Advanced Glycation End Products and Diabetes Mellitus

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Persistent hyperglycemic state in type 2 diabetes mellitus leads to the initiation and progression of non-enzymatic glycation reaction with proteins and lipids and nucleic acids. Glycation reaction leads to the generation of a heterogeneous group of chemical moieties known as advanced glycated end products (AGEs), which play a central role in the pathophysiology of diabetic complications. The engagement of AGEs with its chief cellular receptor, RAGE, activates a myriad of signaling pathways such as MAPK/ERK, TGF-β, JNK, and NF-κB, leading to enhanced oxidative stress and inflammation. The downstream consequences of the AGEs/RAGE axis involve compromised insulin signaling, perturbation of metabolic homeostasis, RAGE-induced pancreatic beta cell toxicity, and epigenetic modifications. The AGEs/RAGE signaling instigated modulation of gene transcription is profoundly associated with the progression of type 2 diabetes mellitus and pathogenesis of diabetic complications.

hyperglycemia type 2 diabetes mellitus advanced glycation end products (AGEs)

1. Sources of Advanced Glycation End Products (AGEs)

Advanced glycation end products (AGEs) accumulation can be through either endogenous or exogenous sources [1]. The exogenous AGEs are present in a wide variety of food items [2]. Cigarette smoke also contains glycation products that are highly reactive and act as a precursor of AGEs formation [1][3]. Exogenous AGEs are found in high levels in the modern Western diet. The thermal processing of food, specifically by using dry heat technology in cooking such as frying, grilling, baking or barbecuing, results in substantial AGEs formation [3]. Food processing to enhance conservation and safety and to improve flavor and appearance also lead to the generation of diverse food-derived AGEs known as glycotoxins. [4][5][6]. The heterogeneity of AGEs depends upon the particular structure of protein-bound AGEs, which defines its novel modification to a particular native protein. The classification of AGEs into protein-bound, peptide-bound or free AGEs predict their rate of absorption or pinpoint potential transporters [7][8]. Depending on the chemical characteristics of dietary AGEs, only 10–30 percent of ingested AGEs are absorbed into the systemic circulation [7]. The mechanism of gastrointestinal metabolism and absorption of food-derived AGEs is yet to be fully elucidated [1][5]. However, it mostly depends upon the molecular weight of the products of protein hydrolysis and the type of required peptide transporters [9]. The unabsorbed AGEs that are delivered to the colon can affect gut microbiota homeostasis and induce an inflammatory response to modify gut integrity [1][3]. This local inflammatory response is associated with increased systemic inflammatory cytokines responsible for compromised glucose control [1][10]. It is now well documented that exogenous AGEs contribute significantly to the body's AGEs pool [1][7][10].

The predominant process of endogenous AGEs formation is through the complex, multistage glycation process Maillard reaction [11]. This nonenzymatic process of glycation is accelerated in hyperglycemic conditions, such as in diabetes mellitus. Maillard reaction generates highly reactive numerous intermediate carbonyl precursors of AGEs [12][13]. Other than this nonenzymatic reaction, dicarbonyls, also known as α-oxoaldehydes, are generated endogenously through glucose autoxidation, polyol pathway, and lipid peroxidation. Previous studies have shown that under sustained hyperglycemic conditions as in type 2 diabetes mellitus, glucose toxicity is induced by increased glucose flux through the glycolytic pathway [14]. The consequence of continuous glycolysis results in dihydroxyacetone phosphate (DHAP) accumulation due to the decline in a crucial glycolytic enzyme, triose phosphate isomerase (TPI), activity. Due to insufficient activity of the enzyme, the interconversion of DHAP and glyceraldehyde-3-phosphate (GAP) catalyzed by TPI is not efficiently possible, thereby leading to the spontaneous formation of the highly reactive bicarbonyl, methylglyoxal [15][16].

An increase in intracellular glucose levels is associated with oxidative stress, autoxidation of glucose, and channels glucose towards the polyol pathway [9][17][18][19]. Lipid peroxidation is also increased in diabetes to produce advanced lipid peroxidation end products (ALEs). Polyunsaturated fatty acids are oxidized to produce reactive carbonyl species such as malondialdehyde and methylglyoxal, leading to the synthesis of the well-characterized ALEs [20]. The dicarbonyl intermediates are the important focal point of endogenous AGEs formation. Additionally, dicarbonyl stress is also generated by ketone metabolism in uncontrolled hyperglycemia [7][20][21].

2. Pathophysiology of AGEs/RAGE in Diabetes Mellitus

Two primary mechanisms are involved in the AGEs-induced pathophysiology of diabetes mellitus. The AGEs exert their deleterious effects, either directly by trapping and cross-linking of proteins, or indirectly by binding to the cell surface receptor [1][13]. AGEs can signal through several receptors, however AGEs interactions with AGEs receptors and their role in mediating cellular responses are yet to be fully elucidated [7][22]. AGEs can modulate cellular functions through binding with Toll-like receptors, scavenger receptors, G-protein-coupled receptors, and pattern recognition receptors [22][23]. Among these, the most important cell surface receptor for AGEs is the receptor for advanced glycation end products (RAGE). It is a member of the immunoglobulin superfamily, which was initially identified and named for its ability to bind with AGEs [24][25]. One of the salient features of the receptor is its capability to bind a broad repertoire of ligands [25][26]. RAGE recognizes three-dimensional structures rather than specific amino acid sequences. This multiligand receptor is considered a pattern-recognition receptor because of its ability to identify the structure of ligand recognition sites [24][25][27].

The human *RAGE* gene is located on chromosome 6 close to major histocompatibility complex III (MHC class III), which indicates its involvement in immune responses [28][29]. The resulting transcribed mRNA translates into a protein of 404 amino acids with a mass of 45–55 kDa [25][30]. Full-length RAGE (fl-RAGE) is comprised of three domains, an extracellular domain (*N*-terminal V-type domain and two C-type (C1 and C2 immunoglobulin domains), a hydrophobic transmembrane domain, and a highly-charged amino acid cytosolic domain [24][25]. The V-type domain from the extracellular region, in particular, interacts with the potential extracellular ligands, while the cytoplasmic tail is critical for intracellular signaling and serves as a scaffolding for the initiation of signal

transduction [31]. In addition to the fl-RAGE, recently, numerous naturally occurring RAGE protein isoforms have also been described. The RAGE primary transcript undergoes alternative splicing and proteolytic cleavage of fl-RAGE under the control of yet-unknown pathways to produce truncated RAGE iso-forms [28][29][32]. The *N*-terminal truncated lacks the ligand-binding domain and is unable to engage glycated end products. The C-terminal truncation majorly forms a pool of soluble RAGE (sRAGE) including endogenous secretory RAGE (esRAGE) generated from alternative splicing and cleaved RAGE (cRAGE) derived from the proteolysis of membrane-bound fl-RAGE by metalloproteases [28][33]. The sRAGE lacks a transmembrane domain and functions as decoy receptor as it releases into the extracellular space and interacts with RAGE ligands preventing membrane-bound fl-RAGE/ligands cell signaling, as well as altering the generation and maturation of potential RAGE ligands. The dominant-negative RAGE (dnRAGE) lacks the cytosolic tail, thus blocking the activation and signaling of fl-RAGE [25][31]. Presumably, both the sRAGE and dnRAGE interfere with fl-RAGE receptor toxic signal transduction and play an antagonistic role in AGEs/RAGE signal transduction [24][33]. The fl-RAGE isoform is the most prevalent RAGE isoform and is present in numerous cell types throughout the body [7][25]. The membrane-bound fl-RAGE is responsible for intracellular RAGE signaling in response to extracellular ligands that lead to activation of the proinflammatory events [1][25]. The AGEs mediated RAGE activation promotes upregulation of RAGE receptor expression. This positive feedback loop indicates that ligand stimulated RAGE receptor acts as a propagation and perpetuation factor [34][35].

During chronic diabetes, persistent hyperglycemia leads to elevated levels of AGEs in the bloodstream, which by engagement to RAGE induces an array of signaling events. AGEs/RAGE interaction triggers a variety of downstream effectors including mitogen-activated protein kinase (MAPK), p38, stress-activated protein kinase/c-Jun *N*-terminal kinase (SAPK/JNK), Ras-mediated extracellular signal-regulated kinase (ERK1/2), and Janus kinase signal transducer and activator of transcription (JAK/STAT) pathway that in turn will lead to sustained activation transcription factors such as NF-κB, STAT3, HIF-1α, and AP-1 [7][36][37].

The activation of JNK promotes the phosphorylation of insulin receptor substrate (IRS-1) at serine residues that leads to negative regulation of insulin signal transduction and induces insulin resistance [38]. The phosphorylation of serine residues in the insulin receptor (IR) and IRS-1 molecule results in diminished enzymatic activity in the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) pathway. The RAGE transduction induced IκB kinase (IKKβ) activation promotes phosphorylation and ubiquitination mediated proteasomal degradation of inhibitor of NF-κB (Iκβ) proteins, thus releasing NF-κB. The activated master transcription factor NF-κB translocates to the nucleus and upregulates the expression of various inflammatory cytokines (IL-1β, IL-6, TNFα) that can cause insulin resistance [38]. The AGEs/RAGE signaling, as well as increased inflammation, leads to activation of MAPK, p38, and protein kinase C (PKC). These kinases will mediate insulin resistance directly by downregulating insulin receptor expression, impair IRS-1 tyrosine phosphorylation, promote IRS-1 serine phosphorylation, leading to defective insulin receptor signaling [38][39][40]. Additionally, recent findings have also implicated abnormal activation of the ERK1/2 signaling pathway in diabetes which will influence the upregulation of several diabetogenic factors and promote adipogenesis [41][42]. The increased inflammation further triggers the activation of additional mediators which increases inflammation, as well as activates the signal transducer and activator of transcription 3 (Stat3) [39]. STAT3 induces insulin resistance in muscles by leading to degradation of IRS-1 through the upregulation of F-Box

Protein 40 (Fbxo40), a muscle-specific E3 ubiquitin ligase [43]. Under similar conditions of hyperglycemia and AGEs accumulation, the interplay between RAGE-induced cellular dysfunction, protein kinases, and inflammation that lead to sustained activation transcription factors such as NF-κB, STAT3, HIF-1α, and AP-1 further attenuates insulin sensitivity in target cells [39][40][44][45]. The persistent activation of NF-κB, in addition to the perpetuation of chronic low-grade inflammation, positively regulates RAGE expression by binding to its proximal promoter region [7][46].

Recently, studies showed that RAGE/NF-κB signaling also activates NLRP3 inflammasome formation, which is a critical component of the innate immune system. The NLRP3 inflammasome in response to cellular stress-signals mediates caspases-1 cleavage and contributes to the maturation and secretion of key inflammatory cytokines IL-1β/IL-18 [47][48]. Various human studies establish a correlation between increased NLRP3 expression and insulin resistance [49][50][51]. The overexpression of RAGE also promotes de novo synthesis of NF-κB p65 (REL A), which results in a high level of transcriptionally active NF-κB, overriding the endogenous negative feedback mechanisms [46][52]. The NF-κB p65 directly induces insulin resistance by repressing the transcription of glucose transporter GLUT4 protein, codified by *Slc2a4* gene in skeletal muscles by binding to the *Slc2a4* gene promoter [53][54][55].

Such abiding AGEs/RAGE interaction, elevated levels of NF-κB, PKC, and NLRP3 inflammasome activation transduce ROS generation, via activation of nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase) [36]. Increased levels of ROS will overburden the activities of superoxide dismutase (SOD) and catalase and will diminish glutathione stores. This imbalance in the intracellular redox state will result in oxidative stress in the endoplasmic reticulum (ER), which is strongly interconnected to mitochondria through mitochondria-associated ER membranes (MAMs). MAMs through the exchange of metabolites and ions between these two organelles maintain cellular homeostasis. The increased ER stress will cause mitochondrial dysfunction, alter redox homeostasis, play a crucial role in damaging cellular processes and the infrastructure of the cell, and contribute to oxidative stress propagation [56][57][58]. The mitochondrial ROS production subsequently activates abnormal activation of several kinases such as MAPK, ERK, IKK, p38, JNK involved in stress responses, which will trigger the vicious cycle of inflammation and ROS generation [59][60]. A plethora of evidence suggests AGEs/RAGE signaling pathway, NF-κB activation, inflammation, and ROS generation are directly related to the pathogenesis of insulin resistance by increased IRS-1serine phosphorylation and degradation, thus blocking the insulin signaling pathway [55][59][61][62].

3. AGEs/RAGE Axis and Pancreatic Beta Cells

Hyperglycemia-induced AGEs load in the pancreas contributes to beta cell toxicity via activation of inflammatory cascades and oxidative stress [63]. High levels of AGEs upregulate RAGE expression in pancreatic islets, as observed in several studies [64]. The AGEs/RAGE axis triggers intracellular signal transduction and activates NF-κB transcription, resulting in chronic inflammation, mitochondrial dysfunction, beta cell impairment, and apoptosis [54][64][65].

Islet amyloid polypeptide (IAPP) is another major factor that contributes to pancreatic beta cell death in diabetes [66]. Substantial evidence reveals that RAGE selectively binds with toxic IAPP intermediates and transduces intracellular signals that lead to NADPH oxidase-mediated ROS generation, induce cellular stress, inflammation, and play a key role in islet amyloidosis–induced beta cell proteotoxicity [67][68]. The aberrant accumulation of these pathological aggregates leads to decreased beta cell mass and increased beta cell apoptosis, as observed in chronic diabetes [69][70]. Several studies showed that inhibition of the RAGE-by-RAGE neutralizing antibody or through the administration of sRAGE in either the in vitro or in vivo model, preserved beta cell morphology and blocked inflammatory mediators and amyloid formation [65][67][68]. Further research on AGEs/RAGE axis contributing to IAPP-induced islet beta cell toxicity can provide the missing pathological link for the diagnostic criteria and therapeutic intervention for beta cell preservation in chronic diabetes.

4. AGEs/RAGE Axis in Diabetic Complications

The engagement of RAGE by AGEs leads to sustained cellular dysfunction, recently termed as “metabolic memory” [71]. The metabolic memory is the long-term influence of previously accumulated AGEs that are capable of maintaining RAGE over-expression, sustained activation of NFκB, prolonged induction of tissue-specific inflammation, initiation and progression of long-term oxidative stress, which is persistent despite the reversal of hyperglycemia [72][73][74]. The phenomenon of this hyperglycemic memory, instigated by the AGEs/RAGE axis, is associated with the pathogenesis of diabetes complications [75][76]. Diabetes-related macrovascular and microvascular complications are responsible for the impaired quality of life, accounting for increased morbidity, disability, mortality, and contributing substantially to healthcare costs [77][78].

Extensive epidemiological data indicate that patients with type 2 diabetes are at higher mortality risk from cardiovascular disease (CVD) compared to non-diabetics, across different races, regions, and sex. The inadequate management of diabetes provokes hyperglycemia-induced cardiovascular events through various mechanisms [77][79]. Evidence supports a direct correlation between the AGEs/RAGE axis, activated signal transduction of MAPK and NFκB cascades and intracellular ROS generation, subsequently leading to the production of several inflammatory and profibrotic factors such as vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), plasminogen activator inhibitor-1 (PAI-1), monocyte chemoattractant protein-1 (MCP-1), and matrix metalloproteinase (MMP)-2 protein [80][81]. Increased expression of these prothrombotic species is involved in arterial stiffness, vascular calcification, and plaque accumulation in atherosclerosis-prone vessels [75][82]. AGEs/RAGE mediates the increase in oxidative stress and enhances the oxidation of low-density lipoprotein (LDL), which is the key player in the pathogenesis of CVD [83]. Oxidized LDL act as a ligand for RAGE, leading to the activation of multiple intracellular pathways such as NF-κB, p38, JNK, and MAPK, augmenting the expression of TGF-β, C-reactive protein (CRP), inflammatory cytokines, and PKC. This leads to increased vascular calcification and hardening of the medial layer of blood vessels, which ultimately contributes to the pathophysiology of CVD [84][85][86][87].

Moreover, the nonenzymatic modifications of collagens and lipoproteins by AGEs in large vessels will result in increased collagen deposition, altering the structural integrity of arteries, disarray of elastic fibers, and the

degeneration of smooth muscle tissue, which are key pathogenic factors in arteriosclerosis [88][89]. The accumulation of AGEs on long-lived matrix proteins (collagen, elastin) is associated with AGEs-related crosslinks which will result in increased arterial stiffness, and endothelial dysfunction and disrupt extracellular matrix-cell (ECM) interactions [90][91][92]. This nonenzymatic modification of collagen is not only implicated in CVD but also profoundly involved in nephropathy, inflammatory bowel disease, osteoporosis, neuropathy, and retinopathy [88][93]. The increased arterial stiffness associated with systemic microinflammation can lead to pressure fluctuations in the microvasculature of different organs, specifically kidneys, and may increase the risk of renal failure. [94][95]. According to the WHO global report in 2016, approximately 12–55 percent of incidences of end-stage renal disorders (ESRD) are attributed to type 2 diabetes [96].

AGEs are metabolic mediators of kidney damage as its correspondent receptor RAGE is expressed by several cell types in the kidney as podocytes [97], tubular epithelial cells, and mesangial cells [72][76]. In uncontrolled hyperglycemia, AGEs accumulation in kidneys is accelerated and it mechanistically activates diverse signal transduction cascades by binding to RAGE [76]. The downstream consequences of AGEs/RAGE interaction are through the activation of NF-κB, MAPK, JNK, and TGFβ, leading to ROS generation. The ROS burden will reduce antioxidant enzymes and cellular glutathione levels, resulting in the up regulation of NADPH oxidase, nitric oxide synthase (NOS), and cyclooxygenase (COX) [76][98][99]. These events will evoke monocyte chemoattractant protein-1 (MCP-1), leading to leukocyte infiltration, over-expression of various cytokines and intracellular adhesion molecules, extracellular matrix accumulation, increased angiotensin II levels, and calcium influx, which will further exacerbate the inflammation [75][76][100][101]. The hallmark of diabetic renal injury includes increased microalbuminuria, renal podocyte injury, podocyte protein accumulation, affected renin-angiotensin system, glomerular and tubular hypertrophy, and kidney fibrosis culminating in gradual loss of kidney architecture and function [90][99][102]. Furthermore, RAGE activation accelerates heparinase secretion, which disintegrates the glomerular filtration barrier by degradation of heparin sulfate, a fundamental part of the glomerular basement membrane (GBM) [90][103]. Several animal and human studies validate the involvement of AGEs/RAGE axis and stimulation of its downstream signaling pathways in the pathophysiology of diabetes and its associated micro-vascular and macro-vascular complications, such as cardiomyopathy, nephropathy, retinopathy, and neurodegeneration [72][74][75][76][101].

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