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Review Article

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Advanced Glycation End Products (AGES): Pathological Entanglement

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Abstract Advanced glycation end products (AGEs) are proteins or lipids that become glycated as a result of exposure to sugars. AGEs are considered as a heterogeneous group of compounds that rise non-enzymatically by the reaction of reducing sugars and other α-carbonylic compounds with amino groups, not only with proteins but also with lipids and nucleic acids. The formation of AGEs is a key pathophysiological event not only in diabetic complications but also in widespread pathologies such as Alzheimer's disease, Parkinson's disease, hypertension, chronic renal failure, decreased skin elasticity, erectile dysfunction, pulmonary fibrosis and atherosclerosis. AGEs once formed disproportionately, initiate a wide range of abnormal responses in cells and tissues that include inappropriate expression of growth factors, alterations in growth dynamics, accumulation of extracellular matrix, promotion of vasoregulatory dysfunction, initiation of death pathways, generation of reactive oxygen species and inflammatory cytokines. Although several anti-AGE compounds have been studied and have been found beneficial in several pathologies yet their unexplored, vast and tremendous potential is to be realized.

Keywords advanced glycation end products, atherosclerosis, Alzheimer's disease,cancer, diabetes

Introduction

Carbohydrates are indispensable nutrients for life but due to the presence of a carbonyl group, reducing sugars (glucose) react non-enzymatically with amino groups on proteins in glycation reactions (Maillard reactions). This reaction is divided into early and advanced phase reactions: the earlier phase covers the reaction progression up to the Amadori rearrangement, and the latter covers the reaction through the subsequent alterations of oxidation, dehydration, condensation etc. eventually generating advanced glycation end products (AGEs) [1].

In 1912 Maillard first observed a browning reaction by heating glycine and glucose now called Maillard reaction which is the driving force of AGEs formation. AGEs are both consumed and endogenously formed; their accumulation is accelerated under hyperglycemic and oxidative stress conditions. AGEs exert their deleterious effects by either accumulating in the circulation and tissues or by receptor-mediated signal transduction. Several receptors bind AGEs, some are specific and contribute to clearance of AGEs, whereas others, like the RAGE receptors, are nonspecific, associated with inflammation, oxidative stress and considered to be mediators of the afore mentioned AGE-related diseases.

AGEs are important in clinical science as they are associated with oxidative stress and inflammation that eventually cause most chronic diseases including cardiovascular diseases, diabetes, chronic kidney diseases and neurodegenerative diseases. Of note, AGEs cause oxidative stress but oxidative stress also leads to AGE formation [2]. AGEs were first recognized as endogenous compounds that formed in excess in diabetes due to hyperglycemia but they can also be generated in conditions of increased oxidative stress even in the absence of hyperglycemia. Food and tobacco are two major exogenous sources of AGEs. The dietary content of AGEs depends on the protein,

lipid and carbohydrate content of the food as well as on the temperature and conditions of cooking, especially moisture. Animal-derived foods cooked at high temperature, for a prolonged time and under dry conditions have the highest content of AGEs. Exogenous AGEs are important contributors to the body's AGE pool, and they are indistinguishable from endogenous AGEs, both in structure and function [3]. AGE formation is a natural process but chronic hyperglycaemia accelerate AGE formation in different tissues [4].

AGEs are the subject of ongoing research and the therapeutic approaches involve preventing the formation of AGEs, breaking crosslinks once formed and prevention of their negative effects. Different types of AGEs are known, depending on the compound from which they originate. Takeuchi et al. (2004) recognized six distinct classes of AGEs: those deriving from glucose (AGE-1), from other carbohydrates such as glyceraldehyde (AGE-2) and from a-dicarbonyls(glycolaldehyde) (AGE-3), methylglyoxal (AGE-4), glyoxal (AGE-5) and 3-deoxyglucosone (AGE-6). All these compounds can react with the amino group of lysine or the terminal amino group of proteins and with the guanidine group of arginine, and also with cysteine[5-6].

Molecular Pharmacology of AGEs

AGEs once formed disproportionately, initiate a wide range of abnormal responses in cells and tissues that include inappropriate expression of growth factors, alterations in growth dynamics, accumulation of extracellular matrix, promotion of vasoregulatory dysfunction and initiation of death pathways. Complex receptor systems have evolved to remove senescent, glycation modified molecules and/or degrade existing AGE crosslinks from tissues thereby limiting their deleterious effects. Such receptors play a critical part in AGE related biology and the pathology associated with diabetes and aging.

Cells possess specific binding sites for AGEs and the major receptor for AGEs is the "Receptor for AGEs", RAGE but other binding proteins have also been described. RAGE is a member of the immunoglobulin receptor family and binds several ligands such as AGEs, HMGB-1, S100 proteins or amyloid beta peptide. Binding of agonists like the AGEs to RAGE results in activation of NADPH-oxidases and other pathways that lead to increased production of reactive oxygen species and activation of ERK, p38 MAP-Kinase, JAK/STAT-pathway, rho-GTPases and phosphoinositol 3 kinases The major downstream target of RAGE is the proinflammatory NfκB- pathway, which in turn leads to elevated RAGE expression and perpetuation of the cellular inflammatory state. This inflammatory state is characterized by the production of inflammatory cytokines such as IL-6, TNFα, MCP-1 strongly depending on the cell type analyzed [7].

ROS production caused by RAGE activation causes a positive feedback loop therefore up-regulating RAGE expression, thus leading to exacerbation of the inflammatory processes [8]. These AGEs modulated processes leads to modification of intracellular proteins that behave abnormally and modification of extracellular matrix components (ECM) which interact abnormally with other matrix components and integrins, expressed on cell surface. These AGE induced crosslinks decrease elasticity in arteries and glomerular mesangium and increase permeability and alteration of cell to ECM interactions. Modifications on proteins can clearly alter structure, enzymatic activity and modification of biological half-life of DNA leading to mutations. When membrane lipids are hit, this might affect transport and signalling processes.

Further, extracellular proteins are well known targets for AGE- modifications. Proteins such as collagen have a relatively long biological half-life and are directly exposed to high levels of glucose outside the cell. Interestingly, modified collagen becomes more resistant to degradation by matrix metalloproteinases (MMPs) which causes accumulation of AGE-modified collagens in the ECM. The occurrence of AGE cross links results in stiffening of the ECM which often compromises organ function and is associated with several chronic diseases such as diabetes, vascular diseases, retinopathy, arthritis and also Alzheimer's syndrome.

Different pathologies where AGEs are implicated include:

1. Diabetes

Diabetes is the world's fastest growing chronic disease which has reached epidemic proportions globally [9]. In the year 2010, 284 million people were recorded as suffering from diabetes mellitus, and it is suggested that this figure will increase to 439 million in the year 2030, thus turning the disease into an epidemic [10].

Type 2 diabetes is the most common form of diabetes, frequently affecting older people but increasingly occurring in young people and children. Type 1 diabetes and gestational diabetes are the other main types of diabetes [9]. Type 1 diabetes (also known as type 1 diabetes mellitus – T1DM) is an autoimmune condition characterized by hyperglycaemia (high blood sugar levels) resulting from the body's inability to produce insulin. Most cases are caused by the destruction of insulin-producing cells in the pancreas by the body's own immune system. Type 1 diabetes need insulin replacement for survival. Type 2 diabetes (also known as type 2 diabetes mellitus– T2DM) usually develops in adulthood, although it is increasingly reported in some child and adolescent populations. It is characterized by hyperglycaemia due to insulin resistance and/ or a deficiency in insulin production. This form of diabetes often runs in families, and typically occurs when risk factors such as obesity, poor nutrition, and lack of physical activity are present. Type 2 diabetes can usually be controlled through lifestyle modifications, but may require insulin treatment over time. Gestational diabetes (gestational diabetes mellitus/GDM) is a form of diabetes that develops during pregnancy in some women. GDM is caused by placental hormones that block the action of insulin, leading to insulin resistance and high blood sugar levels in pregnant women not previously diagnosed with other forms of diabetes. This type of diabetes is short term and usually develops in the second or third trimester of pregnancy, with potentially adverse outcomes for both mother and baby. GDM usually disappears after the baby is born, although it puts the mother at increased risk of developing type 2 diabetes later in life. GDM can recur in later pregnancies.

Hyperglycemia is still considered the principal cause of diabetes complications. Its deleterious effects are attributable, among other things, to the formation of sugar-derived substances called advanced glycation end products (AGEs).

AGEs form at a constant but slow rate in the normal body, starting in early embryonic development, and accumulate with time. However, their formation is markedly accelerated in diabetes because of the increased availability of glucose. AGEs are a heterogeneous group of molecules formed from the nonenzymatic reaction of reducing sugars with free amino groups of proteins, lipids, and nucleic acids. The initial product of this reaction is called a Schiff base, which spontaneously rearranges itself into an Amadori product, as is the case of the well-known hemoglobin A 1c (A1C). These initial reactions are reversible depending on the concentration of the reactants. A lowered glucose concentration will unhook the sugars from the amino groups to which they are attached; conversely, high glucose concentrations will have the opposite effect, if persistent. A series of subsequent reactions, including successions of dehydrations, oxidation-reduction reactions, and other arrangements lead to the formation of AGEs [11].

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.

Diabetic neuropathy is a diabetic manifestation where all the major nervous systems in the body can be affected including the central, autonomic and peripheral. It is known that AGEs accumulate in peripheral nerves of diabetic patients and that the use of anti-AGE agents improves nerve conduction velocities and neuronal blood flow abnormalities [11]. Probably, AGEs bind to insulin and decrease its biologic activity. The apoptotic effects of AGEs were shown to be mediated via mitochondrial electron transport chain inhibition as well as the NADPH oxidase mediated increase in ROS. AGE determine the modification of the peripheral nerve myelin which becomes susceptible to phagocytosis and determines segmental demyelinization, the modification of major axonal cytoskeletal proteins such as tubulin, neurofilament and actin which cause axonal atrophy and degeneration and impaired axonal transport. The glycation of laminin, found in the extracelular matrix also leads to impaired regenerative activity in diabetic neuropathy (Sugimoto 2008). Studies in rat islets showed that RAGE blockade could reverse the apoptotic effects of AGEs.

Diabetes mellitus can produce a stiff myocardium before the development of myocardial fibrosis. The stiff myocardium in the early stages of cardiomyopathy of diabetes mellitus leads to the formation of links throughout the entire collagen molecule, as opposed to the more limited terminal positions for normal crosslinking. AGE determine the acceleration of the crosslinkage process of collagen. This modification of the collagen structures leads to myocardial stiffness. Three major mechanisms may explain the links between hyperglycemia and vascular

complications, including: the increased intracellular oxidative stress induced by hyperglycemia itself, resulting in protein kinase C (particularly the beta isoform) activation and subsequent activation and nuclear translocation of the transcription factor nuclear factor (NF)-κB, leading to enhanced intracellular reactions; increased activity of the sorbitol-aldose reductase pathway; and formation of advanced glycation endproducts (AGE) [12-13].

Further, AGEs cause platelet activation and fibrin stabilization through several mechanisms such the decreased production of Prostaglandin I2 (PGI_2), by increasing the levels of mRNA coding for PAI 1 in endothelial cells (EC) which causes an increase in immunoreactive PAI 1 contents and the antifibrinolytic activity. The results thus suggest that AGE have the ability to cause platelet aggregation and fibrin stabilization, resulting in a predisposition to thrombogenesis and thereby contributing to the development and progression of diabetic vascular complications [14].

2. Alzheimer's Disease and Dementia

Oxidative stress is an important parameter in the initiation and progression of neurodegenerative disorders in which a progressive decline in neural signal transmission is noted, together with neural loss and deposition of aggregated proteins in the brain. Diseases such as Alzheimer's, Parkinson's, Huntington's, Creutzfeld-Jakob and amyotrophic lateral sclerosis belong to this group of disorders. A common feature of these disorders is increased presence of AGEs in the brain, production of ROS, relatively low levels of antioxidant enzymes and elevated levels of iron that participates in redox reactions.

Accumulation of Amyloid beta is the major pathological feature of Alzheimer's disease and expression of the amyloid precursor protein was found to be induced by AGEs. RAGE has been also involved in amyloid β accumulation to the brain. Although accumulation of AGEs is a normal feature of aging [15] in AD, it is accelerated [16]. AGEs modification may explain biochemical features of AD such as extensive protein cross-linking, oxidative stress, and neuronal cell death. In vivo studies found that AGEs are co-localized with protein deposits such as Amyloid beta plaques in AD [17] and presence of high densities of 'neuritic plaques' in the neuropil of the cerebral cortex and hippocampus is widely regarded as a major contributor to the neurodegeneration that occurs in AD brains[18]. There is a growing body of evidence indicating that the interaction of AGEs with their receptor [receptor for AGEs (RAGE)] elicits oxidative stress and inflammatory reactions. In addition, RAGE has been shown to function as a signal-transducing cell surface receptor for Ab 42 to induce reactive oxygen species (ROS). Moreover, RAGE is increased in brains of AD patients [19] and has a role in the regulation of Ab transport across the blood–brain barrier (BBB) [20].

Glycoxidation may affect apolipoproteins (ApoB and ApoE), and these modifications have been proposed to impact on the function of the proteins causing impaired cholesterol and fat supply to neurons; axon damage and inappropriate transmission of neural signals, mitochondrial dysfunction, inflammation and further oxidative damage leading to neuronal malfunctioning and death. AGEs are also associated with cognitive impairment in people with cerebrovascular disease, suggesting a relationship between AGEs and vascular dementia [21]. Moreover, there is evidence that AGEs level is associated with a faster rate of cognitive decline [22-23].

Also, the neurofibrillary tangles (NFT) contain a hyperphosphorylated microtubule associated tau protein and in brains this tau protein is AGE-modified, whereas in some other neurons or non-demented human brains the protein is soluble and not AGE-modified. The process of transglycation leads to an ''oxidative stress dependent'' tangle formation [24]. Nitric oxide may participate in the process, as AGEs are co-localized with iNOS [6].

Accumulation of AGEs in the brains impair neural cells\ through direct covalent crosslinking to the substrates or binding to the surface AGE receptors (RAGEs). The ligand–receptor interaction may perturb cell functions by activating receptor-mediated signal transduction pathways. Interestingly, Ab has been identified as a ligand of RAGE. RAGE is over expressed in the AD brains and acts as a binding site for Ab at the plasma membrane of neurons, microglial cells, and endothelial cells of the vessel wall. Upregulation of RAGE mediates Ab-induced oxidative stress, activation of nuclear factor-kB, neuronal expression of macrophage colony-stimulating factor and cell death. Recent studies show that RAGE-dependent signaling contributes to an impaired learning/ memory in AD-like transgenic models [25].

3. Hypertension and Atherosclerosis

Three major mechanisms links hyperglycemia and vascular complications, including: the increased intracellular oxidative stress (induced by hyperglycemia) resulting in protein kinase C (Beta isoform) activation and subsequent activation and nuclear translocation of the transcription factor nuclear factor (NF)-κB, leading to enhanced intracellular reactions; increased activity of the sorbitol-aldose reductase pathway and formation of AGE.

Hypertension and atherosclerosis are characterized by insulin resistance the cause of which is not known, but may be a result of a combination of genetic and lifestyle factors. In insulin resistance, alterations in glucose and lipid metabolism lead to the production of excess aldehydes including glyoxal and methylglyoxal. These aldehydes react non-enzymatically with free amino and sulfhydryl groups of amino acids of proteins to form AGEs [26]. AGE can be highly deleterious to the integrity and function of blood vessel walls in several ways as they cross bridges among vessel wall macromolecules causing mechanical dysfunction and also cause circulating blood cells to adhere to the vessel wall, trapping molecules such as immunoglobulins and apolipoproteins, which already may have been modified by glycation. However, the impact and relevance of cross bridgings, trapping, and altered protein functions is a non-mechanical source of damage.

AGEs act directly or via receptors to alter the function of many intra- and extracellular proteins including antioxidant and metabolic enzymes, calcium channels, lipoproteins, and transcriptional and structural proteins. This results in endothelial dysfunction, inflammation and oxidative stress. All these changes are characteristic of hypertension and atherosclerosis. Pharmacological inhibition of AGE formation using aminoguanidine resulted in reduced cross linking of proteins in arterial walls. Vice versa, the administration of exogenous AGEs to levels found in diabetics, induced atheroma formation in rabbits [27]. These research findings are further corroborated by the expression pattern of receptors of AGEs in atherosclerotic plaques. CD36 is expressed on macrophages as a major receptor for oxidised LDL [28]. CD36 is expressed in atherosclerotic lesions and considered to trigger the formation of macrophages into foam cells, a major event in the development of atherosclerosis. AGE- binding to CD3 accelerate this process by triggering tyrosine phosphorylation and NFκB activation. SRBI is essential for the reverse cholesterol transport as HDL. SRBI recognizes AGEs and binding of AGE interferes with the uptake of acetylated HDL and suppresses SRBI-mediated efflux of cholesterol from cells. These observations suggest that AGEs inhibit cholesterol reflux which is considered as proatherogenic [29-30].

AGEs also reduce LDL uptake, promoting plaque destabilization via effects on matrix metalloproteinases, inducing neointimal proliferation and inhibiting vascular repair in response to injury. Food-derived AGEs induce significant tumor necrosis factor α activation as well as cell-oxidative and crosslink formation activities and that these actions are mediated by RAGE and non-receptor mechanisms [31]. AGEs have been shown to induce inflammation and intracellular Reactive Oxygen Species (ROS), which leads to the expression of many atherosclerosis-related genes, including VEGF [32].

AGEs also reduce the bioavailability and activity of endothelium derived NO. NO inhibits many of the mechanisms that contribute to atherosclerosis, such as leukocyte adhesion to the vessel wall, vascular smooth muscle growth, platelet adhesion and aggregation, this effect of AGEs on NO may be relevant to atherogenesis. AGEs reduce or block NO activity and this suggests that AGEs reduce the half-life of endothelial NO synthase (eNOS) mRNA through an increased rate of mRNA degradation and reduced eNOS activity. 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. AGEs also may quench and inactivate endothelium-derived NO. Also, the endothelial production of prostacyclin (PGI2) is reduced by AGEs [22-33].

4. Cancer

Almost 25% of all cancers are estimated to be associated with inflammation as sustained inflammatory conditions stimulate tumorigenic signalling pathways and oncogenes activation. Therefore, considering that sustained AGEs (RAGE signalling) leads to increased oxidative stress and inflammation it is not surprising that RAGE ligands are formed and secreted by many types of cancer cells. The increased expression of RAGE has been detected in various tumours including colorectal carcinoma, gastric, pancreatic, pros- tate, breast, brain and ovarian tumors.

RAGE-mediated activation of NF- κ B has a pro-inflammatory effect as it promotes activation of genes for inos, TNF-α, interleukins-1, -6 and cyclooxygenase-2. Cyclooxygenase-2-derived prostaglandin E2 mediates cellular immune tolerance during tumorogenesis and the AGE–RAGE signalling enhances the angiogenic potential of hepatocellular carcinoma by inducing VEGF expression. NF-κB promotes activation of genes for X-linked inhibitor of apoptosis and some members of the B-cell lymphoma family (BcL-2 and BcL-X) involved in antiapoptotic signals [34-36].

Many studies have shown a link between diabetes and cancer [37-38]. In these studies associations between diabetes and non-Hodgkin's lymphoma [39] liver colorectal endometrial, breast and renal cell cancers have been observed. A possible explanation that fits well to epidemiological data lies in the elevated levels of insulin and insulin-like growth factor in diabetic patients. This hyperinsulinemia is due to insulin resistance and therapeutic insulin supplementation. According to this hypothesis, insulin may act as a growth factor for cancer cells and AGE-signalling was also associated with certain tumours because RAGE activation causes cell activation, growth factor expression and activation of NfκB. According to this hypothesis, in prostate cancer RAGE and its ligand amphoterin were found to be overexpressed and blockade of RAGE resulted in reduced tumour cell growth [41].

5. Malaria

Malaria remains one of the most challenging diseases in terms of mortality and drug resistance rates. The World Health Organization (WHO) recorded 198 million cases of malaria in 2013, with approximately 584,000 cases of death, of which 90% occurred in Africa [41]. Around 2,000 people (majority under age five) die per day from malaria [42] and still after many years of research on malaria vaccines, only one candidate reached phase III with an efficacy of ~50% [43].

Accumulation of AGEs in blood, tissues and organs results in chronic toxicity and cell signaling engagement, with deleterious effects on innate and adaptive immune defense. The innate immune response induced by RAGE when activated by AGE is a sterile immune reaction. The sterile inflammatory immune response is similar to infection immune response, including the recruitment of neutrophils, macrophages, cytokines, chemokines, and the induction of T cell-mediated immune responses [44]. The magnitudes of innate as well as the type of adaptive immune responses are strongly influenced by the cellular expression of RAGE in immune effector cells [45]. T helper 2 (Th2) cytokine production, which is frequently downregulated in T cells expressing RAGE, is critical for host defense against blood stage malaria [46].

In malaria endemic areas where populations are exposed to high levels of AGE in food, the chronic activation of RAGE by dietary AGE lead to chronic inflammatory immune response that results in immune tolerance (by upregulation of negative feedback control), cell dysfunction, tissue destruction, and exhaustive immune cells. Also, Depletion of Th2 immune response and impairment of the Th1/Th2 immune response balance, with deleterious effects on the host-pathogen interaction. In populations with AGE-rich cooked foods as their main food source, chronic activation of RAGE by AGE may induce and maintain pro-inflammatory cytokine production, oxidative stress, reactive oxygen species (ROS), and AOPP production, and result in innate immune tolerance, inadequate adaptive immune response, cellular dysfunction, and depletion of anti- oxidative mechanisms. The disturbance of host defense systems may increase susceptibility to malaria in these populations [42,47].

6. Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a systemic inflammatory connective tissue disease with polyarthritis as a prominent feature; however, extra-articular symptoms and signs are always present. It globally affects up to 0.5- 1% of the adult population, with survival rates comparable to coronary artery disease and cancer. RA patients are two to five times more prone to the risk of coronary artery disease, silent myocardial ischemia, sudden cardiac death and overall cardiovascular (CV) mortality risk as compared to general population [48].

The multi ligand receptor RAGE functions through amplification of various proinflammatory pathways that enhances the level of cytokines, adhesion molecule and vascular cell expression. In inflamed RA joints, levels of High Mobility Group Box chromosomal protein-1 (HMGB-1) and S100A12, as well as those of AGEs, are

strikingly increased. High levels of RAGE and proinflammatory adhesion molecules are found to be expressed in the RA synovial tissue (ST) endothelium and macrophages established from RA synovial fluid contain large amounts of RAGE protein. In RA, targeted site i.e synovial tissue is infiltrated by various inflammatory mediator that is characterized by presence of CD68+ macrophages on RAGE antigen and along with this the level of TNFα, cytokine and IL-1 increased at of the inflammatory site which leads to progression of disease[48].

7. Erectile Dysfunction

Erectile dysfunction (ED), defined as the inability to develop and maintain an erection for satisfactory sexual intercourse or activity, is a highly prevalent disease affecting millions of men worldwide with a tendency for widespread increase.

It has been well documented that AGEs progressively accumulate on the tissues and organs which develop chronic complications of diabetes mellitus, such as erectile dysfunction, retinopathy, nephropathy, neuropathy and also macro vascular disease atherosclerosis.[49] In men with poorly controlled diabetes, AGEs were increased in the collagen of the penile tunica and corpus cavernosum, resulting in inhibition of nitric oxide production. The decrease in nitric oxide may impede the contraction and relaxation of corporal smooth muscle, leading to the development of erectile dysfunction. It is conceivable that the penile microcirculation may be affected early by metabolic and blood flow-related factors such as hyperglycaemia, dyslipidemia, blood pressure, oxidative stress and AGEs [49].

Furthermore, impaired dilatation of blood vessels is evident in men with diabetes with erectile dysfunction [50] and when AGEs are increased, level of cGMP declines leading to ED. It has been demonstrated that inhibitors of AGE formation can prevent formation of a range of complications in experimental diabetic animals, including ED [51-52].

Furthermore, AGEs and their receptors have been described to elevate the activity of endothelin-1, a vasoconstrictor, in rat corpus cavernosum[53] and AGEs production is associated with increased superoxide anion. O-linked N-acetylglucosamine (O-GlcNAc) is the major AGE product implicated in cavernosal dysfunction in diabetic patients. It has been reported a significant increase in the O-GlcNAc modification of eNOS and reduced phosphorylation of eNOS at baseline and following electrical stimulation in cavernosal tissue from diabetic rats compared with the controls[54] and to add, increased AGEs has been reported in penile tissue from aged man.

Conclusion

The preclinical and clinical studies of the last decade demonstrated a strong involvement of AGEs not only in micro and macrovascular complications of diabetes mellitus but also in cancer, neurodegenerative and cardiocascular pathologies. Although AGEs have been assigned an important physiological role, yet their uncontrolled levels are targets of several pathologies as described in the present review. Thus inhibition of AGE formation, antagonizing RAGE or suppressing the expression of this receptor may be the viable targets in the treatment of various pathologies.

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