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Advanced Glycation End Products: Mechanisms in the Pathogenesis of Type 2 Diabetes and its Complications -

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is a complex, heterogeneous group of metabolic disorders characterized by insulin resistance and failure of pancreatic β-cell leading to chronic hyperglycemia. Hyperglycemia causes dysfunctions in multiple organs or tissues, which not only decrease life quality and expectancy, but are also becoming a problem regarding the financial burden for healthcare systems. Therefore, the continually increasing of diabetes worldwide, understanding the pathophysiology, the main risk factors, and the underlying molecular mechanisms may establish a basis for prevention and therapy. In this regard, research was performed revealing further evidence of formation of advanced glycation end products (AGEs), which are a complex and heterogeneous group of modified proteins and/or lipids with damaging potential, is one contributing factor. However, it has been reported that AGEs increase the level of reactive oxygen species formation and impair antioxidant systems, on the other hand the formation of some AGEs is induced *per se* under oxidative conditions. However, the role of AGEs in the pathogenesis of T2DM and diabetic complications if they are causal or simply an effect is only partly understood. This review will highlight the mechanisms involvement of AGEs in the development and progression of T2DM and the role of AGEs in the development of diabetic complications.

Keywords: Diabetes, Advance Glycation Products; Insulin Resistance; B-Cell Dysfunction; Diabetic Complications; Inflammation; Oxidative Stress.

INTRODUCTION

Diabetes mellitus is on the rise worldwide. Between 1980 and 2014, the number of people with diabetes has risen from 108 million to 422 million. This number is increase dramatically in the coming years, resulting in both health and economic challenges [1]. In general, diabetes mellitus is a group of metabolic diseases in which the pancreas is unable to produce insulin, insulin production is insufficient or cells cannot effectively use insulin [2].

Under diabetes conditions, there are several sources of reactive oxygen species, among them advanced glycation products (AGEs) [3]. AGEs are a group of heterogeneous products increasingly formed under high glucose level conditions, due to their potential damage, AGEs have been assumed to be involved in the pathogenesis of T2DM and it is complications [4,5]. Additionally, it was recently proposed that another source of AGEs, the diet, contributes to the development of T2DM .The Receptor for Advanced Glycation End products (RAGE) transduces the biological effects of a diverse group of binding molecules, or ligands [6].

The Receptor for Advanced Glycation End products was first identified for its ability to bind the AGEs, which accumulate in diverse settings such as diabetes, inflammation, oxidative stress, aging, and ischemia. In addition to AGEs, distinct ligand families of RAGE, including the S100/calgranulins, high mobility group box 1 (HMGB1), amyloid-peptide (A), and other ligands such as mac-1, phosphatidylserine (PS) and lysophosphatidic acid (LPA) have been identified [7]. The identification of these non-AGE ligands of RAGE expanded the possible milieus in which the biology of RAGE plays pathophysiological roles, such as in inflammation, autoimmunity, and degeneration of neuron [8]. This review will highlight the involvement of AGEs in the development and progression of T2DM. In particular, insulin resistance developments, β cell dysfunction and death also their role in diabetic complications.

AN OVERVIEW OF AGES IN DIABETES

The first link between diabetes and glycated protein when discovery of an altered form of hemoglobin known as HbA1c of patients with diabetes in 1968 [9]. The AGEs formation through the Maillard reaction, which occurs in three phases. First, reducing sugar reacts to a free amino acid mainly lysine and arginine, lipid or nucleic acid, in a non-enzymatic pathway to generating Schiff a Schiff base. A Schiff base is a compound that has the double bond of a carbon to nitrogen. However, Amadori products are relatively unstable so that further parallel and consecutive reactions occur, eventually leading to the formation of an irreversible form of AGE [10].

The initiation of the reaction depends on the concentration of glucose and takes it is place within hours. However, if the glucose concentration decreases, this reaction is reversible [10]. The Maillard reaction is the most common known pathway to form AGEs. Not only during the stages of the Maillard reaction, but also in the intermediates or byproducts in autoxidation of glucose, lipid or the polyol pathway, high reactive carbonyl compounds are formed, such as glyoxal, methylglyoxal or 3-deoxyglucosone are formed [10,11]. Increased concentrations of glyoxal, methylglyoxal as well as 3-deoxyglucosone have been found in the plasma of patients with T2D. Glyoxal, for example, causes Nβ-(carboxymethyl) lysine (CML) formation which is at present the best characterized AGE. Further AGEs formed by glyoxal are glyoxal-derived lysyl dimer (GOLD), Nβ-(carboxymethyl) arginine (CMA), or S-carboxymethylcysteine [12].

Many AGEs are formed by a combination of oxidation with glycation so the reaction called glycoxidation products is triggered by oxidative stress [13]. Two important AGEs form by glycoxidation are pentosidine and Carboxymethyl-lysine (CML). This process takes place in weeks or months, it is an irreversible reaction, the complexity, and diversity of AGE formation makes clear why substances belonging to the group of AGEs are so heterogeneous regarding their chemical and physical properties. Carboxymethyl-lysine, pentosidine, pyrraline, and methylglyoxal (an α-oxaldehyde), they have been used as biomarkers for test the formation of AGEs [14].

A diabetic patient , the formation AGE is accelerated due to high concentration of glucose , AGE precursors and oxidative stress increased levels of AGEs, among them ML, Furthermore, AGEs accumulation in diabetic tissue was shown to correlate with diabetic complications [15]. The damaging potential of AGEs results from direct alterations on both protein structures and functions due to AGEs *per se* or the cross-linking effect of some AGEs. AGEs are found in the extracellular matrix and thus modified matrix proteins impair matrix-matrix and matrix-cell interactions [16].

Besides direct changes in both structures of protein and functions, AGE-mediated damage occurs by binding of AGEs to the RAGE. The ligand binding to RAGE, that will activate NAPDH oxidases activity and thus increases formation ROS intracellular [17]. High level of ROS leads to AGE formation, which triggers all described damaging

mechanisms mediated by AGEs, also activates the transcription factor nuclear factor kappa B (NFβB). Activation of NFβB increases the expression of proinflammatory cytokines such as interleukin-6, tumor necrosis factor and monocyte chemoattractant peptide 1 (MCP-1) as well as RAGE itself [18].

ADVANCED GLYCATION END PRODUCTS AND INSULIN RESISTANCE

Insulin resistance defined as a condition when cells are not able to appropriately respond to the hormone of insulin, which mediates the uptake of glucose. Although not all persons with insulin resistance develop T2DM, it is one relevant factor, which increases the risk for diabetes develop In turn, genetic as well as environmental factors, especially obesity and sedentary behavior, increase the risk for insulin resistant. There is more evidence that AGEs are another risk factor for the development of insulin resistance [19].

Glycated albumin was shown to induce the expression of tumor necrosis factor alpha (TNFβ) which suppresses insulin signaling [20]. Furthermore, protein kinase C alpha (PKCβ) was found as a target of glycated of serum albumin, which is leading to increased serine/threonine phosphorylation of insulin receptor substrate (IRS) 1 and 2 but it impairs their ability to undergo insulin-induced IRS tyrosine phosphorylation. By inhibiting insulin signaling phosphatidylinositol 3-kinase/protein kinase B pathway and inhibition of insulin-mediated metabolism of glucose [21].

Another possible mechanism contributing to insulin resistance is the direct glycation of insulin, glycation sites on insulin have been found *in vivo* as well as when cells and islets were cultured under hyperglycemic conditions, the last possible factor contributing is inhibited the differentiation of 3T3-L1 cells by Glucose-, glyceraldehyde-, or glycolaldehyde-derived AGEs [22]. Further, these AGEs inhibited glucose uptake into 3T3-L1 cells, regardless of the presence or absence of insulin, which was completely prevented by neutralizing antibody raised against RAGE. AGEs increased the intracellular reactive oxygen species (ROS) generation in 3T3-L1 adipocytes, and the effects of AGEs on glucose uptake were completely blocked by the treatment with an anti-oxidant, *N*-acetylcysteine. In addition, AGEs induced the expression of monocyte chemoattractant protein-1, which has been implicated in the development of obesity-associated insulin resistance in adipocytes [23].

THE ROLE OF AGES IN B CELL DYSFUNCTION AND B CELL DEATH

There is a growing evidence that AGEs not only contribute to insulin resistance, also β cells damage leading to impaired functions or even death of the cells. The cytotoxic potential of AGEs on pancreatic β cells was investigated in a number of studies. Shu *et al* [23] reported that Tribbles homolog 3 (TRB3) to damage insulinoma cells (INS-1 cells) and resulted in the apoptosis of INS-1 cells. TRB3 regulated nicotinamide adenine dinucleotide phosphate oxidase activity, promoted ROS synthesis and resulted in oxidative stress in INS-1 cells through the protein kinase C β2 pathway. In contrast, decreased proliferation but ROS-induced cell death in HIT-T15 cells due to treatment with ribose-modified serum was observed by Puddu *et al.* [24] Moreover, Zhu *et al.* indicated that apoptosis in β cells characterized by caspase activation, cytochrome c release and reduced expression of anti-apoptotic bcl2 might be due to RAGE [25].

Further evidence for the AGE-mediated decline in insulin secretion was given by Zhao *et al.* [26] they showed that AGEs block the activity of cytochrome c oxidase and production of adenosine triphosphate (ATP) in islets isolated from mice. Impaired insulin secretion that leads to increases the level of glucose levels which were accompanied by the increased formation of •NO and increase expression of inducible nitric oxide synthase (iNOS) suggesting that AGEs cause the induction of iNOS so that increasing concentrations of •NO inhibit cytochrome c oxidase activity and ATP production (Figure 1). ATP is necessary for insulin secretion as ATP causes the shutdown of ATP-sensitive potassium channels leading to membrane depolarization and the influx of Ca2+. Increased intracellular Ca2+-concentrations trigger the exocytosis of insulin granules [27]. Low ATP levels inhibit this process. Another factor contributing to reduced insulin secretion is the decline in insulin gene transcription. Shu *et al.* reported the impaired insulin secretion of β cells as a result of the downregulation of insulin transcription [26]. They identified that the transcription factor FoxO1 (Forkhead box protein O1) accumulates in the nucleus which in turn decreases the expression of the transcription factor PDX-1 (pancreatic and duodenal homeobox-1) by reducing protein stability Figure 1.

THE ROLE OF AGES IN DIABETIC COMPLICATIONS

Diabetics have an increased risk for the development of several diseases including cardiovascular, kidney, eye, nerves and skin diseases. Most relevant for the development of diabetic complications is the exposure to hyperglycemia. One of the most important injuries which arise from hyperglycemia is damage to the vascular system, if an injury occurs on large or small blood vessel most diabetic diseases can be accordingly grouped into macro- or microvascular complications, respectively. Several mechanisms leading from hyperglycemia to diabetic diseases have been described [28].

Role of AGEs in Ischemic Heart Disease and Atherosclerosis

As already mentioned, the diabetes patients are at high risk of developing cardiovascular disease, one of the common type of cardiovascular diseases is ischemic heart disease in which the blood

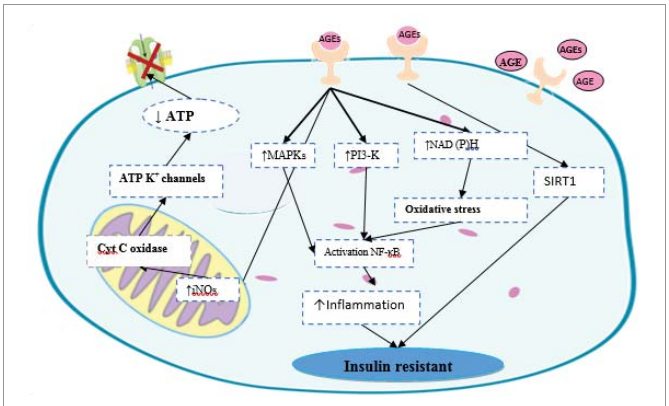

Figure 1: Mechanisms of AGEs leading to insulin resistance in insulin resistance in insulin-sensitive according to [22,28] modification. AGEs are contributing to insulin resistance due to direct modification OF INSULIN, which alters insulin action resulting in impaired glucose uptake, inhibited insulin clearance or further increased insulin secretion. Furthermore, AGEs may contribute to insulin resistance via increased expression of RAGE and decrease expression of SIRT1. AGEs affect insulin signaling and trigger inflammation via stimulation of PKC β and upregulation of TNF α SIRT1 depletion cause changes in insulin signaling and induces inflammation.

supply to the heart is decreased often due to plaque formation in the arterial wall [29]. The association between AGEs and ischemic heart disease of patients with T2DM was investigated in some clinical studies, Borsa et al (2009) found that the atherogenic index was an independent predictor of soluble RAGE levels and AGEs/sRAGE ratio values in furthermore, serum AGE levels may predict ischemic heart disease mortality in persons with T2DM [29].

Atherosclerosis is the underlying cause of most ischemic heart diseases and it has been suggested that AGEs are involved in the development of atherosclerosis the studies identified AGE-mediated mechanisms related to endothelial dysfunction, inflammation and lipid modifications. In particular, it was found that AGEs lead to endothelial dysfunction through their pro-apoptotic effect on both endothelial cells and endothelial progenitor cells [30]. Moreover, AGEs stimulate the expression of genes such as Monocyte Chemoattractant Protein-1(MCP-1), intercellular adhesion molecule 1, vascular cell adhesion molecule 1 and plasminogen activator inhibitor1 [31]. This mediates recruitment and adhesion of inflammatory cells to the vessel wall or further inhibition of fibrinolysis. The expression of MCP-1 and adhesion molecules can be induced by endothelin-1, its expression in turn, is also stimulated by AGEs. In porcine coronary fibroblasts, it was found that AGEs induce the mRNA expression of interleukin- 6, vascular cell adhesion molecule 1 and MCP-1 followed by increased inflammation and leukocyte adhesion [32].

The atherogenic properties of AGEs could be further attributed to the •NO quenching effect of AGEs furthermore, AGEs impair the synthesis of •NO by decreasing it expression as well as the activity the activity of endothelial •NO synthase and •NO mediates a series of intracellular effects that lead to endothelial regeneration, vasodilation, decrease of platelet adhesion, and leukocyte chemotaxis therefore, defects in •NO production and activity are supposed to be major mechanisms of endothelial dysfunction and atherosclerosis in the diabetic patients [33,34].

ROLE OF AGES IN DIABETIC NEPHROPATHY

The kidney is a target for AGE-mediated damage and is a contributor to circulating AGE concentrations as seen in settings such as diabetes because the kidney is the major site of clearance of AGEs [35]. Several experimental studies have clearly demonstrated a pathogenic role for AGEs and RAGE in diabetic nephropathy. Diabetic animals have significant high in renal AGEs and these abnormalities have been linked to different structural aspects of diabetic nephropathy, including glomerular basement membrane thickening, mesangial expansion, glomerulosclerosis, and tubulointerstitial fibrosis [36].

Advance glycation product albumin administration in murine models has resulted in changes, similar to that observed in diabetic nephropathy, including glomerular basement membrane thickening, mesangial matrix expansion, increased collagen IV and Transforming growth factor beta 1 expression [37]. The strongest evidence of a role for AGEs in the increase of diabetic nephropathy has come from studies targeting the AGE-RAGE pathway. Specifically, renal pathological changes are decreased by AGE formation inhibitors such as aminoguanidine. (±)-2-isopropylidenehydrazono- 4-oxo-thiazolidin-5-ylacetanidilide (OPB-9195), and ALT-946 as well as with agents that are postulated to reduce AGE accumulation such as the putative cross-link breaker ALT-711, also known as alagebrium [38-40].

DIABETIC RETINOPATHY

AGE-albumin-induced pericyte death has been assumed to be caused by the interaction of AGE with RAGE, studies reported that AGEs induce ROS formation and decrease protein kinase B/Akt. Or further platelet-derived growth factor signaling contributing to reduced pericyte, survival. Pericytes are cells, which cover capillaries in the retina, and their loss is an early event in diabetic retinopathy followed by the acellular capillaries (capillaries devoid of cells) formation, both microaneurysms and vascular basement membrane thickening. The crosslink of pericycte with endothelial cells is necessary for the maintenance of the blood-retina barrier, so that pericycte loss is also associated with the breakdown of the barrier [41].

The blood-retinal barrier regulates the flux of nutrients, fluids and other blood components into the retina and its breakdown may cause the development of macular edema, which is a main cause for vision loss in diabetes. Another mechanism leading to the breakdown of the blood-retinal barrier is the induction of retinal leukostasis, a state of chronic inflammation, which may contribute to endothelial cell death and increased vascular permeability [42]. The involvement of AGEs in this process has been shown by Moore *et al.* [43] AGEs induce NFβ-B DNA binding, intercellular adhesion molecule 1 expression and further leukocyte adhesion to retinal endothelial cells. *In vivo*, AGE-albumin injection into mice resulted in a breakdown of the blood-retina barrier.

CONCLUSION

High concentrations of different AGEs in particular, accumulation in both the tissue and serum diabetic persons have an important role in the pathogenesis of diabetic complications. The chemical nature of many byproducts of AGEs and their precise role in the development of diabetic complications is under intense investigation. There is much interest on the role of RAGE in the pathogenesis of diabetic complications and the molecular mechanisms involved are being unraveled. The possibility of reducing glycation and tissue AGEs or by AGE-RAGE interactions is still controversially discussed, which could delaying or preventing the onset of diabetic complications. Nevertheless, decrease of hyperglycemia-induced AGE formation as well as the restriction of AGE-rich food items both present targets for therapeutic approaches against the pathological events in diabetes and associated diseases.

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