AGE RAGE Pathways: Cardiovascular Disease and Oxidative Stress

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ABSTRACT

It is well established that Advanced Glycation End Products (AGEs) and their receptor (RAGE) are primarily responsible for the development of cardiovascular disease. As a result, diabetic therapy is very interested in therapeutic strategies that can target the AGE-RAGE axis. The majority of the AGE-RAGE inhibitors showed encouraging outcomes in animal experiments, but more information is needed to completely understand their clinical effects. The main mechanism implicated in the aetiology of cardiovascular disease in people with diabetes is oxidative stress and inflammation mediated by AGE-RAGE interaction. Numerous PPAR-agonists have demonstrated favourable outcomes in the treatment of cardio-metabolic illness situations by inhibiting the AGE-RAGE axis. The body's ubiquitous phenomena of inflammation occur in reaction to environmental stressors such tissue damage, infection by pathogens, or exposure to toxic substances. Rubor (redness), calor (heat), tumour (swelling), colour (pain), and in severe cases, loss of function, are its cardinal symptoms. When exposed, the lungs develop silicotic granulomas with the synthesis of collagen and reticulin fibres. A natural flavonoid called chyrsin has been found to have PPAR-agonist activity as well as antioxidant and anti-inflammatory properties. The RPE insod2 + /animals underwent mononuclear phagocyte-induced apoptosis, which was accompanied with decreased superoxide dismutase 2 (SOD2) and increased superoxide generation. Injections of the serine proteinase inhibitor SERPINA3K decreased proinflammatory factor expression in mice with oxygen-induced retinopathy, decreased ROS production, and increased levels of SOD and GSH.

Introduction

An imbalance between free radicals and antioxidants in the body leads to oxidative stress. Oxygen-containing molecules with an unbalanced number of electrons are known as free radicals. The unequal number makes it simple for them to interact with molecules including DNA, proteins, and lipids. The term "advanced glycation end products," or "AGEs," refers to a broad class of compounds that are created and accumulated as a result of the advanced glycation process. AGE formation is enhanced by diseases like diabetes, renal failure, inflammation, neurodegeneration, and old age. AGEs are also present in cigarettes and food products [1]. Therefore, both endogenous synthesis and exogenous intake of AGEs cause vascular homeostasis to be disrupted. First, AGEs have the potential to crosslink long-lived molecules in the basement membranes, including collagen, leading to processes that increase vascular permeability and weaken structural integrity. This is known as "vascular stiffening". "Advanced glycation end products" refers to proteins, lipids, and nucleic acids that have been permanently altered by reducing sugars or sugar-derived substances (AGEs) [2]. The phrase "oxidative stress" is frequently used to describe a disruption in the pro-oxidant-antioxidant equilibrium that may result in damage. However, in the instance of aldehyde poisoning, oxidative stress is

predominantly caused by the depletion of cellular GSH. Disease-associated oxidative stress may result from a variety of circumstances. The control of protein disulfide bonds as well as the elimination and detoxification of oxidants and electrophiles depend heavily on GSH [3]. It is widely assumed that oxidative stress produced within cells is a crucial mechanism connecting particle exposure to perceptible physiological and biochemical reactions. This theory is based on earlier studies with air pollution PM, like most of NP toxicology [4]. Oxidative stress is a general term that different authors use to describe increased levels of ROS (hydroxyl and superoxide radicals) and reactive nitrogen species (RNS) (such as nitric oxide and peroxynitrite radicals) inside or outside of cells, changes in the gene regulation of oxidative damage repair pathways, and the ensuing oxidative damage to biomolecules [5]. Both direct and indirect methods are used to examine the hypotheses relating to particle-induced oxidative stress. The detection and measurement of the reactive intermediates by spin trapping or by the reaction with fluorescent indicator molecules are examples of direct tests. The Maillard reaction is the name given to the chain of chemical processes those results in the development of AGEs [6]. Both the "browning" of food as it is being cooked and the "browning" of tissue that occurs with ageing are caused by the Maillard process [7]. Early glycation is the term for the initial chemical process in which a sugar is irreversibly bound by non-enzymatic means to amino acid groups on proteins, lipids, or nucleic acids [8]. They create Schiff bases, which can then be rearranged to create Amadori products, which are more stable [9]. The adduction of a carbohydrate to another biomolecule, such as a protein, lipid, or deoxyribonucleic acid, (DNA), is known as glycation. Glycation can happen enzymatically or without the use of enzymes. Glycation caused by an enzyme is known as glycosylation, such as when a glycosidic bond is created utilizing a sugar nucleotide donor during the production of glycoproteins [10]. RAGE staining revealed that the skeletal muscle, lung, and heart have the highest levels of expression of this receptor [11]. RAGE is a transmembrane receptor of the immunoglobulin superfamily that was initially found to bind AGE. It has a cytoplasmic part that mediates the downstream signaling and an extracellular region that, through its V domain, binds damage-associated molecular patterns (DAMPs) [12]. The location of the molecule, the receptor it attaches to, and its reduction-oxidation state all affect how the molecule performs. Despite being discovered in 1973 to bind deoxyribonucleic acid, it was later discovered in 1999 to also be an extracellular secretory product of macrophages in response to lipopolysaccharide (LPS) and a significant facilitator of deadly endotoxemia [13–15]. The amphoterin-binding receptor RAGE is the first HMGB1 receptor to be discovered, and it plays a function in neurite outgrowth in the developing nervous system. As its name suggests, RAGE binds advanced glycation end products (AGEs), but more recently, it has been described to bind to a diverse array of other molecules, including DNA and Ribonucleic acid (RNA). RAGE is a member of the immunoglobulin gene super-family and consists of a 43-amino acid cytoplasmic tail, a short transmembrane domain, and an extracellular domain [16–18].

Oxidative stress

The phrase "oxidative stress" is frequently used to describe a disruption in the pro-oxidant-antioxidant equilibrium that may result in damage. However, in the instance of aldehyde poisoning, oxidative stress is predominantly caused by the depletion of cellular GSH [19]. Disease-associated oxidative stress may result from a variety of circumstances. The control of protein disulfide bonds as well as the elimination and detoxification of oxidants and electrophiles depend heavily on GSH. GSH conjugation of organic hydroperoxides and electrophiles like acrolein or 4-HNE by GSTs and sufficient reduction of hydrogen peroxide by GSH peroxidases would be compromised by GSH depletion below a critical level. This depletion may make cells more sensitive to the toxicity of a particular medication. Through oxidation reactions, oxidative stress affects a number of biological constituents, including proteins, lipids, and deoxyribonucleic acid (DNA) [20]. The term "oxidative stress" describes the cytopathological effects of an imbalance between the generation of free radicals and a cell's capacity to combat them. Free radicals are byproducts of aerobic metabolism in cells and are defined as molecules or molecular fragments with one or more unpaired electrons in their outer orbitals. The most common cellular free radicals are superoxide anion (O_2) and hydroxyl (OH radical dot) species; while hydrogen peroxide (H_2O_2) and peroxynitrito (ONOOradical dot) are also present [21]. The accumulation of ROS, damage to macromolecules (proteins, lipids, and nucleotides), loss of cell function, and death occur from the saturation or impairment of these antioxidant systems. Because of its high oxygen consumption, limited antioxidant activity, and relatively large amount of polyunsaturated lipids, the CNS is particularly susceptible to oxidative stress. ROS formation may also be more likely in areas with high concentrations of redox-transitional metals that can catalyze it. In addition to the production of ROS, a substantial body of research suggests that neurons and glia also produce nitric oxide (NO) during neuroinflammatory and neurodegenerative processes [22].

Reactive oxygen species

Reactive oxygen species (ROS) are byproducts of the reduction of dioxygen (oxygen gas, O_2) by one electron to produce superoxide, an anionic form of oxygen. Oxidative enzymes like cytochrome oxidase and nicotinamide adenine dinucleotide (NADH)/reduced NADPH oxidase (NOX) catalyse the production of superoxide. The enzyme superoxide dismutase (SOD), which catalyses the conversion of superoxide to hydrogen peroxide, has been developed by species that produce O_2 (H_2O_2) [23]. H_2O_2 is broken down by other enzymes, preventing the harmful effects of this ROS. Endothelial, epithelial, vascular smooth muscle, mesangial, podocyte, and other cell types in the kidney create ROS that have an impact on the kidney vasculature [24–26]. It is believed that AGE and the AGE receptor (RAGE) interaction ultimately results in oxidative stress [27]. In a typical state, the kidney's oxidative and antioxidative enzymes produce a balanced amount of NO and superoxide anion. The glomeruli, juxtaglomerular apparatus, arteries, arterioles, and other nephron segments all produce ROS, and the kidney also contains the oxidases NOX 1, 2, and 4, NOS, and COX. NOX 1 and NOX 2 in the renal vasculature produce O_2, while NOX 4 in epithelial cells produces H_2O_2. Catalase and glutathione peroxidase break down superoxide, which is converted to H_2O_2 by superoxide dismutase

[28–30]. Reactive oxygen species (ROS), which aid in oxidative stress, are produced as AGEs are formed. The Maillard reaction between carbs and proteins results in the formation of advanced glycation end products (AGEs). Neurons and the hippocampus have been found to contain AGEs and the AGE receptor (RAGE) in a clinical situation. According to recent research, AGEs and RAGE trigger neurotoxicity through oxidative stress. Sirt1, a NAD + -dependent deacetylase, is associated with ageing and antioxidant activity. Sirt1 may possibly have a neuroprotective function, preventing the death of neuronal cells by lowering oxidative stress, according to recent studies [28–30].

AGE RAGE for Cardiovascular

The development of cardiovascular disease in people with diabetes is significantly influenced by advanced glycation end products (AGEs). RAGE's interaction with AGEs not only causes the production of reactive oxygen species (ROS) and the mobilization of inflammatory cytokines, but it also hastens the onset and progression of cardiovascular disease in people with diabetes [31]. Beginning the AGE-RAGE pathway has been demonstrated to increase nicotinamide adenine dinucleotide phosphate oxidase (Nox)-mediated oxidative stress, which in turn increases the nuclear factor-B (NF-B) signalling pathway, a redox-sensitive transcription factor [32]. Additionally, the AGE-RAGE interaction causes endothelial dysfunction by decreasing the activity of the enzyme endothelial nitric oxide synthase (eNOS), inactivating nitric oxide (NO) to create peroxynitrite, and quenching NO [33]. In fact, it has been demonstrated that RAGE deficiency slows the ischemia injury to the diabetic myocardium and the onset of atherosclerosis. RAGE levels have been found to positively connect with cardiovascular events in type 2 diabetes in a clinical investigation. Because they would help to reduce diabetes and its consequences, treatments that target the AGE-RAGE pathway may be very interesting [34]. Recently, it has been demonstrated that PPAR-agonists such pioglitazone, rosiglitazone, and telmisartan can reduce RAGE-mediated oxidative stress and inflammation to alleviate myocardial damage in diabetics. Honey, propolis, and other plant extracts have been found to contain chysin, a natural flavonoid that is a PPAR-agonist (peroxisome proliferator-activated receptors). By activating PPAR, chysin has been proven to reduce inflammation and the vascular problems brought on by insulin resistance. In a recent study, we demonstrated that chrysin protects rat myocardium damage caused by receptor stimulation by activating PPAR. In diabetic rats, it should be noted that chrysin has been proven to lower serum AGE levels, lessen diabetes-induced endothelial-dependent relaxation impairment, and lessen renal failure [35].

Conclusion

Non-enzymatic glycation of reducing sugars to amino groups in proteins or lipids results in the irreversible production of AGEs, which is then followed by a sequence of rearrangements or oxidation events. Since the level of circulating AGE is substantially higher in diabetes patients, this process – also known as the Maillard reaction – is concentration-dependent. Numerous reactive intermediates, such as glyoxal, methylglyoxal, and 3-deoxyglucosone, together known as oxoaldehydes or dicarbonyls, are also elevated along with the level of AGE. The development of endothelial damage, vascular alteration, proatherogenic, and proinflammatory processes are all caused by the intra- and extracellular pathological changes that AGE and RAGE can cause. As a result, the cardiovascular system is severely compromised, which leads to the vascular problems that are frequently observed in diabetes patients. Strong AGE-RAGE inhibitory drugs are consequently in high demand because the AGE-RAGE axis is thought to be one of the main factors contributing to the development of diabetic vascular problems. The clinical investigations of the majority of AGE-RAGE inhibitors, aside from drugs that lower blood sugar and cholesterol, produced conflicting data about their clinical usefulness and applicability.

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Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. The authors declare no conflict of interest among themselves. The authors alone are responsible for the content and writing of this article.; **Financial interests** The authors declare they have no financial interests.

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