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Review

Glycative Stress and Aging

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ABSTRACT

Skin aging is one of the most visible manifestations of the aging process, prominently influenced by glycative stress. Glycative stress arises from the non-enzymatic reaction between reducing sugars and biomolecules, leading to the formation of advanced glycation end products (AGEs). These AGEs not only contribute to the visible signs of aging, such as wrinkles and loss of elasticity, but also play a pivotal role in the acceleration of systemic aging and the onset of various chronic diseases, including cardiovascular disorders, diabetes complications, neurodegenerative diseases, cancer, and osteoporosis. This review delves into the mechanisms of AGE formation, including glycoxidation, dicarbonyl stress and lip oxidation, and examines their detrimental effects on cellular and tissue function through protein cross-linking, activation of the receptor for advanced glycation end products (RAGE), and induction of oxidative stress. Insights from studies using model organisms such as yeast, Caenorhabditis elegans, Drosophila melanogaster, and mice underscore the conserved impact of glycative stress on lifespan and health span. Furthermore, the review highlights effective strategies to mitigate glycative stress, including antioxidant supplementation, dietary modifications, pharmacological interventions, and lifestyle changes. Emphasizing a low-sugar diet, reducing processed food intake, adopting AGE-limiting cooking methods, and maintaining regular physical activity are identified as key approaches to combat glycative stress. Understanding the role of glycative stress in skin and overall aging is essential for developing targeted interventions that promote healthy aging and reduce the burden of age-related diseases.

Keywords: Glycative Stress, Advanced Glycation End Products (AGEs), Aging, Chronic Diseases, Antioxidants, Dietary Modifications, RAGE, Oxidative Stress

1. Introduction

Aging is a complex and multifactorial process influenced by both genetic and environmental factors[1-3]. Among the various mechanisms that contribute to aging, glycative stress has emerged as a significant player[4-6]. Glycative stress, also known as glycation, refers to the non-enzymatic reaction between reducing sugars and proteins, lipids, or nucleic acids, leading to the formation of advanced glycation end products (AGEs)[5,7]. These AGEs accumulate over time and have been implicated in the acceleration of the aging process and the development of age-related chronic diseases[5,8].

The concept of glycative stress was first introduced in the context of diabetes, where elevated blood glucose levels lead to an increased formation of AGEs. However, it is now recognized that even in non-diabetic individuals, AGEs can form through normal metabolic processes and exogenous sources such as diet and smoking[9]. The accumulation of AGEs has been linked to a wide range of pathologies, including cardiovascular disease, neurodegenerative disorders and kidney dysfunction, all of which are prevalent in the elderly population[10].

Understanding the role of glycative stress in aging is crucial for developing effective interventions to promote healthy aging and prevent age-related diseases. This review aims to provide a

comprehensive overview of the mechanisms underlying glycative stress, with a particular focus on the formation and actions of AGEs. We will also discuss the impact of glycative stress on the aging process and the development of chronic diseases, as well as current and potential future strategies to mitigate its effects. We aim to identify key areas for future research and potential therapeutic applications, ultimately contributing to a better understanding of the aging process and the development of more effective anti-aging strategies.

2. Glycative Stress in Model Organisms

To better understand the role of glycative stress in aging, researchers have extensively studied this phenomenon in various model organisms, including yeast, nematodes, fruit flies and mice. These models have provided valuable insights into the molecular and cellular mechanisms of glycation and the formation of AGEs.

2.1. Yeast (Saccharomyces Cerevisiae)

In yeast, studies have shown that high glucose levels can lead to the formation of AGEs, which in turn affect cellular function and lifespan. For example, hyperglycaemic conditions can induce oxidative stress and reduce the replicative lifespan of yeast cells[11,12]. Furthermore, the addition of AGE inhibitors, such as aminoguanidine, has been shown to extend the lifespan of yeast, highlighting the importance of glycative stress in yeast aging[13,14].

2.2. Nematodes (Caenorhabditis Elegans)

C. elegans is a widely used model organism for studying aging due to its short lifespan and well-characterized genetics. Studies in C. elegans have demonstrated that dietary glucose can increase the formation of AGEs, leading to a reduction in lifespan and an increase in age-related pathologies[4]. Additionally, the expression of human glyoxalase enzymes, which detoxify reactive carbonyl species, has been shown to extend the lifespan of C. elegans, further supporting the role of glycative stress in aging.

2.3. Fruit Flies (Drosophila Melanogaster)

In Drosophila, high-sugar diets have been shown to accelerate the formation of AGEs and reduce lifespan. Genetic and pharmacological interventions that target AGEs, such as overexpression of the enzyme fructosamine-3-kinase, have been found to mitigate the negative effects of high-sugar diets and extend the lifespan of fruit flies[15,16]. These studies highlight the conserved nature of glycative stress across different species.

2.4. Mice (Mus Musculus)

Mice are a more complex model organism that share many physiological and genetic similarities with humans. In mouse models, high-glucose diets and genetic manipulations that increase AGE formation have been shown to accelerate aging and promote the development of age-related diseases, such as atherosclerosis, nephropathy and cognitive decline[17-19]. Conversely, interventions that reduce AGE levels, such as caloric restriction and the use of AGE inhibitors, have been shown to improve health span and extend lifespan in mice.

By exploring the intricate relationship between glycative stress and aging in these model organisms, this review seeks to highlight the importance of targeting AGEs and their associated pathways in geriatric medicine. Through a detailed examination of the existing literature, we aim to identify key areas for future research and potential therapeutic applications, ultimately contributing to a better understanding of the aging process and the development of more effective anti-aging strategies.

3. Glycation Stress

3.1. Non-Enzymatic Glycation Reaction and Its Products

Non-enzymatic glycation, also known as the Maillard reaction, is a spontaneous chemical process that occurs between reducing sugars (such as glucose, fructose and ribose) and amino groups in proteins, lipids, or nucleic acids[20]. This reaction proceeds through several stages, ultimately leading to the formation of advanced glycation end products (AGEs). The initial step involves the formation of a Schiff base, which then undergoes rearrangement to form an Amadori product. Over time, these Amadori products can undergo further reactions, including dehydration, oxidation and cross-linking, resulting in the formation of stable and irreversible AGEs[20].

AGEs are a heterogeneous group of compounds characterized by their yellow-brown fluorescence, cross-linking properties and ability to interact with specific receptors, such as the receptor for advanced glycation end products (RAGE). These properties make AGEs significant contributors to the pathophysiology of various age-related diseases.

3.2. Pathway for AGE Formation

The formation of AGEs can occur through several pathways, each yielding different types of AGEs. One of the most well-characterized pathways is the glucose-derived pathway, also known as glycoxidation[20]. In this pathway, reducing sugars such as glucose react non-enzymatically with amino groups in proteins, lipids, or nucleic acids to form Schiff bases, which then rearrange to form Amadori products. Over time, these Amadori products undergo further reactions, including oxidative cleavage, leading to the formation of stable and irreversible AGEs.

3.2.1. Glucose-Derived AGEs (Glycoxidation): Nε-(Carboxymethyl)lysine (CML) is one of the most common and well-studied AGEs formed through this pathway. CML is generated via the oxidative cleavage of Amadori products and serves as a marker of both glycation and oxidative stress. Another prominent glucose-derived AGE is Pentosidine, which is formed through the cross-linking of lysine and arginine residues. Pentosidine is often used as a biomarker of cumulative tissue damage and has been associated with increased stiffness in connective tissues, contributing to conditions such as hypertension and atherosclerosis[21,22].

3.2.2. Methylglyoxal-Derived AGEs (Dicarbonyl Stress): Another significant pathway for AGE formation is the methylglyoxal-derived pathway, also referred to as dicarbonyl stress. Methylglyoxal is a highly reactive dicarbonyl compound that is produced as a byproduct of glycolysis and is a major contributor to AGE formation. Methylglyoxal reacts with lysine residues to form Nε-(Carboxyethyl)lysine (CEL), another well-characterized AGE. CEL is a robust marker of dicarbonyl stress and is implicated in various pathologies, including diabetic complications and neurodegenerative diseases[23]. Additionally, methylglyoxal can react with arginine residues to form Argpyrimidine, an AGE that has been linked to the development of diabetic complications and neurodegenerative diseases. The

high reactivity of methylglyoxal makes it a potent driver of AGE formation, and its accumulation can lead to significant cellular and tissue damage.

3.2.3. Lipid-Derived AGEs (Lipoxidation): Lipid-derived AGEs or lipoxidation products, are formed through the reaction of lipid peroxidation products with proteins. Malondialdehyde (MDA), a product of lipid peroxidation, can react with proteins to form MDA-derived AGEs. These AGEs are often found in atherosclerotic plaques and have been linked to cardiovascular disease. The formation of MDA-derived AGEs contributes to the progression of atherosclerosis by promoting inflammation and endothelial dysfunction. Another important lipid peroxidation product is 4-Hydroxynonenal (HNE), which can also form HNE-derived AGEs.

HNE is a highly reactive aldehyde that can modify proteins, leading to the formation of stable adducts. HNE-derived AGEs have been implicated in the pathogenesis of various diseases, including Alzheimer's disease and cancer. The accumulation of HNE-derived AGEs can lead to cellular dysfunction, oxidative stress, and the activation of pro-inflammatory signaling pathways, further exacerbating the progression of these diseases[20].

3.3. Mechanism of Action of AGEs

AGEs exert their detrimental effects through multiple mechanisms, including direct structural modifications, activation of signalling pathways and induction of oxidative stress. One of the primary ways AGEs affect cells and tissues is through the formation of covalent cross-links between proteins[9,24]. These cross-links lead to the accumulation of insoluble aggregates, which can be particularly detrimental in connective tissues. For example, AGEs contribute to the increased stiffness of blood vessels, which can lead to the development of hypertension and other cardiovascular diseases. The cross-linking of collagen and other extracellular matrix proteins by AGEs impairs the normal elasticity and function of these tissues, leading to reduced flexibility and increased mechanical stress.

In addition to forming cross-links, AGEs can modify the active sites of enzymes, leading to their inactivation. This disruption of enzymatic activity can disrupt metabolic pathways and cellular homeostasis. For instance, the inactivation of matrix metalloproteinases (MMPs) by AGEs can impair the remodelling of the extracellular matrix, contributing to fibrosis and tissue dysfunction[11,25]. MMPs play a crucial role in maintaining the integrity and functionality of the extracellular matrix and their inactivation by AGEs can lead to the accumulation of damaged and dysfunctional matrix components, further exacerbating tissue damage.

AGEs also interact with the receptor for advanced glycation end products (RAGE) on the cell surface, activating a variety of intracellular signalling pathways. The binding of AGEs to RAGE can trigger the activation of nuclear factor-kappa B (NF-κB), mitogen-activated protein kinase (MAPK), and Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathways[26,27]. These pathways promote the production of pro-inflammatory cytokines, adhesion molecules, and growth factors, leading to chronic inflammation and tissue damage. The activation of these signalling pathways by AGEs contributes to the persistent inflammatory state observed in many age-related diseases[28-30].

Furthermore, AGEs can induce the production of reactive oxygen species (ROS) through the activation of NADPH oxidase and other oxidative enzymes. This oxidative stress can further damage cellular components, including DNA, proteins and lipids and contribute to the progression of age-related diseases[31]. ROS can cause oxidative modifications to cellular macromolecules, leading to the accumulation of dysfunctional and damaged proteins, lipids, and DNA. This cycle of oxidative stress and cellular damage can accelerate the aging process and contribute to the development of various chronic diseases.

Additionally, AGEs have been shown to accumulate in mitochondria, leading to impaired mitochondrial function and increased ROS production. Mitochondria are the primary site of cellular energy production and are highly susceptible to oxidative stress. The accumulation of AGEs in mitochondria can disrupt the electron transport chain and impair ATP production, leading to further oxidative stress and the release of more ROS[26]. This vicious cycle of oxidative stress and mitochondrial dysfunction can accelerate the aging process and contribute to the development of age-related diseases, such as neurodegenerative disorders and cardiovascular diseases.

In summary, the multifaceted nature of AGEs, involving direct structural modifications, activation of signalling pathways and induction of oxidative stress, highlights their significant role in the aging process and the development of age-related diseases.

4. Impact of Glycative Stress on Aging

4.1. Accelerating the Aging Process

Glycative stress, characterized by the accumulation of advanced glycation end products (AGEs), plays a significant role in accelerating the natural aging process. As individuals age, the body's ability to detoxify and repair damage from glycation reactions diminishes, leading to a progressive increase in AGE levels[32,33]. This accumulation of AGEs can have profound effects on cellular and tissue function, contributing to the hallmarks of aging.

One of the primary mechanisms by which glycative stress accelerates aging is through the formation of covalent cross-links between proteins. These cross-links, formed by AGEs, lead to the accumulation of insoluble aggregates that impair the normal function and elasticity of tissues. For example, in the cardiovascular system, the cross-linking of collagen and elastin by AGEs results in increased arterial stiffness, which is a key factor in the development of hypertension and atherosclerosis[10,26,34]. The stiffening of blood vessels not only increases the workload on the heart but also impairs blood flow, leading to reduced oxygen and nutrient delivery to tissues, further exacerbating the aging process.

Additionally, AGEs can modify the active sites of enzymes, leading to their inactivation. This disruption of enzymatic activity can disrupt metabolic pathways and cellular homeostasis. For instance, the inactivation of matrix metalloproteinases (MMPs) by AGEs impairs the remodeling of the extracellular matrix, contributing to fibrosis and tissue dysfunction. MMPs play a crucial role in maintaining the integrity and functionality of the extracellular matrix, and their inactivation by AGEs can lead to the accumulation of damaged and dysfunctional matrix components, further exacerbating tissue damage and accelerating the aging process[35,36].

Moreover, AGEs interact with the receptor for advanced glycation end products (RAGE) on the cell surface, activating a variety of intracellular signaling pathways. The binding of AGEs to RAGE can trigger the activation of nuclear factor-kappa B (NF-κB), mitogen-activated protein kinase (MAPK) and Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathways[37,38]. These pathways promote the production of pro-inflammatory cytokines, adhesion molecules and growth factors, leading to chronic inflammation and tissue damage. Chronic inflammation, driven by the persistent activation of these signaling pathways, is a well-known driver of the aging process and is associated with a wide range of age-related diseases.

Finally, AGEs can induce the production of reactive oxygen species (ROS) through the activation of NADPH oxidase and other oxidative enzymes. This oxidative stress can further damage cellular components, including DNA, proteins, lipids and contribute to the progression of age-related diseases. ROS can cause oxidative modifications to cellular macromolecules, leading to the accumulation of dysfunctional and damaged proteins, lipids, and DNA. This cycle of oxidative stress and cellular damage can accelerate the aging process, leading to the premature onset of age-related conditions.

4.2. Development of Chronic Diseases

Long-term exposure to high concentrations of AGEs is associated with the development of various chronic diseases, many of which are more prevalent in older populations. The accumulation of AGEs and the resulting glycative stress contribute to the pathogenesis of these diseases through multiple mechanisms, including inflammation, oxidative stress and structural modifications[34].

4.2.1. Cardiovascular Disease: AGEs are known to accumulate in the walls of blood vessels, leading to increased arterial stiffness and the development of atherosclerotic plaques. The cross-linking of collagen and elastin by AGEs impairs the normal elasticity of blood vessels, contributing to hypertension and an increased risk of cardiovascular events such as heart attacks and strokes. Additionally, the interaction of AGEs with RAGE on the surface of endothelial cells promotes the production of pro-inflammatory cytokines and adhesion molecules, leading to chronic inflammation and endothelial dysfunction, further exacerbating the development of atherosclerosis.

4.2.2. Diabetes and Its Complications: In individuals with diabetes, the elevated blood glucose levels lead to increased non-enzymatic glycation and the formation of AGEs. These AGEs contribute to the development of diabetic complications, including nephropathy, retinopathy and neuropathy. In the kidneys, the accumulation of AGEs leads to the cross-linking of glomerular basement membrane proteins, impairing filtration and contributing to the development of diabetic nephropathy[39,40]. In the retina, AGEs can cause the cross-linking of retinal capillary basement membranes, leading to microvascular damage and the development of diabetic retinopathy. In the peripheral nerves, the accumulation of AGEs can impair nerve conduction and contribute to the development of diabetic neuropathy[41-43].

4.2.3. Neurodegenerative Diseases: AGEs have been implicated in the pathogenesis of several neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease. In the brain, the accumulation of AGEs can lead to the cross-linking of proteins, such as amyloid-β and tau, contributing to the formation of amyloid plaques and neurofibrillary tangles, which are hallmarks of Alzheimer's disease. Additionally, AGEs can activate microglia and astrocytes, leading to chronic neuroinflammation and the release of pro-inflammatory cytokines, further exacerbating neuronal damage[36,38]. In Parkinson's disease, the accumulation of AGEs has been linked to the aggregation of α-synuclein, a key protein involved in the formation of Lewy bodies, and the impairment of mitochondrial function, leading to increased oxidative stress and neuronal death[37].

4.2.4. Cancer: AGEs have also been implicated in the development and progression of cancer. The formation of AGEs can lead to the modification of proteins and DNA, promoting genetic instability and the activation of oncogenic signaling pathways. Additionally, the interaction of AGEs with RAGE can promote the production of pro-inflammatory cytokines and growth factors, creating a tumor-promoting microenvironment. The chronic inflammation and oxidative stress induced by AGEs can also contribute to the development of cancer by promoting the survival and proliferation of cancer cells and by impairing the immune response against tumor cells[44,45].

4.2.5. Osteoporosis: The accumulation of AGEs in bone tissue can lead to the cross-linking of collagen fibers, impairing the normal turnover and remodeling of bone. This can result in decreased bone density and increased fragility, contributing to the development of osteoporosis[46-48]. The impaired bone remodeling and the increased brittleness of bone tissue make individuals more susceptible to fractures, a common and serious complication of osteoporosis.

4.3. Methods to Prevent or Mitigate the Negative Effects of Glycative Stress

Several strategies have been developed to prevent or mitigate the negative effects of glycative stress, including the use of antioxidants, dietary modifications, and pharmacological interventions.

Antioxidants play a crucial role in neutralizing reactive oxygen species (ROS) and reducing oxidative stress, which is a major contributor to the formation of AGEs. Common antioxidants include vitamins C and E, which can scavenge free radicals and protect cellular components from oxidative damage[49,50]. Additionally, polyphenols, found in fruits, vegetables and tea, have been shown to inhibit the formation of AGEs and reduce oxidative stress. For example, resveratrol, a polyphenol found in red wine, has been shown to have anti-glycation and anti-inflammatory properties, potentially reducing the accumulation of AGEs and the development of age-related diseases[49-51].

Also, Dietary modifications can significantly reduce the intake of exogenous AGEs and the formation of endogenous AGEs. A diet rich in fresh fruits, vegetables, whole grains, and lean proteins, and low in processed foods, high-fat foods and foods cooked at high temperatures (such as grilled or fried foods), can help reduce the overall burden of AGEs[45]. Cooking methods that involve lower temperatures, such as steaming, boiling and poaching, can also reduce the formation of AGEs. Additionally, the consumption of foods with a low glycemic index can help maintain stable blood glucose levels, reducing the rate of non-enzymatic glycation and the formation of AGEs[38].

Several pharmacological agents have been developed to target the formation and accumulation of AGEs. Aldose reductase inhibitors, such as epalrestat, have been shown to reduce the formation of AGEs by inhibiting the conversion of glucose to sorbitol, a precursor in the polyol pathway. Pyridoxamine, a form of vitamin B6, has been shown to inhibit the formation of AGEs by scavenging dicarbonyl compounds, such as methylglyoxal. Additionally, RAGE antagonists, such as soluble RAGE (sRAGE) and RAGE antibodies, have been developed to block the interaction of AGEs with RAGE, thereby reducing the activation of pro-inflammatory signaling pathways and the development of chronic inflammation.

However, it's important that lifestyle changes, such as regular exercise and smoking cessation, can also help reduce the burden of AGEs. Regular physical activity has been shown to improve insulin sensitivity, reduce oxidative stress, and enhance the body's ability to detoxify and repair damage from glycation reactions. Smoking, on the other hand, is a significant source of exogenous AGEs and can exacerbate the formation of endogenous AGEs through the generation of ROS and the induction of oxidative stress[33,52]. Quitting smoking can therefore significantly reduce the overall burden of AGEs and the risk of developing age-related diseases.

In conclusion, the impact of glycative stress on aging is multifaceted, involving the acceleration of the natural aging process and the development of various chronic diseases. By understanding the mechanisms by which AGEs contribute to these processes, effective strategies can be developed to prevent or mitigate the negative effects of glycative stress. The use of antioxidants, dietary modifications, pharmacological interventions and lifestyle changes can all play a crucial role in reducing the burden of AGEs and promoting healthy aging.

5. Conclusion

In summary, glycative stress plays a pivotal role in the aging process and the development of various chronic diseases through the accumulation of advanced glycation end products (AGEs). This review has elucidated the mechanisms by which AGEs are formed, their detrimental effects on cellular and tissue function, and their contribution to age-related pathologies such as cardiovascular disease, diabetes complications, neurodegenerative disorders, cancer and osteoporosis. Studies across multiple model organisms, including yeast, nematodes, fruit flies and mice, have consistently demonstrated the conserved nature of glycative stress and its impact on lifespan and health span.

Moreover, strategies to mitigate the negative effects of glycative stress-such as the use of antioxidants, dietary modifications, pharmacological interventions, and lifestyle changes-have shown promise in reducing AGE accumulation and promoting healthier aging. Emphasizing a low-sugar diet, minimizing the intake of processed foods, adopting cooking methods that limit AGE formation, and maintaining regular physical activity are practical approaches that individuals can incorporate into their daily lives to combat glycative stress.

As the global population continues to age, understanding and addressing glycative stress becomes increasingly important for improving quality of life and reducing the burden of age-related diseases. Future research should focus on developing more effective interventions and exploring the underlying mechanisms of AGE-related damage. By fostering a proactive and health-conscious lifestyle, individuals can significantly influence their aging trajectory and enhance their overall well-being.

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