissue matrix. Glucose autoxidation, glucose conversion to fructose, lipid oxidation, and Schiff base oxidative cleavage all lead to stable AGEs (Figure 1). The role of AGEs in the onset and progression of metabolic dysfunction has recently been identified by mediating inflammation and increased Reactive Oxygen Species (ROS) via the activation of intracellular pathways.[1] The adverse effects of AGEs have been reported to be due to two primary mechanisms. First, AGEs bind directly to proteins and indirectly to receptors on the surface of various cells, trapping and crosslinking them. Second, a number of signaling pathways, (e.g. nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinases (MAPKs), are activated when AGEs bind to receptors.[6] This activation can result in changes in chemotaxis, angiogenesis, oxidative stress, cell proliferation, and programmed cell death.[7] This review summarizes the molecular process by which AGEs are formed and their role in metabolic dysfunction.

In the process of cooking, processing, and storing foods, dietary AGEs are formed by nonenzymatic browning (*i.e.*, the Maillard reaction), which occurs when a carbonyl group of a reducing sugar reacts with a primary amine group. The methods and temperatures used in processing and cooking, as well as the contents of proteins, fats, and sugars, all affect the formation of AGEs.[8] During long-term or high-temperature cooking methods such as roasting, grilling, and frying, foods are subjected to thermal processing, which leads to the formation of AGEs.[9]

Living organisms and stored or heat-processed foods can also produce AGEs spontaneously. High-protein foods like meat, eggs, and milk, as well as foods with high fat contents like oil and nuts, are therefore highly correlated with the production of AGEs.[8] When food is stored for a long time, AGEs are continuously generated, and their formation rate is affected by storage time. Previous works demonstrated a significant effect of storage temperature on AGE concentration.[10]

AGE- Receptor for Advanced Glycation Endproducts (RAGE) binding in human diseases: intracellular effects

RAGE have multiple isoforms resulting from alternative splicing, which allows it to perform diverse functions across different tissues.[11] Full-Length RAGE: This is the membrane-bound form and is the most commonly studied isoform. It contains an extracellular ligand-binding domain, a transmembrane domain, and a cytoplasmic tail crucial for signaling. sRAGE (Soluble RAGE): This isoform is generated either by proteolytic cleavage of the membrane-bound RAGE or by alternative splicing, leading to a lack of the transmembrane and cytoplasmic domains; sRAGE acts as a decoy receptor, binding ligands in the extracellular space and preventing them from activating cell surface RAGE. N-terminal truncated RAGE (Nt-RAGE): This isoform lacks the N-terminal ligand-binding domain, potentially modifying the receptor's interaction with ligands and its signaling pathways.[12]

RAGE expression is most prominent especially in alveolar epithelial cells, where the full-length form is highly expressed. RAGE is also significantly expressed in endothelial cells, contributing to vascular inflammation and atherosclerosis. The heart expresses RAGE, particularly in conditions such as diabetes, where it contributes to cardiac remodeling. RAGE is expressed in the kidneys, where it is involved in diabetic nephropathy and other renal diseases.[13] In the central nervous system, RAGE is found on neurons, glial cells, and the blood-brain barrier, playing roles in neuroinflammation and neurodegenerative diseases.[14]

RAGE expression can be upregulated in various tissues in response to chronic inflammation, oxidative stress, and the accumulation of its ligands, such as AGEs, S100 proteins, and amyloid-beta peptides. This upregulation is often associated with patholog-

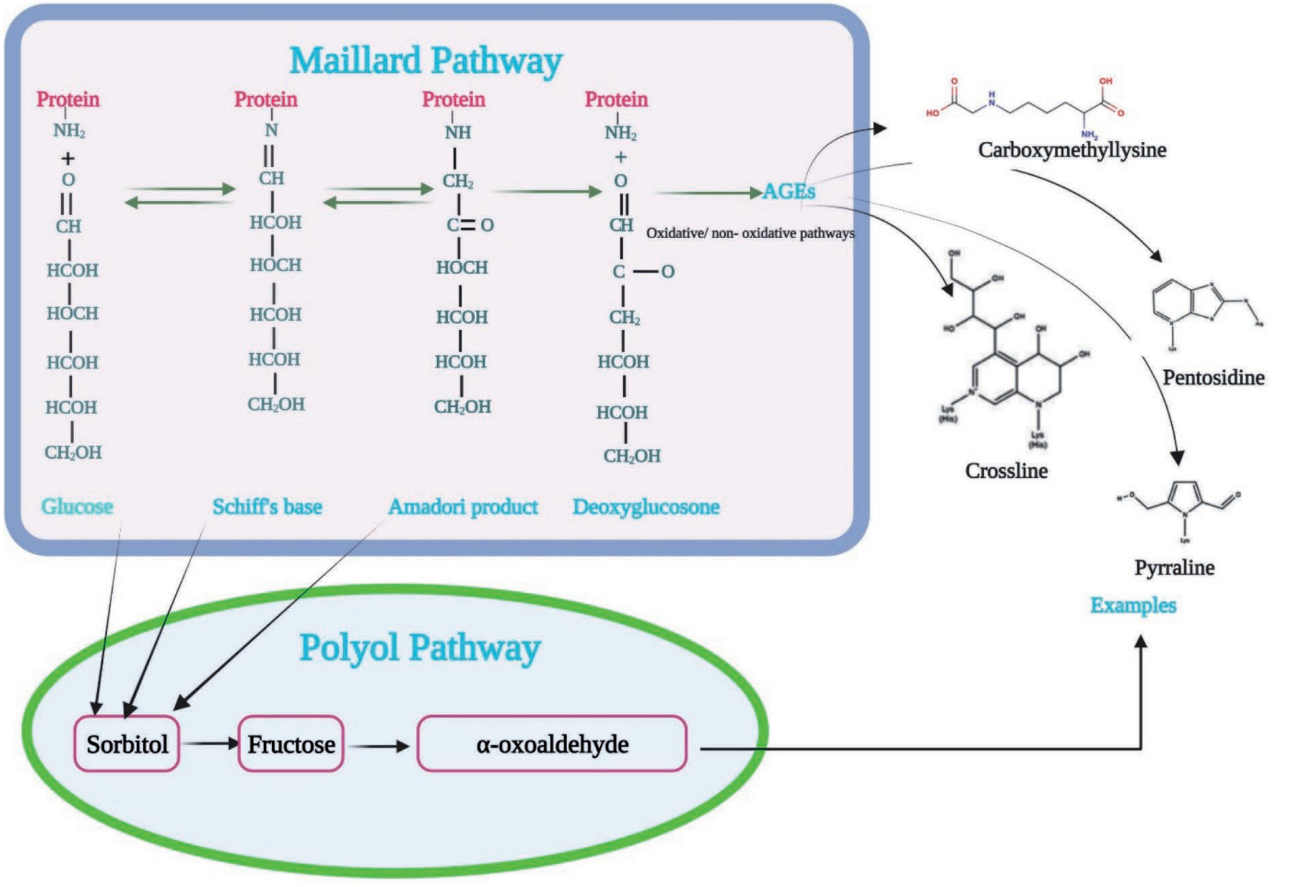

Figure 1. Formation of AGEs by the Maillard and polyol pathways (Image created with Biorender.com, Aug 15, 2023; one-month subscription).

ical conditions like diabetes, atherosclerosis, Alzheimer's Disease (AD), and cancer.[14]

The accumulation of AGEs in the body leads to the activation of multiple signaling pathways in a series of cell membrane receptors implicated in the pathogenesis of diabetes and associated conditions such as enhanced inflammation, as well as in AD, cardiovascular disorders, and renal damage.[15,16] The activation of RAGE in turn activates the NF-κB transcription factor, which promotes the expression of pro-inflammatory cytokines, growth factors, and adhesive molecules. A RAGE-mediated increase in oxidative stress is accompanied by an increase in NF-κB stimulation.[17] Moreover, it has been reported that AGE-RAGE engagement increases the phosphorylation of *p21ras* and the MAPK and activates NF-κB so that it can start regulating its target genes in the nucleus (Figure 2).[18] AGE/RAGE signaling activates NF-κB and its translocation to the nucleus, where it enhances transcription of target genes such as endothelin-1, intercellular adhesion molecule-1 (ICAM-1), E-selectin and tissue growth factor. NF-κB influences both inflammation and atherosclerosis.[19] Inflammatory, proliferative, angiogenic, fibrotic, thrombogenic, and apoptotic reactions are caused by MAPK, phosphoinositol 3 kinase (PI3K), and Janus kinase/signal transducers and activators of transcription (JAK-STAT) activity.[20] By activating Nicotinamide Adenine Dinucleotide Phosphate Hydrogen (NADPH) oxidase and mitochondrial pathways, AGE/RAGE binding increases ROS levels.[21] Other endogenous antioxidant defenses, including Glutathione (GSH), ascorbic acid, and Superoxide Dismutase (SOD), are reduced as well.[21] Glycation plays a significant role in oxidative stress; the depletion of GSH also reduces Glyoxalase-I (Glo-1) activity and leads to an increase in glyoxal and methylglyoxal (MG) concentrations. Glyoxal and MG are formed

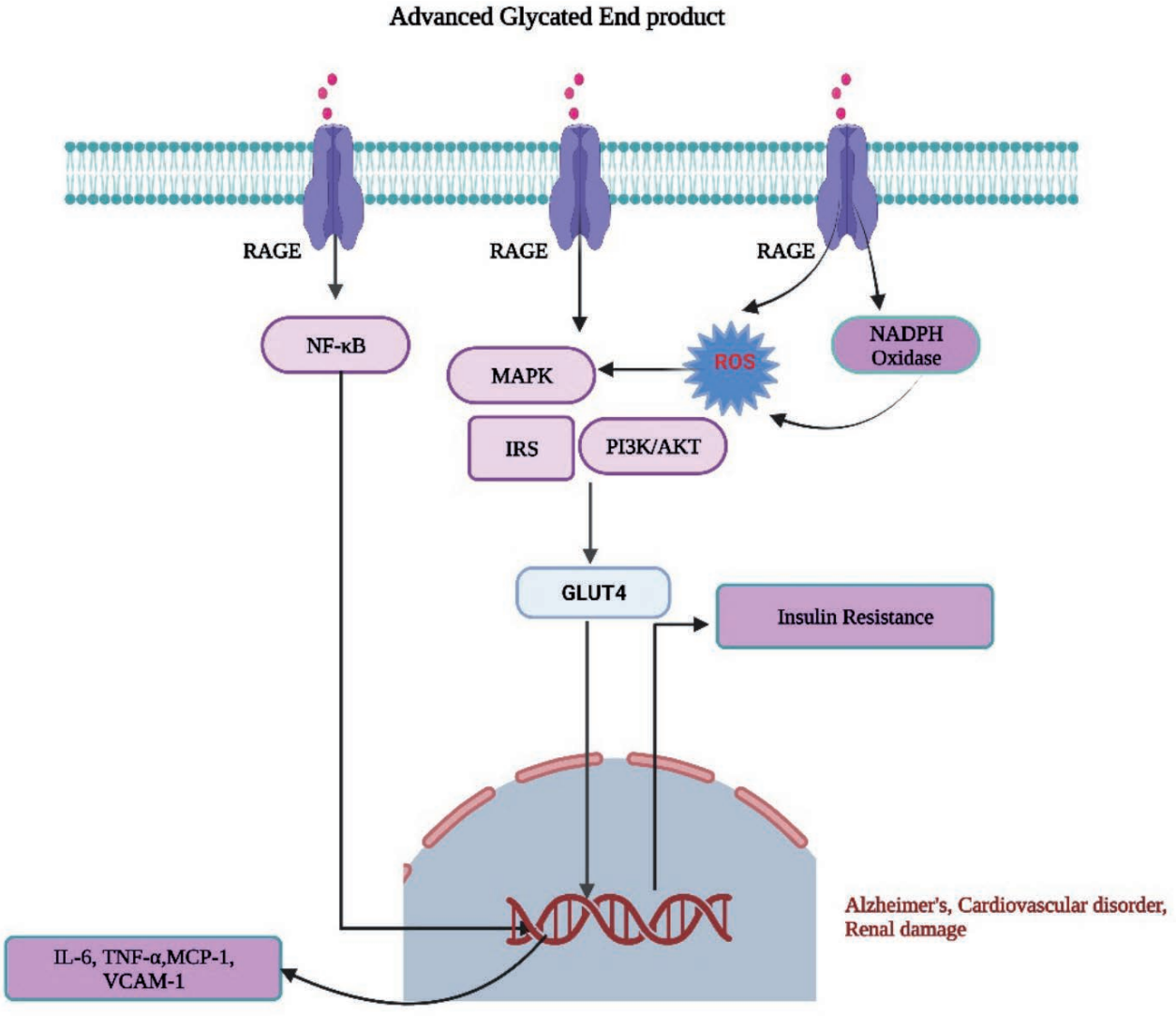

Figure 2. Involvement of Advanced Glycated End products-Receptor Advanced Glycated Endproduct (AGEs-RAGE) in the pathogenesis of Alzheimer's disease, cardiovascular disorders, and kidney damage is mediated through many signaling pathways. NF-κB, Nuclear factor kappa B, MAPK, Mitogen-activated protein kinases, ROS, Reactive oxygen species, NADPH, Nicotinamide adenine dinucleotide phosphate, IRS, Insulin Receptor Substrate, PI3K/AKT, Phosphatidylinositol 3-kinase /protein kinase B, GLUT4, Insulin-regulated glucose transporter, IL6, Interleukin 6, TNF-α, Tumor necrosis factor alpha, MCP-1, Monocyte chemoattractant protein-1, VCAM-1, Vascular cell adhesion protein 1. (Image created with Biorender.com, dated Aug 15, 2023; one month subscription).

non-enzymatically as a result of glycolysis and can result in the formation of AGEs.[22]

ROS and AGEs

Advanced glycation end products are transduced intracellularly by RAGE, which increases intracellular ROS levels. By interacting with receptors, AGEs can produce ROS by activating microsomal enzymes, mitochondrial respiratory chains, NADPH oxidases, arachidonic acids and xanthine oxidase pathways.[23,24] Other teams have noted significant increases in ROS inside macrophages,[25] cardiomyocytes,[26] and endothelial cells.[27] Under various pathological conditions, the activation of the AGE-RAGE axis increases oxidative stress. That situation affects mitochondrial functioning and ultimately impacts cell metabolism (Figure 2).[27]

Stress progression resulting from ROS generation

As a result, oxidative stress caused by AGEs contributes to the aging process; AGE-indexed levels of hemoglobin A1C (HbA1c) in the blood have been used as an index to control blood sugar levels in clinical practice for diabetic patients.[6] Diabetic patients have been shown to have significantly higher serum 3-deoxyglucosone (3-DG) levels than controls.[28] A lower nerve conduction velocity was also associated with higher serum 3-DG levels in patients with diabetes. As a result of excess blood glucose, AGEs are produced in various organs; that situation in turn increases oxidative stress. A hyperglycemic environment associated with diabetes is believed to increase oxidative stress, which can lead to diabetic complications.[29]

RAGE-AGE on PI3K/AKT and MAPK kinase signaling

Insulin receptor substrate-1 (IRS-1) is phosphorylated at serine residues, resulting in decreased enzymatic activity in the PI3K/AKT (Phosphatidylinositol 3-kinase /protein kinase B) pathway.[30] Inhibitor of NF-κB (IκB)[31] transduction promotes the phosphorylation- and ubiquitination-mediated proteasomal degradation of inhibitors of IκB proteins, thereby releasing NF-κB from cells.[31] Inflammatory cytokines (IL-6, TNF-α, and IL-1β) are upregulated by the activated master transcription factor NF-κB, which translocates to the nucleus and increases insulin resistance.[32,33] MAPK, p38, and Protein kinase C (PKC) are activated as a result of AGEs/RAGE signaling and increased inflammation. Via downregulation of insulin receptor expression, impaired IRS-1 tyrosine phosphorylation, and promoted IRS-1 serine phosphorylation, these kinases directly trigger insulin resistance.[34] The extracellular signal-regulated kinases1/2 (ERK1/2) signaling pathway has also been implicated in diabetes as a promotor of adipogenesis by upregulating several diabetogenic factors.[35] Insulin resistance in muscles is induced by signal transducer and activator of transcription 3 (STAT3) by upregulating Fbxo40, an E3 ubiquitin ligase specific to muscles.[35] It has been shown that the interaction between hyperglycemia and AGE accumulation, protein kinases, and inflammation leads to sustained activation of transcription factors such as NF-κB, Hypoxia-Inducible Factor (HIF-1), Activator protein 1 (AP-1), and STAT3 in target cells, further reducing insulin sensitivity.[36] By binding to the proximal promoter region of RAGE, the chronic low-grade inflammation that is caused by persistent activation of NF-κB also positively regulates RAGE expression.[37]

AGEs and vascular complications

A significant number of macrovascular and microvascular complications are associated with AGEs. Studies have shown that AGEs affect vasculature via inflammation and oxidative stress, glycation of Low-Density Lipoprotein (LDL) and High-Density Lipoprotein (HDL), activation of the pro-inflammatory inducible Nitric Oxide Synthase (iNOS), decreased availability of Nitric Oxide (NO).[38] This situation can result in toxic concentrations of NO. Peroxynitrite is formed after NO reacts with oxygen radicals to create an extremely reactive metabolite that interacts with proteins and DNA to trigger nitrative stress, DNA damage, and apoptosis of vascular cells.[39] Animal models and *in vitro* studies have shown that atherosclerosis is the product of the association among AGEs and endothelial cells, platelets, monocytes/macrophages, and vascular smooth muscle cells.[40,41]

Liu *et al.* demonstrated that methylglyoxal decreases endothelial angiogenesis *in vitro* via RAGE-mediated, peroxynitrite-dependent, and autophagy-induced degradation of vascular endothelial growth factor receptor 2 (VEGFR2); these authors partially explained the mechanisms of impaired angiogenesis induced by AGEs using endothelial cells and mouse aortas.[42] VEGFR2 acts as the principal receptor for vascular endothelial growth factor signaling to trigger vasodilation, endothelial cell migration, and proliferation.[43] Diabetic patients and healthy individuals both exhibit strong activation of platelets by AGEs.[44] During degranulation, specific granules in the platelets fuse with the plasma membrane. RAGE may be accordingly translocated to the surface of platelets.[44] A significant increase in platelet glycoproteins, including glycoprotein GPIIb, has also been observed. NADPH hyperactivity is observed when AGE binds to RAGE, leading to ROS generation, cyclooxygenase activity, and thromboxane A2 generation in platelets. This situation can contribute to micro-thrombosis.[45] In order to understand the specific mechanisms responsible for these effects, additional studies are necessary.

AGEs and cognitive disorders

Dementia, amnesia, and delirium are examples of cognitive disorders, which are associated with a loss of spatial and temporal orientation. An individual may experience a temporary or progressive cognitive disorder depending on the underlying cause. There is increasing evidence that elevated levels of AGEs in the bloodstream are emerging as a risk factor for cognitive impairment and are linked to neurodegenerative diseases such as AD and Parkinson's Disease (PD), as well as mental illnesses.[46,47] AGEs represent a rare form of protein molecule found in β-amyloid plaques and Neurofibrillary Tangles (NFTs), and are formed when carbonyl or dicarbonyl compounds react with lysine or arginine groups on proteins. There is a larger number of AGEs present in plaque fractions of AD brains compared with samples from age-matched controls. NFTs and senile plaques have also been shown to contain AGEs.[48] It is now widely accepted that AGEs contribute actively to the progression of AD; however, some authors have suggested that they are very late-stage markers of disease.[48] Amyloid-β (Aβ), and RAGE-positive granules are co-located in the regions surrounding blood vessels, where astrocyte end-feet are often found. If these granules are co-localized in these areas, it may

be related to changes in the vascular environment or inflammatory responses affecting the blood-brain barrier. This situation suggests that glycated Aβ is taken up by RAGE for degradation via the lysosomal pathway.[49] Diabetes mellitus has also been linked to AD due to the increased deposition of brain AGEs and RAGEs, which may represent a part of a common pro-inflammatory pathway.[49] Immunohistochemical analyses of human postmortem samples have demonstrated that patients with AD and diabetes have significantly higher levels of AGEs, more amyloid plaques, higher levels of RAGE- and tau-positive cells, and greater microglial activation in their brains than patients with only AD.[50]

Li *et al.* reported that glycation of Aβ elevated RAGE levels and activated glycogen synthase kinase-3 (GSK-3).[51] Inhibition and reversal of this pathway to prevent neuronal damage were achieved via RAGE antibodies or GSK-3. Both *in vitro* and *in vivo* studies have demonstrated that AGEs upregulate the expression of amyloid precursor proteins, which in turn increases the levels of β-amyloid. The ROS inhibitor N-acetyl-L-cysteine can effectively prevent increases in β-amyloid.[52] In the neurons of the hippocampus and parahippocampal gyrus, the AGE-derived product glyceraldehyde occurs in cytosol; it inhibits the carbonyl stress-causing glyceraldehyde-3-phosphate dehydrogenase (GAPDH). It is therefore believed that the brain accumulates glyceraldehyde as well as MG.[53] AD results from this vicious cycle; it is clear that glycation plays a significant role in AD.

PD patients exhibit higher levels of glycation than age-matched control subjects in the cerebral cortex, amygdala, and substantia nigra.[54] Additionally, patients with PD have been found to express RAGE. Each of the 15 lysine residues in Alpha-synuclein is a potential glycation site.[55] As a result of glycation, protein aggregates are nucleated and oligomers form. This process in turn stabilizes the oligomers. It is important to note that alphasyn is now considered to be more toxic as an oligomeric species than as an aggregate.[56] Guerrero *et al.* have proposed that glycated synuclein may be toxic to neuronal cells via multiple mechanisms.[55] It is believed that oligomeric and monomeric forms of glycated alpha-syn increase oxidative stress within cells. The result is a deleterious cycle leading to the death of neuronal cells. Glycated alpha-syn oligomers may additionally not be cleared by proteasomes; that situation can result in neuronal death from proteasome dysfunction. Proteasome-deficient cells are eliminated via autophagy.[57] In addition, glycated alpha-syn may cause neuroinflammation by activating microglia.[58] The release of NF-κB may be triggered by interactions between glycated alpha-syn and RAGE. Neuronal cells are damaged by these signaling proteins, which initiate signaling cascades in the brain (Figure 3).[59] In addition to regulating RAGE expression, NF-κB induces the expression of RAGE proteins. NF-κB is released more readily with increased RAGE receptor expression.[59]

The interaction between elevated levels of AGE and RAGE would enhance the production of ROS. An elevation in ROS levels would lead to AD via neuronal damage and the development of Aβ and Aβ plaques. The interaction of sRAGE with AGE would result in a diminished quantity of AGE available to engage with RAGE, hence reducing the production of ROS. A reduction in sRAGE levels would elevate the production of ROS, contributing to AD.

AGEs and kidneys

Pathologically decreased AGE turnover may result from the quantitation of AGEs trapped in the circulatory system or the accumulation of new AGEs produced locally from preexisting proteins.[60] Diabetic nephropathy is associated with AGE formation and deposition. RAGE plays a role in vascular damage, glomerulosclerosis, and podocyte activation in diabetic nephropathy.[61] There is a high likelihood that AGEs will accumulate in the mesangial cells, podocytes, basement membranes, tubules and endothelial cells of the kidneys. In addition to delayed protein turnover, renal diseases can also lead to an accelerated oxidative stress, which increases the likelihood of AGE formation and accumulation. As a result of this increase, AGEs progress, creating a vicious cycle.[62] Prominent characteristics of diabetic nephropathy include a thickening of the basement membranes of the kidneys and the mesangial extracellular matrix in the tubulointerstitial space, damage to the microvascular system, and the presence of fibrotic changes.[61] Uesugi *et al.* examined the immunohistochemical localizations of glycoxidation products in glomerular lesions and the vasculature of patients with early and advanced diabetic nephropathy.[62] Enhanced accumulation of Carboxymethyl Lysine (CML) was noted in the expanded mesangial matrix and early nodular lesions were observed to have thickened glomerular capillaries in the arterial walls of patients with advanced diabetic nephropathy; similar results were not noted in the kidneys of healthy individuals.[63]

CML modifications of proteins engage cellular RAGE in a physiologically relevant manner.[64] A study used Nuclear Magnetic Resonance Spectroscopy (NMR) spectroscopy to demonstrate that free CML and carboxyethyl lysine were unable to bind to RAGE. That finding indicates that modified amino acids need to be incorporated into negatively charged regions of AGE proteins in order to interact with it.[65] As a consistent cellular response, the interaction between AGEs and RAGE triggers intracellular signaling that activates the proinflammatory transcription factor NF-κB. Due to the presence of NF-κB binding sites in the promoter region of the *RAGE* gene, the activation upregulates gene expression; *RAGE* expression is also activated by TNF-α through NF-κB. RAGE is activated by ligands that produce ROS. Activated NADPH oxidase is a central target of RAGE and may have a significant impact on cellular functions.[66] Extracellular AGEs, as well as their interactions with RAGE

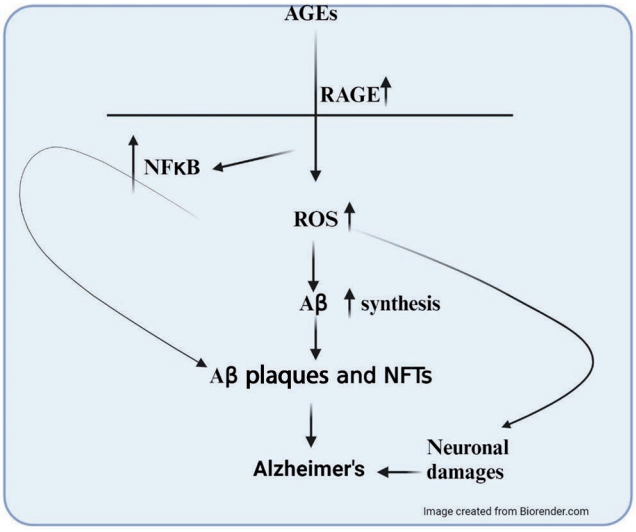

Figure 3. Schematic representation of the Advanced Glycated End products-Receptor Advanced Glycated Endproduct (AGE–RAGE) axis in the etiology of Alzheimer's disease. NF-κB, Nuclear Factor kappa-light-chain-enhancer of activated B cells, ROS, Reactive Oxygen Species, NFT, Neurofibrillary Tangles. (Image created with Biorender.com dated Aug 15, 2023; one month subscription).

receptors and other binding proteins, contribute to changes in renal cell signaling; intracellular AGEs affect MAP kinase and NF-κB signaling. Chymase is a member of a vast group of serine proteases found in mast cells. It plays crucial roles in several processes such as blood coagulation, apoptosis, inflammation, and host immunity. In diabetes, chymase plays an important role in generating angiotensin II.[66] By activating the RAGE-ERK1/2 MAP kinase pathway, AGEs induce the expression of chymase and the generation of angiotensin II in human smooth muscle cells. AGEs mediate diabetic complications by activating Suppressor of Mothers against Decapentaplegic (Smad signaling) in renal and vascular cells.[67,68] RAGE-ERK-p38-MAP kinase-Smad3 cross-talk induces tubular expression of connective Tissue Growth Factor (TGF) independent of TGF-beta in the presence of AGEs. AGEs directly alter tissue structure and function by excessively cross-linking matrix molecules such as collagen.[69]

Podocytes actively uptake AGEs. Bovine serum albumin modified with AGEs induced p27Kip1 mRNA and protein expression in differentiated podocytes. An increase in necrotic, but not apoptotic, podocytes was observed following this induction. A study of podocytes in culture found that high levels of glucose increase the expression of mRNA and protein p27Kip1.[70] Podocyte hypertrophy was associated with increased expression of p27Kip1.[71] An angiotensin II receptor blocker attenuated the effects of high glucose on the expression and hypertrophy of podocytes, suggesting that some of these effects might be mediated by angiotensin II.[72] Furthermore, a recent study reported that podocytes express angiotensin type 1 and 2 receptors and that the angiotensin type 2 receptor is responsible for upregulation of RAGE expression in podocytes.[73] In order to achieve these effects, NF-κB must be activated.[74] Interactions between AGEs and RAGE have been implicated in podocyte pathology in diabetic nephropathy. A number of other renal diseases, including lupus nephritis (kidney inflammation), have also been associated with AGE-RAGE activation.[75]

AGEs and stroke

Stroke is a common, severe neurovascular disorder this is an important cause of disability and mortality.[76] During the acute phase of stroke, soluble RAGE levels are elevated in the blood.[77] RAGE is expressed on the surface of neurons and glial cells in the brain.[78] Patients with unilateral cerebral infarctions and mice with experimental strokes have been found to exhibit elevated levels of RAGE in biopsy samples taken one day after the stroke.[79] The cardio-cerebrovascular consequences of diabetes also depend on interactions between AGE-RAGE and oxidative stress. Following focal cerebral ischemia, the amount of irreversible damage and necrosis that results from AGE-modified proteins and peptides increases. As a result, the number of skin AGEs measured via Silent Atrial Fibrillation (SAF) is a useful metric for predicting the outcome of patients with diabetes mellitus who experience an ischemic stroke.[80] A significant proportion of accumulated AGEs interact with RAGEs in order to produce persistent vascular inflammation. A post-stroke inflammatory response associated with AGE-RAGE interactions has been linked to more severe brain damage and cardiac injury due to excessive downstream inflammatory indicators.[81,82] AGEs confer detrimental effects by activating signaling cascades via RAGE. Astrocytes, microglia, neurons, mononuclear cells, and endothelial cells are all examples of peripheral and central nervous system cells that express RAGE.[83] Diabetic patients' cardio-cerebrovascular risks are influenced by many factors, including hyperglycemia, vascular risk factors such as hypertension and dyslipidemia, and genetic, demographic, and lifestyle factors.[84,85] Due to their roughly doubled risk of an ischemic stroke compared with healthy individuals, diabetic individuals must take secondary prevention measures to prevent debilitating strokes. Lacunar infarcts can also be more subtle among diabetics; such events increase the risk of dementia and result in a faster loss of cognitive function from diabetes.[86]

RAGE is a mediator of ischemic brain damage and contributes to inflammation as well as to ischemic brain damage. Stroke appears to be associated with high-mobility group box 1 ligands released from necrotic cells.[87,88] RAGE has been shown to play a significant role in experimental models of cerebral ischemia.[89] A high level of RAGE in the blood is an independent predictor of poor outcomes for stroke in individuals with type 2 diabetes.[90] An inflammatory response mediated by High mobility group box 1 protein (HMGB1) may occur after a stroke mediated by RAGE.[91] The early stages of stroke are characterized by sustained oxidative toxicity and hypoxia in neurons. When microglia and astrocytes are activated, HMGB1 undergoes acetylation and phosphorylation, which decreases its affinity for DNA. In response to ischemia-reperfusion, HMGB1 is released passively into the extracellular space as cell membranes are destroyed.[92,93] Comprehensive therapeutic strategies are necessary to combat neurodegenerative damage and improve motor recovery to improve the quality of life for diabetic ischemic stroke patients. Diabetic ischemic stroke should be treated with a comprehensive therapeutic strategy that includes agents to reduce the AGE-RAGE axis, improved biomarkers for risk stratification, better renal dysfunction management, and adjunctive anti-inflammatory/antioxidant therapies.[94]

AGEs and cardiac diseases

Epidemiological evidence has revealed that AGE-RAGE interactions are associated with heart failure in humans.[95–97] Heart failure is independently associated with high serum levels of the specific AGE pentosidine.[98] One study examined patients suffering from congestive heart failure for CML- and N_{ε}-carboxy-ethyl-lysine (CEL)-related AGEs.[99] Plasma CML-AGE levels were related to disease prognosis and severity, but CEL-AGE levels were not associated with heart failure.[100] Another study performed left ventricular endomyocardial biopsies on 28 healthy patients and 36 patients with reduced Left Ventricular Ejection Fraction (LVEF).[101] Cardiomyocyte resting tension was more relevant in subjects with normal LVEF than fibrosis and AGE accumulation in the heart. A higher level of soluble RAGE was also observed in patients who had compared with patients who did not have.[102,103] According to these studies, serum soluble RAGE may serve as an independent prognostic factor and a stratification factor in patients suffering from heart failure.[104] In clinical terms, an accumulation of AGEs reduces arterial compliance and increases pulse pressure in the interstitial and vascular tissues. These cross-linked proteins, including laminin, elastin, and matrix collagen, undergo conformational changes that affect both their structural and functional characteristics.[105] As a result, they influence the physiological properties of matrix proteins (e.g., elasticity and hydrophobicity). Increased thrombogenicity and accelerated atherosclerosis at the coronary vascular level may confer both indirect effects of AGEs on endothelial dysfunction and direct myocardial changes as a result of cross-linking of proteins within the myocardial matrix.[106] In addition, systemic vascular effects can lead to an increase in the heart's afterload.[107,108] In light of this mechanism, interventions aimed at reducing AGE accumulation in cardiac patients would be beneficial. However, experimental and limited clinical evidence suggests that angiotensin receptor blockers and angiotensin-con-

verting enzyme inhibitors may reduce the formation of AGEs.[109] An alternative approach may involve interventions with benfothiamine or pyridoxamine in patients with conditions other than cardiac dysfunction to reduce AGE formation.

Conclusions

Circulating AGEs play a very likely role in human diseases; there are many diseases associated with oxidative stress caused by AGEs. AGEs are irrefutable contributors to oxidative stress, inflammation, and protein modification. As a potential approach to preventing chronic diseases, activation of RAGE by AGEs can activate the NF-κB pathway, increasing pro-inflammatory cytokines. Especially in endothelial cells, this causes vascular inflammation and atherosclerosis. AGE-RAGE interaction activates the MAPK pathway, which regulates cell proliferation, differentiation, and stress responses. This pathway promotes diabetic problems. The JAK/STAT pathway activated by the AGE-RAGE interaction in the kidneys can express fibrotic genes and cause diabetic nephropathy. Dietary awareness and restriction of AGE-rich foods can significantly reduce the accumulation of AGEs in the body. By minimizing the intake of foods cooked at high temperatures, such as fried, grilled, or roasted items, and opting for cooking methods like boiling, steaming, or poaching, individuals can lower their AGE consumption. Additionally, a diet rich in antioxidants from fruits, vegetables, and whole grains can help neutralize AGEs and mitigate their harmful effects. Overall, conscious dietary choices focused on reducing AGE intake and enhancing antioxidant consumption can play a crucial role in lowering AGE accumulation and improving long-term health outcomes.

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