Review

MOLECULAR METABOLISM

Vascular effects of advanced glycation endproducts: Clinical effects and molecular mechanisms

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ABSTRACT

The enhanced generation and accumulation of advanced glycation endproducts (AGEs) have been linked to increased risk for macrovascular and microvascular complications associated with diabetes mellitus. AGEs result from the nonenzymatic reaction of reducing sugars with proteins, lipids, and nucleic acids, potentially altering their function by disrupting molecular conformation, promoting cross-linking, altering enzyme activity, reducing their clearance, and impairing receptor recognition. AGEs may also activate specific receptors, like the receptor for AGEs (RAGE), which is present on the surface of all cells relevant to atherosclerotic processes, triggering oxidative stress, inflammation and apoptosis. Understanding the pathogenic mechanisms of AGEs is paramount to develop strategies against diabetic and cardiovascular complications.

Keywords Advanced glycation endproducts; Endothelium; Vascular

1. INTRODUCTION

Morbidity and mortality among people with diabetes mellitus are mostly triggered by premature cardiovascular disease (CVD) [1,2]. Elevated levels of circulating advanced glycation endproducts (AGEs) in the presence of hyperglycemia are believed to play a major role in the pathogenesis of macrovascular and microvascular disease observed in diabetes mellitus [3–6]. This review briefly describes the source of AGEs, their mechanisms of action and the specific effects on cells implicated in vascular homeostasis. Furthermore, key data from animal studies is presented along with the clinical evidence for their effects at the macrovascular and microvascular levels.

1.1. Literature research

A PubMed search was performed until September 2013 using the terms "advanced glycation endproducts" in combination with the terms "microvascular", "macrovascular", "endothelium", "retinopathy", "nephropathy", "neuropathy" or "cardiovascular".

2. DEFINITION AND SYNTHESIS OF AGEs

AGEs are a heterogeneous group of compounds formed by the nonenzymatic glycation of proteins, lipids or nucleic acids [7,8] within the so-called "Maillard reaction", a tribute to the French scientist Louis Camille Maillard (1878–1936). This reaction consists of several steps (Figure 1). The first, reversible step takes place between the carbonyl group of a reducing sugar and an aminoterminal group of a protein, lipid or nucleic acid generating a so-called "Schiff base". By structural irreversible rearrangements, more stable keto-amines are formed, called Amadori products (e.g. the $HbA1_c$) [9]. The Amadori products undergo further structural changes through oxidation, dehydration and degradation to finally yield highly stable AGEs compounds [9,10].

The carbonyl groups necessary for the reaction do not exclusively originate from carbohydrate metabolism, but can be also formed during lipid or protein degradation [11]. When the carbonyl group originates from the lipid catabolism (e.g. malondialdehyde), the products of the reaction are termed "advanced lipoxidation endproducts" (ALEs) [11]. However, the differentiation between AGEs and ALEs is not always possible: N^{ε}-carboxymethyllysine (CML), for example, can be formed during either carbohydrate or lipid catabolism and can therefore be attributed both terms AGE or ALE.

Usually the reaction leading to the formation of AGEs may take weeks to years and may affect especially long-lived substrates like collagen [12]. Under certain conditions, such as increased substrate availability (e.g. hyperglycemia), increased temperature and increased oxidative stress, the formation of AGEs can be reduced to several hours [13], also affecting short-lived substrates like hormones (e.g. insulin), enzymes,

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Received November 9, 2013 • Revision received November 17, 2013 • Accepted November 18, 2013 • Available online 7 December 2013

http://dx.doi.org/10.1016/j.molmet.2013.11.006

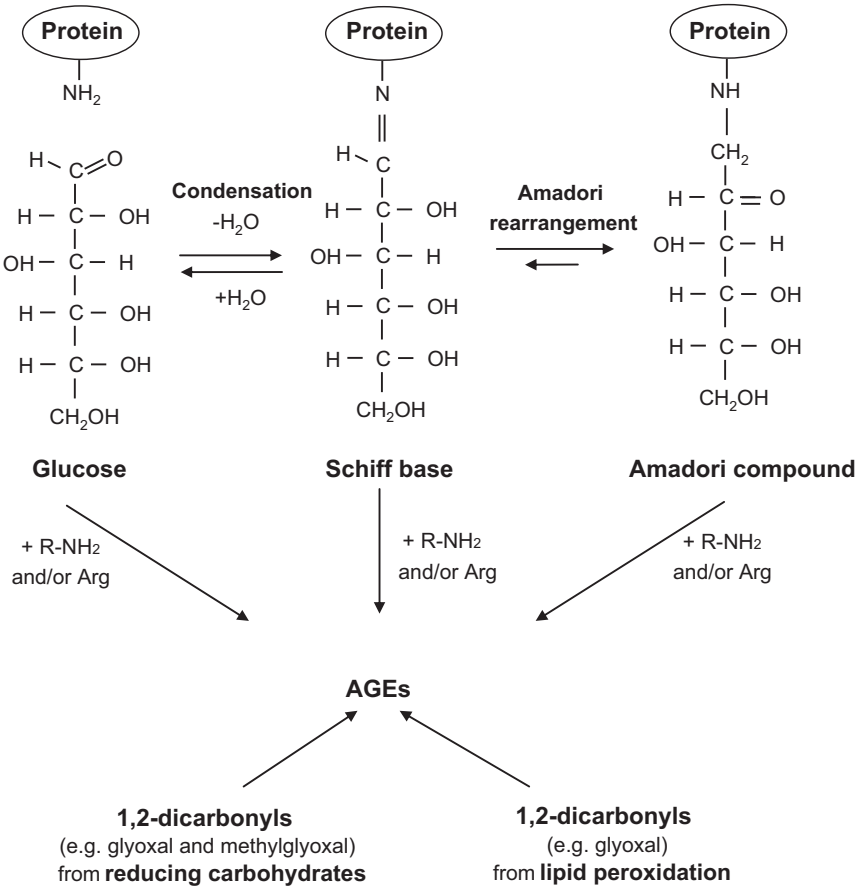

Figure 1: The synthesis of advanced glycation endproducts (AGEs) is a nonenzymatic reaction where in its classical form the reactive carbonyl group of a sugar reacts with the nucleophilic amino group of an amino acid (e.g. arginine = Arg) or a protein (R-NH_2). Adapted from Ahmed et al., Mol. Nutr. Food Res. 2005, 49:691–699 and T. Henle, Amino Acids 2005, 29:313–322.

amino acids or lipids and thus inducing functional and/or structural changes [14–18]. Highly reactive dicarbonyl compounds are generated during the conversion of Amadori products to AGEs, with methylglyoxal (MG) and 3-deoxyglucosone being the most studied AGE dicarbonyl precursors [19,20]. AGEs act either by modifying substrates, or by interacting with specific receptors; these mechanisms will be detailed in the course of this article.

Three main groups of AGEs have been described: (1) fluorescent cross-linking AGEs (e.g. pentosidine and crossline); (2) non-fluorescent cross-linking AGEs such as imidazolium dilysine cross-links resulting from reactions between glyoxal derivatives and lysine residues; (3) non-cross-linking AGEs (e.g. CML) [21–24].

3. SOURCES AND METABOLISM OF AGES

AGEs can be formed within the organism (endogenous source) or can originate from exogenous sources. Although AGEs are better known as by-products of hyperglycemia, they also form within food during heat-enhanced cooking [25]. Evidence has accumulated that dietary AGEs are partially absorbed [26,27] and either retained in the body or excreted in the urine [27–29]. These dietary AGEs represent an important source for circulating AGEs under in vivo conditions [30–32]. Moreover, smoking also serves as an additional exogenous source of AGEs [33].

The most important mechanisms involved in the degradation of endogenous AGEs are extracellular proteolysis as well as the AGEs-receptor (AGER1)-mediated intracellular uptake and degradation within cells like tissue macrophages (Figure 3) [8]. The degradation of AGEs by macrophages generates low-molecular, soluble peptides, also known as "second generation AGEs" that leave the cells, appear in blood and are finally excreted by the kidney depending on the kidney function [29,34]. In the liver, Kupffer cells and endothelial cells also seem to play an important role in the endocytosis and degradation of glycated substrates [35]. Under physiologic conditions, AGEs accumulate with age [36], but their accumulation seems to be exacerbated by some pathologic conditions: diabetes mellitus, renal failure, cardiovascular disease, Alzheimer's disease, rheumatoid arthritis, and others [3,10,31,37–39]. In these conditions, AGEs do not seem to be innocent bystanders, but rather contribute to pathophysiologic alterations.

4. METHODS FOR MEASURING AGES

Several methods are available for the measurement of AGEs. Circulating or tissue-bound AGEs can be measured by (i) enzyme-linked immunosorbent assays (ELISA) using monoclonal or polyclonal antibodies [30], (ii) fluorescence spectroscopy using the fluorescence properties of some AGEs [40], or (iii) high-performance liquid chromatography (HPLC) and mass spectrometry (MS), with the later method being probably the most reliable [10]. MS-based methods allow, for example, for measurements of the AGEs' representative CML in the urine by combining isotope dilution and gas chromatography (GC)–MS analysis. This method is sensitive, reproducible,

