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Review Article

Advanced Glycation End Products: A Review

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Abstract: On exposure to aldose sugar advanced glycosylation end products (AGEs) which may be proteins or lipids in nature undergo glycation. AGEs have been found to be prevalent in the blood of diabetic persons and they tend to accelerate atherosclerosis. Besides, the accumulation of AGEs in many different cell types also affect their structure and function. AGEs can also cause other effects that lead to a variety of microvascular and macrovascular complications through the formation of cross-links between molecules in the basement membrane of the extracellular matrix and by engaging the receptor for advanced glycation end products (RAGE). Activation of RAGE by AGEs results in alteration of the transcription factor, nuclear factor $_{k}$B and its target genes. Soluble AGEs activate monocytes, whereas AGEs in the basement membrane suppress the monocyte migration. AGE-bound RAGE also enhances the endothelial permeability to macromolecules. AGEs block nitric oxide activity in the endothelium and cause the production of reactive oxygen species (ROS). Since there are risisng evidences pertaining to adverse effects of AGEs on the vasculature of diabetic patients, different theraputic studies to inhibit AGEs are under investigations.
Keywords: Advanced glycosylation end products, diabetes mellitus, vascular function.

INTRODUCTION

As early as 1912, Louis Camille Maillard for the first time explained the browning of proteins in food and called it as Maillard reaction. This is also known as non-enzymatic glycation of proteins, or a process which links chronic hyperglycemia to a series of physiopathological alterations considered important in the development of chronic complications of different diseases like diabetes and hyperlipidemia.[1] The further rearrangement of these glycated proteins give rise to a stable Amadori product that degrades into a variety of compounds which are more reactive than the sugars from which they are derived. [2] These propagators again form yellow-brown, often fluorescent (some are non fluorescent), irreversible compounds, usually called Advanced Glycation EndProducts (AGEs) or Maillard products. [3] AGEs are formed in vivo in hyperglycemic environments and during aging and contribute to the pathophysiology of vascular disease in diabetic subject. [4]

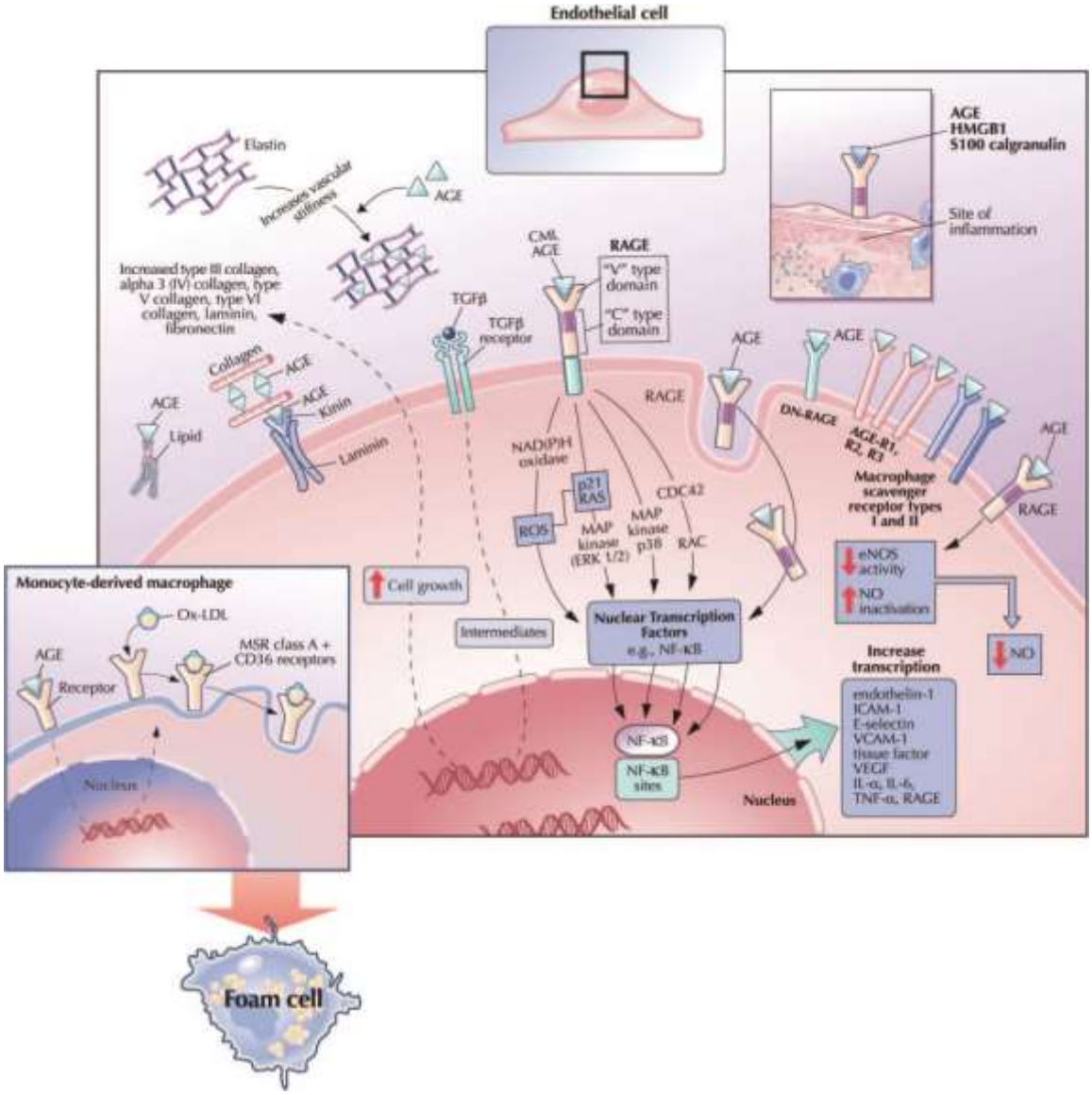
AGEs accumulate in the wall of blood vessels, where they may alter the cellular architecture and function. AGEs tend to contribute in both the microvascular and macrovascular complications of diabetes. As reviewed by Brownlee, [5] AGEs may also alter the extracellular matrix (ECM), modify the action of hormones, cytokines, and free radicals via involvement of receptors on cell surface, and an impact on the function of intracellular proteins.

This review summarizes AGEs formation and biochemistry, cellular receptors for AGE, AGE-induced effects on extracellular and intracellular functions.

Biochemistry of Advanced Glycation End Products

Major factors which proved to be crucial in the formation of AGEs include the rate of formation of glycoxidation from protein, the amount of sugar in blood, and the extent of oxidant stress in the environment. [6]. If one or more of these conditions is present, both intracellular and extracellular proteins may be glycated and oxidized. The AGE formation process or the Maillard reaction begins from Schiff bases and the Amadori product, a 1-amino-1-deoxyketose, produced by the reaction of the carbonyl group of a reducing sugar, such as glucose with proteins, lipids, and amino groups of nucleic acids. [7] During Amadori reorganization, these highly reactive intermediate carbonyl groups, called α_dicarbonyls or oxoaldehydes, products of which include 3-deoxyglucosone and methylglyoxal that accumulate. [8] Such build-up is known as “carbonyl stress.” The α_dicarbonyls have the ability to react with amino, sulfhydryl and guanidine, functional groups present in proteins. The reaction leads to denaturation, browning and cross-linking of the targeted proteins. [9] In addition, the α_dicarbonyls can react with lysine and arginine, functional groups on proteins, leading to the formation of stable AGE compounds, such as N^{ε}_(carboxymethyl) lysine (CML), which are nonfluorescent AGEs. [10] It has been found that

CMLs are also formed in vitro from LDL incubated with copper ions and glucose and therefore are believed to be both lipid and protein adducts. [11] AGEs thus formed remain nearly irreversible. [6] Various studies further provide the evidence that enzymes, like glyoxalase-1, have the ability to detoxify AGE precursors and inhibit AGE production. This is evident from the presence of deoxyfructose, a reduction product of 3-deoxyglucosone in human urine as well as plasma. [5]



The extracellular and intracellular effects of AGEs. In the ECM, AGEs form on a variety of different molecules, including lipids, collagen, laminin, elastin, and vitronectin. The formation of AGEs on ECM molecules alters the constitution of the matrix and increases stiffness. AGEs also activate the transforming growth factor (TGF)-β receptor to stimulate cell growth, leading to increased ECM production. AGEs that bind to RAGE on the endothelial cell surface lead to a signaling cascade, stimulating NAD(P)H oxidase and increasing ROS, p21 RAS, and MAPKs. In addition, the ligand-RAGE interaction also may stimulate signaling via p38 MAPK and Rac/Cdc. A key target of RAGE signaling is NF-κB. NF-κB is translocated to the nucleus, where it increases transcription of a number of different proteins, including endothelin-1, ICAM-1, E-selectin, and tissue factor. AGE and ligands for RAGE, such as HMGB1 and S100 calgranulins, trigger inflammatory pathways. AGE may decrease NO availability by the decreased activity of NOS and by quenching NO. sAGEs activate monocytes, causing increased expression of macrophage scavenger receptor (MSR) class A receptors and CD36 receptors, leading to increased OxLDL uptake and foam cell formation. DN indicates dominant-negative.

Receptors for Advanced Glycation End Products

Various receptors for AGEs have been well documented, one of which termed RAGE, initiates the intracellular signalling that disrupts cellular function through its recognition and binding of AGEs. Receptor for AGE (RAGE) is reported to be a member of the

immunoglobulin super family of receptors. [12] The human RAGE gene is on chromosome 6 in the major histocompatibility complex between genes for class II and class III. [13] Nuclear factor (NF) _κB sites, an interferon-γ response element, and an NF–interleukin-6 (IL-6) DNA binding motif are located on the RAGE promoter. NF- κB sites control cellular expression of RAGE and linking of RAGE to the inflammatory response. [14] RAGE has a 332–amino acid extracellular component, consisting of 2 "C"-type domains preceded by 1 "V"-type immunoglobulin-like domain. RAGE has a single transmembrane domain followed by a highly charged 43–amino acid cytosolic tail. The V domain in the N-terminus is important in ligand binding, and the cytosolic tail is critical for RAGE-induced intracellular signaling. A form of RAGE that lacks the cytosolic tail but stays embedded in the membrane where it binds AGEs functions as a dominant-negative RAGE is unable to transduce a cell signal on ligand engagement. [15] RAGE may be complexed with another polypeptide, termed LF-L, for its affinity to lactoferrin, at least, in certain cell types. LF-L can bind AGEs and can also bind noncovalently to the extracellular domain of RAGE. [16] RAGE is minimally expressed in normal tissue and vasculature. However, RAGE is upregulated when AGE ligands accumulate, an example of positive-feedback activation. [17] Upregulation of RAGE occurs on cells such as endothelial cells, smooth muscle cells, and mononuclear phagocytes in diabetic vasculature. [18] In blood vessels of diabetic subjects RAGE ligands include AGEs of at least 2 varieties: CML adducts and hydroimidazolones. [19] CML-AGEs are the most prevalent AGEs in vivo. CML adducts are signal-transducing ligands for RAGE, both in vitro and in vivo. [20] Hydroimidazolone AGEs are derived from methylglyoxal and 3-deoxyglucosone. [21] Other receptors, like AGE-R1 (oligosaccharyl transferase-48), -R2 (80K-H phosphoprotein), and -R3 (galectin-3), and the class A macrophage scavenger receptor types I and II, also are able to recognize and bind AGE ligands, but they have not been shown to transduce cellular signals after engagement by AGEs. [22] Instead, they tend to render the clearance and possible detoxification of AGEs. [23] AGE-R1 is a type 1 single transmembrane integral protein. AGE-R1 has a small extracellular N-terminal domain and a cytoplasmic C-terminal domain. AGE-R2 is an 80- to 90-kD protein involved in the intracellular signaling of various receptors, like the fibroblast growth factor receptor. [22] AGE-R2 contains a tyrosine-phosphorylated section in the plasma membrane of the cell. [24] AGE-R3, whose binding domain is at the C-terminus, also binds AGE ligands with high affinity. [25] Two class B scavenger receptors, CD36 and class B type I are also known to bind AGE ligands. CD36 is not involved in the clearance of AGEs from the circulation, but it plays an important role in the induction of oxidative stress in the cell. [26] AGE ligands interfere with scavenger receptor class B type I uptake of HDL cholesterol. [27] AGEs can bind to and are recognized by the class E scavenger receptor, lectin-like oxidized LDL receptor-1 (LOX-1), and AGEs increase LOX-1 expression in diabetic rats. [28] Fasciclin, epidermal growth factor–like, laminin-type epidermal growth factor– like, and link domain–containing scavenger receptor-1 and -2 (FEEL-1 and FEEL-2) also are scavenger receptors that bind AGEs. [29]

Effects of AGEs on Extracellular Function

General mechanisms through which AGEs contribute to diabetic complications include the following: (1) formation of cross-links between key molecules in the basement membrane of the ECM, permanently altering cellular structure and (2) interaction of AGEs with RAGE on cell surfaces, altering cellular function (the Figure). Formation of AGEs in the ECM occurs on proteins with a slow turnover rate. Accumulation of AGEs on proteins in the ECM results in formation of cross-links, which in turn can "trap" other local macromolecules. [30] AGEs are capable of altering the properties of the large matrix proteins collagen, vitronectin, and laminin, through AGE-AGE intermolecular covalent bonds, or crosslinking. [31] AGE cross-linking on type I collagen and elastin increases the surface area of ECM, and so the vasculature becomes more siff. [5] Glycation also increase synthesis of type III collagen, α3(IV) collagen, type V collagen, type VI collagen, laminin, and fibronectin in the ECM, most likely via upregulation of a transforming growth factor-β intermediate. [33] AGEs are also known to disrupt binding of the noncollagenous domain (NC-1) to the helix-rich domain on type IV collagen from the basement membrane and inhibit the formation of a matrix-like structure. [5] Formation of AGEs on laminin results in reduced binding to type IV collagen, reduced polymer elongation, and reduced binding of heparan sulfate proteoglycan. [34] Glycation of laminin and type I and type IV collagens are major molecules in the basement membrane, results in reduced adhesion to endothelial cells for both matrix glycoproteins. [35] In diabetic subjects, the glycation of these proteins can cause to disparities in the rate production, growth, and secretory activity of different types of cells. [36] Further studies suggest that AGE formation leads to a reduction in the binding of collagen and heparan to the adhesive matrix molecule vitronectin. [5] Apparently AGE-induced alterations of vitronectin and laminin may explain the reduction in binding of heparan sulfate proteoglycan, a stimulant of other matrix molecules in the vessel wall, to the diabetic basement membrane. [5] As evidenced by the increased production of lipid-linked AGEs in LDL samples from persons with and without diabetes AGEs also formed on lipids. Glycated LDL reduces nitric oxide (NO) production and suppresses uptake and clearance of LDL through its receptor on endothelial cells. [37]

Effects of AGEs on Intracellular Function

AGEs are also produced on intracellular proteins. Intracellular AGEs can change cellular properties that are critical in vascular homeostasis. [38] The rate of AGE production on intracellular proteins becomes slowest in the presence of glucose but it is more rapid with intracellular natural sugars, like fructose, glyceraldehyde- 3-phopshate, and glucose-6-phosphate. [5] There are reports that ten times more fructose-derived AGEs are formed after 5 days than glucose derived AGEs in vivo. [39] Intracellular production of AGE is significantly increased in endothelial cells after 1 week in a hyperglycemic environment. [40] Intracellularly, basic fibroblast growth factor is one of the proteins that may be glycated. [41] AGE modification of this protein can drastically reduce the mitogenic activity of endothelial cell cytosol up to 70%.[41] Circulating AGEs can also interact with endothelial RAGEs, which may cause perturbation of cellular properties, like as upregulation of the transcription factor NF-κB. [42] Activation of RAGEs by AGEs can transduce multiple signals, such as NAD(P)H oxidase, $p21^{ras}$, the mitogen-activated protein kinases (MAPKs), extracellular signal–regulated kinase 1/2 and p38, and the GTPases Cdc42 and Rac, resulting in activation and translocation of nuclear transcription factors, including NF-κB, which transcribes its target genes (the Figure). [43,44] Among these are endothelin-1, vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), E-selectin, tissue factor, thrombomodulin, vascular endothelial growth factor (VEGF), and likely, proinflammatory cytokines, including IL-1α, IL-6, and tumor necrosis factor-α, and RAGE itself. [45] Blockade of RAGE with anti-RAGE IgG or soluble RAGE (sRAGE), the extracellular ligand, results in suppression of NF-κB activation. [46]

Advanced Glycation End Products and the Endothelial Cell

Literature reveal that sAGEs are chemotactic for human blood monocytes both in vitro and in vivo. AGEs on the subendothelium are able to induce the migration of monocyte migration across an endothelial cell monolayer. [47,48] In human umbilical vein endothelial cells, inhibitors of NF-κB greatly reduce high glucose–induced monocyte adhesion, suggesting that the activation of NF-κB is essential in AGE-induced monocyte adhesion and migration[48]. Activation of RAGE by AGEs makes endothelium more permeable to macromolecules, yet another receptor-mediated effect of AGEs on the diabetic vasculature. [42] AGEs located on proteins, in addition to immobilized AGEs on the subendothelium, can also bind RAGE on the endothelium to induce hyperpermeability.[49] Administration of sRAGE results in inhibition vascular leakage in the intestine and skin of streptozotocin-treated rats. AGE-bound RAGE on the endothelium also results in alteration of the cell surface structure, from that of an anticoagulant to a procoagulant endothelium, via reduced thrombomodulin activity concomitant with increased tissue factor expression. [49]

Advanced Glycation End Products and the Macrophage

Although sAGEs are known to activate the migration of monocytes, but AGEs located in basement membranes inhibit monocyte migration, and there by induce a process called “apoptaxis.” AGEs have been reported to contribute to the expression of oxidized LDL (OxLDL) receptors in human monocyte–derived macrophages. [50] AGEs are also shown to induce gene expression of 2 important OxLDL receptors: macrophage scavenger receptor class A and CD36. [50] The increased expression of these receptors results in enhanced OxLDL uptake, causing foam cell transformation (the Figure). Activation of monocytes by AGE-modified human serum albumin also leads to expression of IL-1β and tumor necrosis factor-α mRNA. [51] There are reports that AGEs can also alter cellular coagulant properties, partly via the monocyte-produced procoagulant, tissue factor, and decreased expression of the endothelial anticoagulant cofactor, thrombomodulin. [42]

Advanced Glycation End Products and the Smooth Muscle Cell

It is reported that addition of AGE-albumin to rat pulmonary artery smooth muscle cells results in increased levels of GTP-bound $p21^{ras}$ and activation of ERK1 and ERK2 (ie, MAPKs), whereas addition of nonglycated albumin to the same type of cells yields basal levels of GTP-bound $p21^{ras}$ and nonactivated MAPKs.[52] The role of $p21^{ras}$ is critical for signal transduction of AGEs, as it becomes apparent when Cys^{118}, a molecular target of ROS on $p21^{ras}$, gets mutated and overexpressed in PC12 cells expressing RAGE. The mutated PC12 cells becomes nonresponsive to AGE albumin, whereas the wild-type cells normally respond to AGE-albumin by activating ERK 1/2 kinases. [52]

Advanced Glycation End Products Effects on NO

AGEs are known to reduce the bioavailability and activity of endothelium derived NO (Figure). Since NO can inhibit many of the mechanisms that contribute to atherosclerosis, such as leukocyte adhesion to the vessel wall, vascular smooth muscle growth, and platelet adhesion and aggregation, this effect of AGEs on NO may be relevant to atherogenesis. [53,54] Indeed, Hogan et al [39] have demonstrated that matrix-bound and sAGEs inhibit the antiproliferative effects of NO. Moreover, impaired vasodilation in diabetes may be a result of AGEs’reduction of NO activity. [55] The levels of serum AGEs in patients with type 2 diabetes are inversely related to the degree of endothelium-dependent and endothelium independent vasodilation. [56] Several mechanisms by which AGEs reduce or block NO activity have been proposed. One mechanism suggests that AGEs reduce

the half-life of endothelial NO synthase (eNOS) mRNA through an increased rate of mRNA degradation and reduced eNOS activity. [57] Another mechanism proposes that AGEs impair NO production via the binding of CML residues to endothelial AGE receptors, causing a reduction in phosphorylation of serine residues in eNOS, resulting in deactivation of the enzyme. [58] AGEs also may quench and inactivate endothelium-derived NO. [39] Also, the endothelial production of prostacyclin (PGI_2) is reduced by AGEs. In addition to affecting the activity of these 2 major vasodilators, AGEs also enhance the expression of endothelin-1, via NF-κB, in bovine aortic endothelial cells incubated with erythrocytes from patients with type 2 diabetes. [59] AGE-bound RAGE in the endothelium results in the production of reactive oxygen intermediates, triggered, at least in part, through the activation of NADPH oxidase. [60] AGE-RAGE interaction stimulates the production of reactive oxygen intermediates, which in turn activate a range of signaling pathways, the consequences of which include activation of NF-κB. [60]

The Specific Advanced Glycation End Products : CML-AGEs

AGE-RAGE–produced oxidative stress is known to activate NF-κB and affect the transcriptional activation of numerous cytokines and adhesion molecules, many of which are closely linked to inflammation and atherosclerosis, as discussed earlier. [60] Through the appearance of thiobarbituric acid–reactive substances (TBARS) and activation of NF-κB, mononuclear phagocytes are also affected by oxidative processes resulting from the presence of AGEs. In addition, AGEs found on the surface of erythrocytes can bind to RAGE, increasing TBARS levels and activating NF-κB. The source of reactive oxygen species (ROS) on erythrocytes of diabetic subjects is most likely AGEs bound to the erythrocyte surface, as oxidant stress is not produced following engagement of RAGE by antibodies. [61] There is induction of oxidant stress leading to activation of NF-κB, induction of heme oxygenase mRNA, and TBARS in the tissues of mice when infused with AGE- albumin. [60]

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