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Invited Review

Advanced glycation endproducts in food and their effects on health

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ABSTRACT

Advanced glycation endproducts (AGEs) form by Maillard-reactions after initial binding of aldehydes with amines or amides in heated foods or in living organisms. The mechanisms of formation may include ionic as well as oxidative and radical pathways. The reactions may proceed within proteins to form high-molecular weight (HMW) AGEs or among small molecules to form low-molecular weight (LMW) AGEs. All free amino acids form AGEs, but lysine or arginine side chains dominate AGE formation within proteins. The analysis of AGEs in foods and body fluids is most often performed by ELISA or LC-MS; however, none of the methodologies cover all HMW and LMW AGEs. Most research is, therefore, carried out using 'representative' AGE compounds, most often N^{ε}-carboxymethyl-lysine (CML). Only LMW AGEs, including peptide-bound forms, and carbonyls may be absorbed from the gut and contribute to the body burden of AGEs. Some AGEs interact with specific pro- or anti-inflammatory receptors. Most studies on the biological effects of AGEs have been carried out by administering heated foods. The pro-inflammatory and deteriorating biological effects of AGEs in these studies, therefore, need further confirmation. The current review points out several research needs in order to address important questions on AGEs in foods and health.

Contents

Abbreviations: AGEAGE, advanced glycation endproduct; AGER1, advanced glycation endproduct receptor 1; ALE, advanced lipoxidation endproduct; apoE, apolipoprotein E; BSA, bovine serum albumin; CEL, N^{ε}-carboxyethyllysine; CML, N^{ε}-carboxymethyl-lysine; CROSSPY, 1,4-bis(5-amino-5-carboxy-1-pentyl)pyrazinium radical cation; DAD, diode array detector; DODIC, imidazolium cross-link derived from 3-deoxyglucosone and lysine-arginine; DOLD, imidazolium cross-link derived from 3-deoxyglucosone and lysine-lysine; ELISA, enzyme-linked immunosorbent assay; GO, glyoxal; GODIC, imidazolium cross-link derived from glyoxal and lysine-arginine; GOLD, imidazolium cross-link derived from glyoxal and lysine-lysine; GC, gas chromatography; HMW, high molecular weight; HPLC, high performance liquid chromatography; LDL, low-density lipoprotein; LMW, low molecular weight; MAPK, mitogen-activated protein kinases; MG, methylglyoxal; MG-H, methylglyoxal-derived hydroimidazolone; MODIC, imidazolium cross-link derived from methylglyoxal and lysine-arginine; MOLD, imidazolium cross-link derived from methylglyoxal and lysine-lysine; MRP, Maillard reaction product; MS, mass spectrometry; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor kappa B; PBMC, peripheral blood mononuclear cells; RAGE, receptor for advanced glycation endproducts; SIRT1, sirtuin-1; sRAGE, soluble receptor for advanced glycation endproducts; T2D, type 2 diabetes; T1D, type 1 diabetes; 1-DG, 1-deoxyglucosone; 3-DG, 3-deoxyglucosone.

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1. Introduction

Type 2 diabetes (diabetes) is a global health problem of increasing prevalence and it has reached epidemic proportions in many countries (Amos et al., 1997; Danaei et al., 2011; Fox et al., 2006; King et al., 1998; Wild et al., 2004). The risk of premature death is estimated to be doubled in individuals with diabetes. Diabetes is now the sixth leading cause of death (World Health Organization, 2013). Routine statistics based on death certificates seriously underestimate mortality from diabetes as cause of death is most often a cardiovascular or renal disease, which is, however, related to or caused by diabetes (Danaei et al., 2006; Lee, 2003). Obesity is a major risk factor for glucose intolerance and diabetes, and it is closely linked to the growing prevalence of diabetes (Hossain et al., 2007). Dietary and exercise interventions are important components of strategies for preventing the onset of diabetes in overweight and obese individuals, and others at risk of/developing diabetes.

The consumption of highly processed foods, and of fat and sugar, has increased dramatically over the past 30 years (Cordain et al., 2005). These changes in the diet are associated with an increased exposure to advanced glycation endproducts (AGEs), which are compounds formed in food during heating. AGEs are products of the Maillard reaction, where sugar moieties in food react with proteins resulting in protein cross-linking and product browning, together with formation of flavor and aroma compounds (Henle, 2005).

A high concentration of AGEs in the circulation was first described in relation to development of diabetic complications. AGEs were thought to be formed *in vivo* as a result of the high blood sugar concentrations present in diabetes (Brownlee, 1995). Since then, dietary AGEs have also been related to the development of insulin resistance and diabetes in animals, and more recently also in humans (Vlassara and Striker, 2011). Many different AGE compounds are formed during heat treatment of food, depending on the type of food and method of heat treatment. However, only a few markers have been quantified in the majority of studies due to the analytical challenges (Henle, 2005). Absorption, bioavailability, and effects of AGEs *in vivo* are in general poorly understood, and reliable analytical methods for measuring AGEs in food and in the human body are currently lacking.

There is a need to identify and address the current knowledge gaps in order to clarify the significance of AGEs in the development of diabetes. This would inform and focus future AGE research by integrating aspects of food science, analytical food chemistry, nutrition, and clinical endocrinology. Within AGE research, several important reviews have been published in the area of food science (Ames, 2008a; Henle, 2005; Henle et al., 1998; Rizzi, 2003; Wu et al., 2011a), analytical food chemistry (Ames, 2008a; Henle, 2008), and human nutrition (Ames, 2007; Calder et al., 2011; Chuyen, 2006; Henle, 2007; Kellow and Savige, 2013; Sebekova and Somoza, 2007; Tessier and Birlouez-Aragon, 2012; Vlassara and Striker, 2011). However, none of these reviews have attempted to use a cross-disciplinary approach covering all these research areas simultaneously to critically assess their importance for AGE-related health outcomes. This review has been undertaken to rethink AGEs in food science, analytical food chemistry, clinical nutrition, and nutrition-related diseases. The objective is to identify gaps in current understanding of the role of AGEs in the development of diseases and to point out some of the most important road blocks for advancing AGE research.

2. Formation of AGEs

AGEs can be formed from a variety of precursors for the Maillard reaction. In this chapter the focus is on formation in foods, including reactants, mechanisms, and inhibitors, since this is the major source of exposure to humans. Endogenous formation in live organisms including the human body is also an important source of AGEs and this is covered in the last section.

2.1. AGEs are formed as part of the Maillard reaction in food

Thermal processing is an important part of modern food preparation that can increase palatability, prolong shelf-life, and reduce