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Review Article

Role of advanced glycation end products in cellular signaling ☆

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ABSTRACT

Improvements in health care and lifestyle have led to an elevated lifespan and increased focus on age-associated diseases, such as neurodegeneration, cardiovascular disease, frailty and arteriosclerosis. In all these chronic diseases protein, lipid or nucleic acid modifications are involved, including cross-linked and non-degradable aggregates, such as advanced glycation end products (AGEs). Formation of endogenous or uptake of dietary AGEs can lead to further protein modifications and activation of several inflammatory signaling pathways. This review will give an overview of the most prominent AGE-mediated signaling cascades, AGE receptor interactions, prevention of AGE formation and the impact of AGEs during pathophysiological processes.

Contents

Abbreviations: ADAMST, a disintegrin and metalloproteinase with a thrombospondin type 1 motif; AGE, advanced glycation end products; E, from embryonic day; EGFR, epidermal growth factor receptor; ERK, extracellular-signal regulated kinase; F3NK, fructosamine 3-phosphokinase; FKHRL1, forkhead transcription factor; HMGB1, high-mobility-group-protein B1; HNE, 4-hydroxy-*trans*-2-nonenal; Jak1/2, Janus kinase 1/2; LDL, low density lipoprotein; HDL, high density lipoprotein; MDA, malondialdehyde; MEKK, mitogen-activated protein/ERK kinase kinases; MnSOD, manganese superoxide dismutase; Nf-κB, nuclear factor-light-chain-enhancer of activated B; PIK3, phosphoinositol 3 kinase; RAGE, receptor of AGEs; RCC, reactive carbonyl compounds; S100B, S100 calcium binding protein B; SIRt1, NAD^+-dependent deacetylase and survival factor 1; SR-A, scavenger receptor class A; Stat 1/2, signal transducers and activators of transcription 1/2; VSMC, vascular smooth muscle cells

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Introduction

The pursuit of immortality and eternal youth has fascinated people for thousands of years and led to a growing interest in aging and clinical research. Since 1840 life expectancy has increased enormously and according to statistics will increase further to 90 years until 2050 [1]. Over the past few decades improvements in health care (including managements of infectious diseases) and supply of nutritional compounds are the main reasons for the increasing lifespan. But the older people get, the higher the risk of acquirement of age-related diseases is. As a result, the number of age-associated and chronic diseases has increased constantly [2]. In addition to the rising age, a worldwide rapid increase in Western lifestyle—including elevated consumption of highly processed food and sugar, smoking as well as little physical activity already in the young generation—increases the incidence in chronic diseases [3–6]. In particular, neurodegenerative and cardiovascular diseases play the most important roles in limiting quality of life of the aging population. Furthermore, the main problem is that such diseases are no longer limited to elderly people. More often, young and middle-aged people are affected by such diseases, resulting in reduced working capacity, loss of life quality and a financial burden for the healthcare system. A lot of chronic diseases are associated with accumulation of age-related modified biomolecules. Normally, cell constituents which are no longer functional are repaired or removed by cellular defense mechanisms. Aggravated by the fact that endogenous repair and degradation systems become increasingly impaired during the aging process, damaged and dysfunctional cell components can accumulate and become non-degradable. In the process of normal aging, a gradual accumulation of modified proteins, lipids and nucleic acids in body fluids or cells is not unusual. Elevated levels of damaged and accumulated proteins are responsible for forming bulky aggregates and plaques that are common for neurodegenerative and vascular diseases [7,8]. An increase of oxidative stress during aging promotes further protein modifications and leads to the impairment of defense mechanisms over time [9–13]. Additionally, it is believed that high intake of glucose and fat, due to the Western diet, accelerate the development of chronic diseases, such as arteriosclerosis, sarcopenia, cataracts, Parkinson′s disease, vascular dementia and diabetes [14–18]. Furthermore, genetic predisposition and increasing amounts of environmental reactive substances, such as xenobiotics, pharmaceuticals and toxins also have the ability to accelerate chronic diseases [19] Consequently, a lot of different causes may be responsible for the modification of biomolecules. Protein glycation, oxidation and nitration are the most important non-enzymatic protein modifications involved in the formation of endogenous protein aggregates.

At the moment one of the best studied substance classes is the heterogeneous group of advanced glycation end products. The spontaneous discovery of AGEs goes back to the investigation of the non-enzymatic browning reaction by Maillard in 1912 [20]. He was the first to observe and describe brown-colored end products after the reaction of glucose with the amino acid glycin. Today, AGEs are widely used by the food industry to improve taste, safety and bioavailability of food [21]. The formation of AGEs during food preparations is a very fast procedure, given that formation of AGEs rises in parallel to the increasing temperature and sugar concentration. Due to the lower temperature, AGE formation *in vivo* is a prolonged process. It is in general believed that the long-term formation of AGEs *in vivo* affects especially long-lived proteins, such as hemoglobin, alkaline phosphatase, lysozyme, collagen or elastin [22,23]. In the case of collagen, AGE cross-links are responsible for stiffening of the extracellular matrix (ECM) and often involved in organ and vessel dysfunction [24]. In addition to their long biological half-life, they are also directly exposed to the high extracellular glucose levels and therefore an appropriate target. This glycation results in alteration of protein structure and makes them more resistance to degradation processes, ending in the accumulation of cross-linked products in cells and body tissues [23]. Due to the amount of reactive substances that can cause cellular modifications, this review focuses primarily on role of AGEs in cellular signaling. Different precursors, arising out of glycation or lipid peroxidation are responsible for the formation of endogenous advanced glycation end products *in vivo*.

Formation of advanced glycation end products

During the aging process but also increasingly in young generations, a rise in blood glucose levels due to the Western lifestyle is no longer an uncommon feature. Over the years, elevated blood glucose levels will lead to insulin deficiency, resulting in hyperglycemia, kidney disease and eye disorders, the main secondary diseases of diabetes type 2. Apart from increased blood glucose levels, an increase in intra- and extracellular stress is also crucial for such diseases.

In addition, there are several studies which demonstrating a positive effect on metabolism by mild oxidative stress [25–27]. Throughout phagocytosis ROS play a crucial role in the defense of pathogens, suggesting the protective effect of mild doses of oxidative stress [28]. However, elevated levels of ROS lead to oxidation of proteins, lipids and nucleic acids increases. Normally, there is a balance between oxidants and antioxidant defense. During aging, the equilibrium of prooxidants and antioxidants shifts to the former, leading to a marked rise in reactive oxygen species (ROS). Usually, oxidized proteins are degraded by the 20S proteasome of the Ubiquitin–Proteasome-System (UPS) [29–31]. Located in the cytosol and nucleus of each cell, it is responsible for the degradation of short-lived and unfolded oxidized proteins. The cylindrical proteasome consists of two main parts, two outer α-rings for binding the substrate and two inner β-rings responsible for the proteolytic activity. Formation of cross-linked proteins, can cause inhibition of the UPS [31]. Due to their bulky structure, AGEs are able to block the entry of the proteasomal core [20,32,33]. The resulting decrease in proteolytic activity leads to an increase