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Invited Review

Advanced glycation endproducts in food and their effects on health

Malene W. Poulsen [a], Rikke V. Hedegaard [b], Jeanette M. Andersen [a,c], Barbora de Courten [d,e], Susanne Bügel [a], John Nielsen [c], Leif H. Skibsted [b], Lars O. Dragsted [a,*]

[a] Department of Nutrition, Exercise and Sports, Faculty of Science, University of Copenhagen, Rolighedsvej 30, 1958 Frederiksberg C, Denmark
[b] Department of Food Science, Faculty of Science, University of Copenhagen, Rolighedsvej 30, 1958 Frederiksberg C, Denmark
[c] Department of Drug Design and Pharmacology, Faculty of Health and Medical Sciences, University of Copenhagen, Universitetsparken 2, 2100 Copenhagen Ø, Denmark
[d] Baker IDI Heart and Diabetes Institute, 75 Commercial Rd., Melbourne, Victoria 3004, Australia
[e] Department of Biomedical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Blegdamsvej 3, 2200 Copenhagen N, Denmark

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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.

* Corresponding author. Address: Department of Nutrition, Exercise and Sports, Rolighedsvej 30, 1958 Frederiksberg C, Denmark. Tel.: +45 35 33 24 70; fax: +45 35 33 24 83.

E-mail address: ldra@life.ku.dk (L.O. Dragsted).

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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

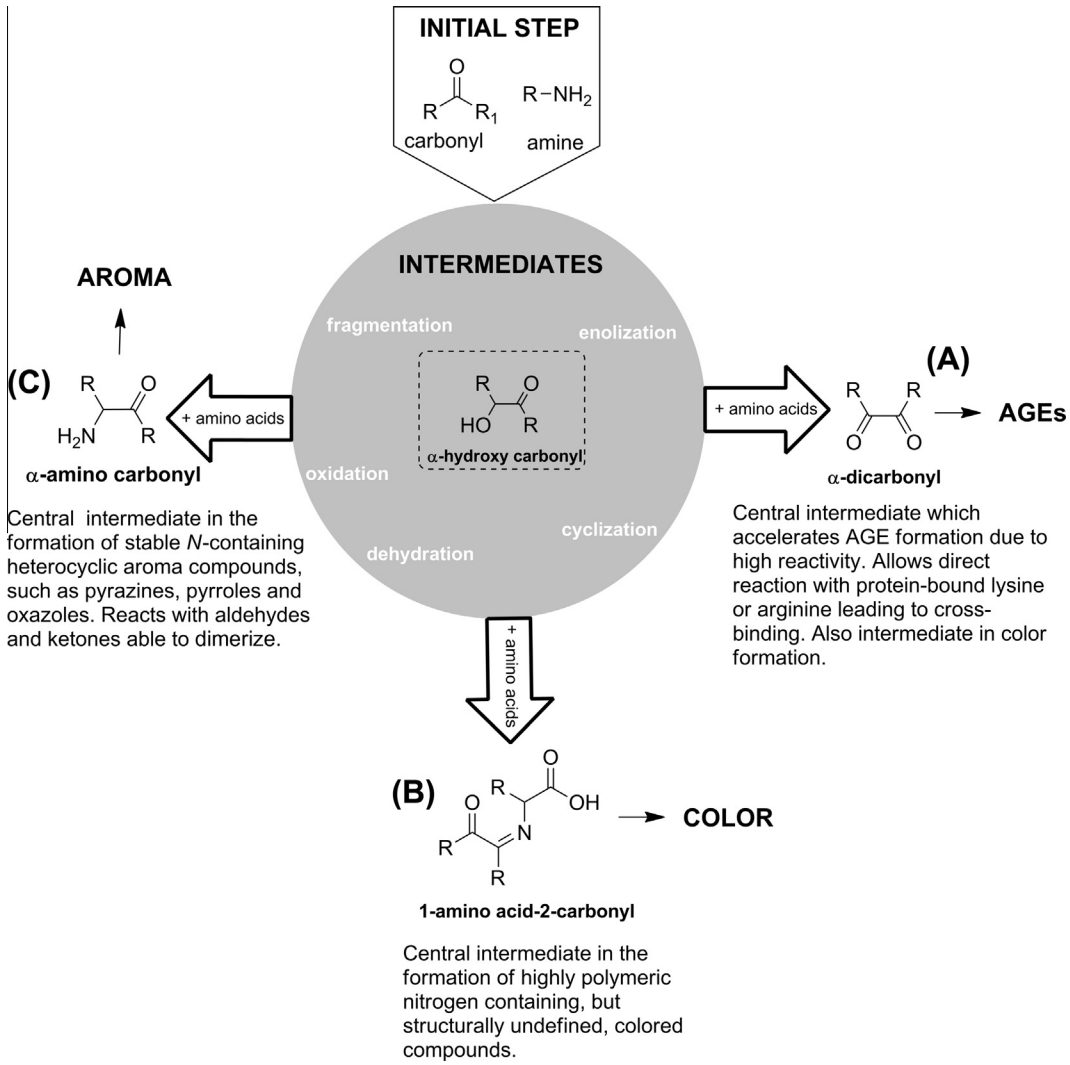

Fig. 1. Overview of the Maillard reaction showing the initial reaction step between a carbonyl and an amine together with key intermediates leading to aroma, color, and advanced glycation endproducts (AGEs). Three important groups of precursor molecules are presented, which can all be generated from α-hydroxycarbonyls: α-dicarbonyls (A), 2-(amino acid)-carbonyl compounds (B), and 2-aminocarbonyls (C).

Table 1
Content of AGEs in selected food products as calculated from quantitative data in the literature.

Food category	AGE content	Marker	Method	References
Coffee	47 kU/L	CML	ELISA	(Goldberg et al., 2004)
	–	CML	LC-MS/MS	Not available
	10.8–39.9 mg/kg protein	Pentosidine	HPLC	(Henle et al., 1997)
	50–175 μmol/L	Ornithino-imidazolinone	FAB-MS	(Henle, 2003)
	Up to 250 mg/g dry matter	Melanoidins	MALDI-TOF	(Borrelli et al., 2002)
Milk products	345 kU/L	CML	ELISA	(Goldberg et al., 2004)
	Up to 50 μmol/L	CML	HPLC	(Henle et al., 1997)
	Up to 1015 mg/kg protein	CML	RP-HPLC	(Drusch et al., 1999)
	0.337–2.066 μmol/L	CML	LC-MS/MS	(Ahmed et al., 2005)
	0.662–1.537 μmol/L	CEL		
	0.765–2.495 μmol/L	MG-H1		
	2–17 μmol/L	Pyrraline	HPLC	(Henle et al., 1997)
	500–2000 μmol/L	Pentosidine	HPLC	(Henle et al., 1997)
	–	Ornithino-imidazolinone	FAB-MS	(Henle, 2003)
Bakery products	Up to 3000 μmol/kg	Amadori products	HPLC or FAB-MS	(Henle, 2003)
	Up to 320 μmol/kg	CML		
	Up to 160 μmol/kg	Pyrraline		
	Up to 1400 μmol/kg	Ornithino-imidazolinone		

AGE = advanced glycation endproduct; CEL = N^{ε}-carboxyethyllysine; CML = N^{ε}-carboxymethyl-lysine; ELISA = enzyme-linked immunosorbent assay; FAB-MS = fast atom bombardment-mass spectrometry; HPLC = high-performance liquid chromatography; LC-MS/MS = liquid chromatography-tandem mass spectrometry; MALDI-TOF = matrix-assisted laser desorption/ionization time-of-flight; MG-H1 = methylglyoxal-derived hydroimidazolone; RP = reversed phase.

food-borne diseases. Many commercially processed foods such as dry mixes or canned soups, which often contain larger amounts of protein and carbohydrates, undergo Maillard reaction during heat-processing and they continue to brown during storage. AGEs are products of the Maillard reaction, which is initiated by the non-enzymatic reaction between a carbonyl compound and an amine group. The reaction progresses with formation of numerous Maillard reaction product (MRP) intermediates with different molecular size and composition, depending on the reacting compounds (Fig. 1). A great variety of compounds with different composition and molecular weight can be included into the food-derived AGEs, due to the presence of a large variety of AGE precursors, including reducing sugars, amino acids and peptides with free amino groups, as well as non-protein-bound amino groups.

The Maillard reaction leads to formation of a diverse range of aroma compounds, color compounds, and AGEs. The reaction is often divided into three stages: initial, intermediate, and final. The first, reversible steps in the Maillard reaction involve condensation of a carbonyl with an amine moiety and lead to formation of a Schiff base adduct. This reaction is followed by rearrangement of the Schiff base into a colorless ketoamine known as the Amadori product (Sell, 1997), which is further degraded in the intermediate stage into more "advanced" products. The diverse products of the intermediate stage are colorless or yellow derivatives, which are highly unsaturated and prone to polymerization. As the Maillard reaction proceeds, numerous reactive intermediates, including AGEs, are formed through a series of sequential and parallel reactions involving enolization, dehydration, cyclization, fragmentation, and oxidation. The condensation products of the intermediate stage are called pre-melanoidins because they lead to the final stage with formation of low molecular weight (LMW) or high molecular weight (HMW) brownish melanoidins. This process runs simultaneous with AGE formation (Finot and Magnenat, 1981; Nursten, 2005a). The exact boundary between HMW and LMW AGEs is not very clear (Finot and Magnenat, 1981). AGEs belonging to the HMW group may be distinguished from the LMW group by being protein-bound whereas the LMW AGEs are mainly derived from free amines, peptides, and amino acids. In a model system with glucose and alanine/glycine as precursors, the majority of the colored compounds formed were shown to have molecular weights <1000 Da. Final compounds with molecular weights >3000 Da were found only in trace amounts indicating that HMW AGEs or melanoidins may not readily form from LMW precursors. In contrast, reaction between the milk protein, casein, and glucose leads to a drastic increase in the molecular weights of the final colored products with values up to >100,000 Da (Hofmann, 1998b). In a product like coffee, melanoidins account for up to 25% of the dry matter (Table 1). Melanoidins are important for staling but also for antiradical properties of coffee (Hofmann et al., 2001; Hofmann and Schieberle, 2002). In general, there is a lack of information on the exact molecular structure and function of melanoidins. They are thought by some authors to provide health benefits, but may also impose health risks (Kato and Tsuchida, 1981; Somoza, 2005; Tressl et al., 1998). A further discussion of the chemistry or biological actions of melanoidins is beyond the scope of this review.

2.2. AGEs, aroma, and color products

A diversity of products is formed in the Maillard reaction, depending on the processing conditions. Some products may be formed in relatively high yields (up to 30%) under specific conditions. Other compounds are formed at ppb levels or even lower, but may be essential for color, taste, or biological actions. It has been found that changes by external (oxidizing conditions) or internal (formation of reductones) factors in the redox potential of a Maillard model system lead to an altered distribution between three important groups of precursor molecules, which may all be formed from α-hydroxycarbonyls: α-dicarbonyls (A), 2-(amino acid)-carbonyl compounds (B), and 2-aminocarbonyls (C) (Fig. 1) (Yaylayan et al., 2005). The α-hydroxycarbonyls and their three main products together constitute four precursors that might be a key in controlling the balance between aroma or color forming pathways versus formation of AGEs. The latter are the so-called pathogenic pathways (Yaylayan et al., 2005). Another intermediate of the Maillard reaction, the compound acetylformoin, has been characterized as *a chemical switch* directing the formation of different colored compounds depending on the presence of either primary or secondary amino acids as reactants (Hofmann, 1998a; Yaylayan et al., 2005). There may be other "chemical switches" between pathways leading to AGEs versus pathways leading to aroma and/or colored compounds. These could be essential in controlling formation of AGEs in food without compromising quality, but they have not yet been identified.

2.3. Reactants of the Maillard reaction

In Maillard reactions, an amine moiety, i.e. from amines, amino acids, peptides, or proteins, reacts with a carbonyl group present in reducing sugars, oxidized lipids, vitamin C, or quinones (Zamora and Hidalgo, 2005). Primary amines are more reactive than secondary amines, while tertiary amines are inactive. Thus, the primary amino group present in the side-chains of lysine is the most reactive precursor amine in proteins, but the arginine guanidino group or any *N*-terminal amino group is also reactive. For foods containing free amino acids, the free amino group also reacts (Fig. 2) (Ledl and Schleicher, 1990). The structure of the actual reacting amino moiety will determine the structure of the "advanced" Maillard derivatives formed, including AGEs (Finot and Magnenat, 1981). When the amine moiety is linked to a protein, the reaction can result in cross-linking or other irreversible modifications of the protein, which may lead to functional changes. Pentosidine is an example of a cross-linker generated by the reaction of a pentose with lysine and arginine residues of proteins (Van Nguyen, 2006). Several other cross-linkers have been identified, such as lysine dimers resulting from the reaction between two lysine side-chains and two molecules of glyoxal (GO), methylglyoxal (MG), or 3-deoxyglucosone (3-DG), named GOLD, MOLD, and DOLD, respectively, together with crosslinks between arginine and lysine, named GODIC, MODIC, and DODIC (Fig. 2) (Ahmed et al., 2002).

The reacting carbonyl group in AGE formation is often a reducing sugar. Monosaccharides (glucose and fructose), reducing disaccharides (maltose and lactose), oligo- and polysaccharides, as well as reducing pentoses (e.g. in meat) are participating in the formation of AGEs (Zamora and Hidalgo, 2005). Sugars linked through glycoside bonds in glycoproteins, glycolipids, plant glycosides, or non-reducing disaccharides, such as sucrose, can only participate in the formation of AGEs after cleavage of the glycosidic bond (Ledl and Schleicher, 1990). Endogenously, glucose is the most frequently found reducing sugar and also the most investigated carbonyl precursor under physiological conditions (Ledl and Schleicher, 1990). Once generated by the thermal treatment of carbohydrates some intermediates of the Maillard reaction accelerate further reactions. The reacting sugar is degraded and may undergo a retro-aldol cleavage of the carbon chain, leading to several α-dicarbonyl compounds, such as 2-hexosulose, 1- and 3-deoxysone, MG, and GO (Hofmann et al., 2000). These very reactive 1,2-dicarbonyls are also formed from reducing carbohydrates without involvement of amines; a process commonly called "caramelization" (Hollnagel and Kroh, 1998). The 1,2-dicarbonyls may also be formed from Amadori products or from Schiff bases via the so-called Namiki pathway (Fig. 3) (Hayashi and Namiki, 1980;

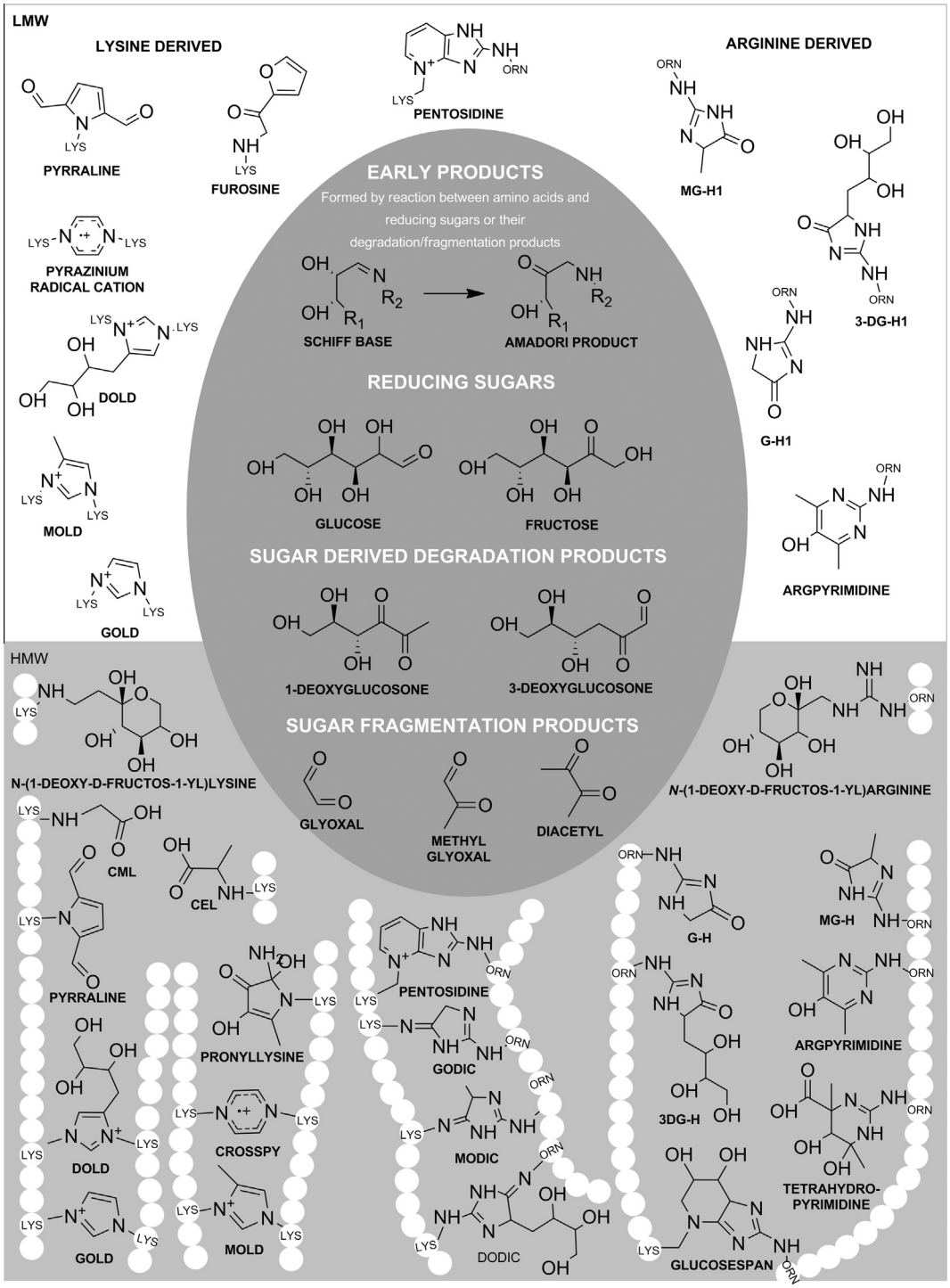

Fig. 2. Structures of selected low molecular weight (LMW) and high molecular weight (HMW) advanced glycation endproducts (AGEs) derived from the amino acids lysine (LYS), arginine (ORN ~ornithine residue), or both. Initial intermediate products of AGE formation are shown in the middle elliptic area together with the structure of common reducing sugars and their degradation and fragmentation products.

Namiki and Hayashi, 1983). Several 1,2-dicarbonyl compounds originating from mono- and disaccharides (like maltose or lactose) have been isolated from reaction mixtures, but little information is available about their presence in real food matrices (Hellwig et al., 2010). These dicarbonyls represent major precursors for the formation of important flavor compounds from free amino acids, although they are formed only in catalytic amounts. The dicarbonyls are also highly reactive towards proteins, leading to the formation of protein-bound amino acid derivatives (Henle, 2005). The guanidino group of arginine residues in protein only reacts in the presence of GO, MG, or 3-DG (and not with glucose in the initial stage), which leads to hydroimidazolones. Once formed, hydroimidazolones will lead to cross-linked products such as imidazopyridinium bridges in proteins (Ledl and Schleicher, 1990).

N^{ε}-carboxymethyl-lysine (CML) is a frequently used marker of AGEs formed in food (or endogenously in living organisms as dis-

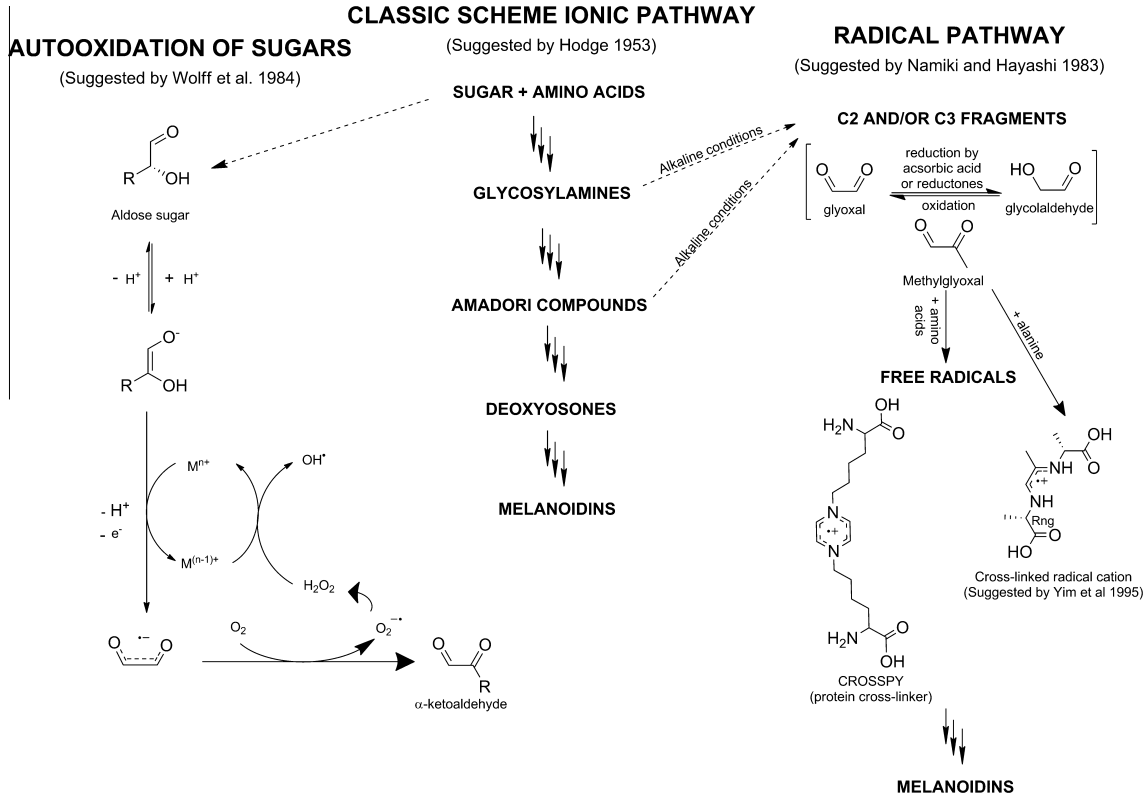

Fig. 3. Pathways leading to browning products in food including the classical scheme proposed by Hodge in 1953 and selected pathways involving formation of intermediary radicals, either by the reaction between sugar fragmentation products and amino acids or by autoxidation of sugars.

cussed in Section 2.8). CML can be formed through various pathways, for example by condensation of glucose with the ε-amino group of lysine, where the Amadori rearrangement product fructoselysine is produced as an unstable intermediate and subsequently undergoes oxidation to form CML. Another pathway depends on reaction of GO directly with the ε-amino group in lysine, while in an analogous reaction MG forms N^{ε}-carboxyethyl-lysine (CEL) (Ames, 2008a). Another frequently measured compound is furosine, which is formed by acid hydrolysis of the protein-bound Amadori product of lysine (Fig. 2) (Krause et al., 2003).

2.4. Radicals and AGE formation

Even though the Maillard reactions have been intensively studied since their discovery in 1912 by the French chemist, Louis Camille Maillard, the participation of radicals as reaction intermediates has received little attention. This is probably because detection of radicals is troubled by analytical difficulties, which are partially caused by the complex matrix arising as the Maillard reaction proceeds. In addition, direct observation of radicals at low concentrations requires highly specialized instrumentation, such as electron spin resonance spectrometers (Rizzi, 2003).

The Maillard reaction has now been recognized as an ionic pathway predominating at pH 5, but increasing pH facilitates oxidative conditions and increases radical participation (Fig. 3) (Cammerer and Kroh, 1996; Hodge, 1953). The structure of the reacting amino acid has comparatively little effect on the radical/ionic ratio, especially at high pH (Cammerer and Kroh, 1996). Radical production seems, therefore, mainly to depend on the sugar structure. Monosaccharides are more prone to radical formation due to the rate limiting bond cleavage of the glycosidic bond of disaccharides prior to oxidation (Georgescu et al., 1999).

Simple monosaccharides have been shown to autoxidize under physiological conditions forming reactive dicarbonyl compounds and hydrogen peroxide via reactive intermediates of oxygen and carbon-centered radicals (Wolff et al., 1984). Radical intermediates in the metal-ion catalyzed oxidation of glyceraldehyde have been proposed to be major reactants in a general mechanism for the oxidation of carbohydrate molecules containing an α-hydroxy-β-keto moiety, R-CHOHC=O. The carbohydrate enolate is oxidized in a one-electron oxidation by a transition metal ion to form a radical anion that undergoes further oxidation by molecular oxygen to yield an α-ketoaldehyde as a final product (Fig. 3) (Wolff et al., 1984). Electron spin resonance and the spin trap DMPO were used for direct detection of the radicals formed by incubating glyceraldehyde at 37 °C and pH 8.6, thereby providing evidence for the presence of hydroxyl (·OH) and carbon-centered (·C(OH)C=O) radical intermediates (Rizzi, 2003). GO is the exclusive dicarbonyl product of glucose autoxidation and seems to be a key intermediate in oxidative browning and protein cross-linking (Wellsknecht et al., 1995). The formation of the AGE accelerating intermediates MG and GO seems to occur through fragmentation of sugars by a mechanism involving radicals.

Model studies have shown that approximately 50% of the CML formed in a glucose/lysine system originates from oxidation of Amadori products, whereas 40–50% originates from a pre-Amadori stage largely independent from glucose autoxidation and probably related to the so-called Namiki pathway of the Maillard reactions (Fig. 3) (Glomb and Monnier, 1995). The quantitative contribution of individual pathways on the formation of 1,2-dicarbonyls in food is still unclear. However, in one study, the degradation of lactose via lactulose to dicarbonyls during heating of milk seemed quantitatively more important than the degradation of the Amadori product, lactuloselysine (Berg and Vanboekel, 1994). In contrast, the production of 1-deoxyglucosone (1-DG) and 3-DG apparently does

not involve radicals, because their formation proceeds faster at a lower pH and is totally unaffected by the presence of transition metal ions (Liedke and Eichner, 2002). Maillard browning and degradation of Amadori compounds are known to be enhanced in the presence of molecular oxygen and transition metal ions.

The sugar fragmentation and protein conformational changes observed are dependent on hydroxyl radicals produced by glucose autoxidation or a closely related process. The Namiki pathway involves formation of stable intermediary radicals formed in the early Maillard reaction steps prior to the Amadori rearrangement products (Hayashi et al., 1977; Hofmann et al., 1999). Strong electron spin resonance signals have been observed in reaction mixtures of casein-MG, serum albumin-MG, and methylamine-MG (Pethig and Szentgyorgyi, 1977). These stable radicals have been identified as *N*,*N*'-dialkylpyrazine-cations and originate from the primary Schiff base. The glycolaldehyde alkylimine formed by a reverse aldol reaction of the Schiff base can lead to a dialkylpyrazinium radical cation after self-condensation (Hayashi and Namiki, 1986; Namiki and Hayashi, 1975). The formation of dialkylpyrazinium radical cations is pH dependent starting at neutral pH and increasing up to pH 11 (Liedke and Eichner, 2002). Heated aqueous solutions of bovine serum albumin (BSA) and glycolaldehyde revealed the protein-bound 1,4-bis(5-amino-5-carboxy-1-pentyl)pyrazinium radical cation (CROSSPY) as a previously unknown type of cross-linking of proteins formed both during food processing and *in vivo* (Fig. 3) (Liedke and Eichner, 2002; Yim et al., 1995). The formation of stable pyrazinium radicals in the early stage of the Maillard reaction (Namiki and Hayashi, 1981) has been studied intensively, whereas the possible interaction of short-lived intermediary radicals from sugar fragmentation products (Cammerer and Kroh, 1996) or the consequences of the formation of H_2O_2 in the presence of transition metals such as Fe or Cu is less well understood.

2.5. Modulators of AGE formation

The involvement of oxidative reaction steps with participation of radicals in the generation of central AGE intermediates can explain the underlying mechanism behind inhibitors, such as antioxidants. Antioxidants may accordingly protect against structural damage caused by the exposure of protein to glucose under oxidative conditions (Coussons et al., 1996; Hunt et al., 1988) and limit sugar fragmentation with formation of the very reactive AGE accelerators GO and MG. A deeper understanding of the role of radicals and other intermediates in the formation of AGEs, either endogenously or in food material, may provide the basis for new remedies to inhibit AGE formation. This could facilitate better control of heat-processing of foods, at the same time preventing potential deleterious effects on health of both exogenous and endogenous AGEs (Rizzi, 2003).

Various other natural compounds or synthetic ingredients have been examined in relation to inhibition or reversion of glycation. The goal is to control the Maillard reaction and increase the formation of color and aroma while preventing formation of AGEs. Formation of AGEs can be decreased by inhibitors, such as aminoguanidine, which is considered an effective AGE inhibitor by several authors in both *in vitro* and *in vivo* conditions (Uribarri et al., 2010). The prototype inhibitors are aminoguanidine, the B6-vitamer pyridoxamine (Voziyan and Hudson, 2005), and various antioxidants. Aminoguanidine has a guanidino group similar to arginine and primarily acts as a scavenger of α-dicarbonyls i.e. at the pre-Amadori stage in the Maillard reaction. Pyridoxamine primarily blocks the oxidative degradation of Amadori products (Brownlee, 1992). One focus area is the benefits of certain plants with apparent anti-glycation properties (Kim et al., 2011a). In glycation model systems based on BSA reacting with glucose or fructose, *Chrysanthemum* species strongly inhibited the formation of AGEs, including fluorescent AGEs such as pentosidine. Notably, the inhibition rate correlated with the levels of polyphenol and flavonoid components (Tsuji-Naito et al., 2009). In an *in vitro* assay for glycation of BSA by glucose the radical scavenger and metal chelator, chlorogenic acid, inhibited AGE formation with an IC50 of 148 μM and was more effective than aminoguanidine (IC50; 807 μM) (Kim et al., 2011a). Several aqueous extracts of fruit and vegetable seeds have been found to be efficient inhibitors of the reactions between glucose or MG with BSA *in vitro* (Mesias et al., 2013). Their efficiency was independent of antioxidant potential or phenolic content and therefore point to inhibitors in common foods affecting other relevant mechanisms of AGE formation.

Modulating the formation of AGEs in food products is very product dependent, since any change in processing parameters (e.g. temperature), composition (e.g. content of precursors, pH, and water content), or addition of inhibitors will influence the quality of the food. Heating processes are in many food products essential for preservation and balance between taste, appearance, and consumer acceptability. Therefore, any modulation of the content of AGEs by changes in processing must be product optimized.

2.6. Factors affecting the rate of AGE formation during cooking

The rate of formation and the diversity of the generated AGEs in food depend on factors such as composition, availability of precursors, presence of transition metals, and availability of pro- and antioxidants. Reaction time, processing temperature, concentrations of reactants, availability of water, and pH are particularly well known to have a decisive effect on the rate of the Maillard reaction (Vlassara and Uribarri, 2004). As a rule of thumb, the rate of the Maillard reaction at least doubles when the temperature is increased by 10 °C (Ledl and Schleicher, 1990). If browning is used to measure the progress of the Maillard reaction, then four weeks at 20 °C, 3 h at 100 °C, and 5 min at 150 °C give approximately the same result (Ledl and Schleicher, 1990). Factors like pH (Nursten, 2005b) and water activity greatly affect the rate of formation of MRPs. The initial pH of the reactants and the buffering capacity of the system influence both the rate and the direction of the pathway of the Maillard reaction. The rate of the Maillard reaction is considered to be low at acidic pH, but increases with increasing pH until a maximum is reached around pH 10 (O'Brien and Morrissey, 1989). Deficiency of H^+ ions, which are required to catalyze both the Amadori and Heyns rearrangements, is rate determining at high pH values (O'Brien and Morrissey, 1989). As the Maillard reaction proceeds the pH of the system decreases due to the consumption of basic amino groups and simultaneous formation of short chain acids. The reaction rate of the Maillard reaction increases exponentially with rising moisture content due to enhanced mobility of reactants, until it reaches a maximum in the intermediate moisture range (water activity, a_w 0.4–0.7) (Labuza et al., 1970; O'Brien and Morrissey, 1989). At higher moisture levels, a decrease in reaction rate is observed due to dilution of the reactants in the aqueous phase. Water is a product of the reaction, and it is probable that the law of mass action also leads to a decreased rate of reaction at high moisture levels (O'Brien and Morrissey, 1989).

Dry heat cooking has been found to promote formation of dietary AGEs as determined by immunological methods. Levels were up to 100-fold above that found in uncooked food for most food categories (Uribarri et al., 2010). However, AGE formation seems to be reduced by heating in an oven at high humidity, shorter cooking times, lower cooking temperatures, or by the use of acidic ingredients, such as lemon juice or vinegar. As an example, continuing AGE formation in already cooked meat was prevented by

exposure to acidic solutions (marinades) of lemon juice and vinegar (Uribarri et al., 2010).

2.7. Advanced lipoxidation endproducts

Advanced lipoxidation endproducts (ALEs) resulting from lipid peroxidation involves carbonyl–amine reactions and aldol condensations. ALEs are often found in high fat foods rich in phospholipids, such as meat (Hidalgo and Zamora, 2005). The role of lipids and ALEs in the formation of AGEs in food is still unclear, but is linked to liability of lipids to oxidize (Zamora and Hidalgo, 2005). The Maillard reaction and lipid peroxidation follow similar reaction pathways and share common intermediates, although the non-enzymatic chemistry of carbohydrates may either be non-oxidative or oxidative, whereas non-enzymatic lipid degradation requires oxidative conditions in order to form reactive intermediates (Hidalgo and Zamora, 2005). Lipid oxidation products are also able to modify the Maillard reaction by either promoting the reaction or by reacting with intermediates (Capuano et al., 2010). Due to these interrelationships between the Maillard pathway and lipid oxidation, AGE formation could be considered as initiated both by lipids and carbohydrates. Lipids interact in the Maillard reaction both with the amino group of the polar head of phospholipids and with the aldehydes resulting from metal catalyzed oxidation of unsaturated fatty acids (Zamora and Hidalgo, 2005). GO and MG can be produced by oxidation of lipids (Cammerer et al., 1999; Cobb and Day, 1965; Niyatishirkhodaee and Shibamoto, 1993) and of Amadori products (Cammerer et al., 1999; Hayashi and Namiki, 1986; Hidalgo and Zamora, 2005). Amino-containing lipids can induce both lipid glycation and peroxidation; e.g. products like 4-hydroxy-nonenal and CML can be derived from both lipid and protein glycoxidation (Bucala et al., 1993; Fu et al., 1996; Vlassara and Uribarri, 2004). Glycoxidation products can accelerate generation of free radicals resulting in oxidative and carbonyl stress. Carbonyl stress is a term used to encompass all reactions in biological systems driven by dicarbonyl compounds (Vlassara and Uribarri, 2004).

2.8. Endogenous AGE formation and inhibition

Glycation reactions also occur endogenously in all tissues and body fluids under physiological conditions (Ahmed et al., 2005). AGEs are formed physiologically at lower temperatures than in food, and therefore a lower diversity of compounds is found. As already mentioned, glucose is the most frequently found reducing sugar and also the most investigated carbonyl precursor under physiological conditions (Ledl and Schleicher, 1990). Physiologically formed AGEs are defined as the non-enzymatic reaction of glucose, α-oxoaldehydes, and other saccharide derivatives, with proteins, nucleotides, and lipids, in the human body (Ames, 2007; Thornalley, 1999). Endogenous glycation was demonstrated for the first time with the identification of the hemoglobin variant HbA_{1c}, in which the *N*-terminal valine residue reacted with glucose to form *N*-α-fructosylvaline (Rahbar et al., 1969). Four types of processes have been identified in the formation of AGEs under physiological conditions (Ahmed et al., 2002): (i) monosaccharide autoxidation (autoxidative glycosylation) or the degradation of saccharides unattached to a protein, (ii) Schiff's base fragmentation, (iii) fructosamine degradation, and (iv) α,β-dicarbonyl compounds formed from the degradation of glycolytic intermediates and lipid peroxidation. Many of the AGEs found in foods have also been found *in vivo*, including hydroimidazolones (derived from MG, GO, and 3-DG), CML, CEL, pyrraline, the bis(lysyl)imidazolium derivatives (MOLD, GOLD, and DOLD), pentosidine, argpyrimidine, and arginine-derived N_δ-(4-carboxy-4,6-dimethyl-5,6-dihydroxy-1,4,5,6-tetrahydropyrimidin-2-yl)-ornithine (Fig. 2) (Ahmed et al., 2002). Important sites of glycation are lysyl side chains and *N*-terminal amino groups and arginyl guanidine groups of proteins, guanyl bases of nucleotides, and amino groups of phosphatidylethanolamine and phosphatidylserine (Thornalley, 1999). In principle, all such sites are available for glycation, but the amino groups and guanidino groups with low pK_a values and non-base paired nucleotides are more susceptible than others (Thornalley, 1999). The degree of glycation of a particular group depends on a number of factors, including the concentration of the substrate group, the glycating agent, the availability of catalytic factors such as phosphate or inhibitors such as pyridoxamine, the presence of redox active transition metal ions (Fe^{3+}, Cu^{2+}), the time of exposure to these agents, and the half-life of the protein. Glycation is most abundant in long-lived, extracellular proteins, which are particularly exposed to abnormally high concentrations of glucose and other saccharide derivatives, as seen in diabetes. The proportion of glycated proteins in physiological systems is generally 0.01–1% of lysine and arginine residues. However, the abundance of Schiff's base adducts, fructosamine, and AGEs in human serum albumin in blood plasma are approximately 1–5%, 6–15%, and 0.01–7%, respectively (Baynes et al., 1984; Day et al., 1979; Thornalley et al., 1999). A higher percentage of glycation is found in phospholipids with 0.1–16% being glycated (Thornalley, 1999). The term AGEs, while literally referring to non-reactive terminal products, such as CML or pentosidine, is sometimes also used to include many reactive intermediates of the Maillard reaction such as the AGE precursors 1-DG or 3-DG and their reactive derivatives MG and GO (Vlassara and Uribarri, 2004). Physiologically, the latter forms are largely derived from triose phosphate intermediates during glycolysis (Thornalley et al., 1999), but the contribution from other pathways and from dietary sources may be considerable. For instance, the Atkins's diet has been shown to increase levels of MG in the circulation (Beisswenger et al., 2005) while spermidine has been shown to reduce glycation in diabetic rats (Jafarnejad et al., 2008). AGEs derived from nucleotides and phospholipids have not been extensively studied but should be included in the definition of AGEs when considering endogenous formation.

Endogenous inhibitors of AGE formation may be pharmaceuticals, food-derived compounds, endogenous scavengers, or enzymes. Aminoguanidine has shown efficiency in animal studies, but a human trial was discontinued due to side effects and lack of efficiency (Thornalley, 2003). Pyridoxamine has also been shown to affect AGE-related effects in a mouse model (Unoki-Kubota et al., 2010) and reduced excretion of AGEs in a human trial (Williams et al., 2007) while spermidine had similar effects in diabetic rats (Jafarnejad et al., 2008). Chlorogenic acid, a phenolic acid abundant in coffee beans and potato peel, is known as a radical scavenger and metal chelator and seems also to interfere with glucose absorption and modulation of gene expression of antioxidant enzymes (Kim et al., 2011a). Chlorogenic acid was further found to prevent high glucose-induced cytotoxicity in human lens epithelial (HLE-B3) cells in a dose-dependent manner, suggesting a potential therapeutic use of chlorogenic acid for prevention of complications of diabetes, such as cataracts (Kim et al., 2011b). In addition, chlorogenic acid and the iso-flavonoid glycoside puerarin were found to prevent MG glycation in skin explants used to study glycation and antiglycation activities of cosmetic products (Gasser et al., 2011).

Endogenously, AGE formation is limited by detoxification pathways. This relates particularly to detoxification of potent AGE precursors. Of importance is the glyoxalase system, which is an enzymatic defense against MG glycation catalyzed by reduced glutathione. More than 99% of endogenously formed MG is converted to harmless products (mainly lactate) by the glyoxalase system (Rabbani and Thornalley, 2012). Polymorphisms are known to affect enzyme activity (Peculis et al., 2013), and have been strongly implicated in diabetic complications and atherosclerosis (Wu

et al., 2011b,c). Interestingly, the glyoxalase system is under control of the transcription factor, Nrf-2, which is also controlling phase 2 defense enzymes and apoptosis (Xue et al., 2012). This provides a potential way to up-regulate glyoxalase and reduce dicarbonyl formation by exogenous factors, including several plant secondary metabolites found in the diet.

3. Measurement of AGEs

3.1. Methods

The broad range of polarities and the physical properties of AGEs make purification of samples prior to analysis and the retention and separation of AGEs by chromatography challenging. The ultimate goal is to quantify as many as possible, and ideally all AGEs in one run. However, most of the analytical work so far has been done on CML, and there is no commonly accepted method for detecting AGEs, or any commercially available kits. Standardized methods and reference materials are needed if different laboratories are to compare AGE results in a meaningful way (Smit and Lutgers, 2004).

The methods for quantification of AGEs can be divided into instrumental and immunochemical methods. The instrumental methods include high performance liquid chromatography (HPLC) methods coupled to various detectors, including diode array detector (DAD) (Rufian-Henares et al., 2004), fluorescence detector (Hartkopf et al., 1994; Munch et al., 1997), tandem mass spectrometer (MS/MS) (Ahmed et al., 2002) and gas chromatography (GC) coupled with MS (Charissou et al., 2007). The immunochemical method is primarily enzyme-linked immunosorbent assay (ELISA) (Goldberg et al., 2004).

HPLC-DAD has been used to detect the pyrraline content in certain foods, e.g. enteral formula (Rufián-Henares et al., 2004), but to use this method, UV active compounds are needed. Fluorescence has been used as a detector for AGEs that are either fluorescent, such as pentosidine, or non-fluorescent, such as CML, after derivatization with *o*-phthaldialdehyde (Hartkopf et al., 1994; Munch et al., 1997). CML has been quantified by this method in meals from two different diets (Delgado-Andrade et al., 2007). Methods have also been developed recently to measure the concentration of AGEs directly in the skin noninvasively by fluorescent techniques (Meerwaldt et al., 2005). However, stand-alone fluorescence detectors give no indication about the nature of specific fluorophores and may not be completely specific to AGEs (Thornalley, 2005). GC–MS has been used to determine the amount of CML in different food samples, including milk and meat. When GC–MS is used, volatile derivatives are needed, introducing an extra step prior to analysis (Charissou et al., 2007).

LC-MS/MS has been used for different AGEs, but mostly CML (Zhang et al., 2009). The use of LC-MS/MS increases the sensitivity compared to UV and fluorescence and needs no derivatization. The method of choice for MS/MS detection is multiple reaction monitoring, where a selected parent ion fragments into specific daughter ions. This mass transition and the retention time should, in the ideal case, be relevant only to one compound, making the method exact and suited for quantification. The use for each analyte in a sample of an added isotope-labeled analog having the same retention time but a higher mass, reduces errors resulting from e.g. matrix effect or loss of analyte during sample pre-processing.

The ELISA technique has been used extensively to measure AGEs, including nonspecific AGEs (Koschinsky et al., 1997; Makita et al., 1992), CML (Goldberg et al., 2004; Uribarri et al., 2010), and MG-derivatives (Uribarri et al., 2010). A competitive ELISA with an apparently more specific anti-CML monoclonal antibody (4G9) has also been developed and used to measure CML expressed as AGE units per 100 g food (Goldberg et al., 2004; Uribarri et al., 2010). This has been used in a large range of foods and the data used to form a public database (Uribarri et al., 2010). Recently, levels of MG-derivatives, determined by an anti-MG monoclonal antibody (3D11 mAb), have been included in this database for selected foods.

In order to base the quantification on ELISA, it is necessary that the cross-reactivity of the antibodies used is well-characterized. A thorough analysis of the epitope is needed, and a thorough understanding of the exact chemical structure of what is actually being recognized. In the literature the ELISA methods are generally only tested for cross-reactivity against a few other AGE-modified structures and a few unmodified structures (Cai et al., 2002; Mitsuhashi et al., 1997; Vlassara et al., 2002). Cross-reactivity with CEL has been observed with the monoclonal antibody 6D12, which was supposed to be selective against CML (Koito et al., 2004). Besides the characterization of the antibody the ELISA method needs to be validated in each matrix, for example by spiking, as the antigen–antibody interaction is dependent on the chemical environment (Henle, 2008). This does not seem to have been done for the wide range of food items analyzed so far (Goldberg et al., 2004; Uribarri et al., 2010) and the results of these analyses may therefore be partially misleading.

Quantification of AGEs has mainly been done by ELISA and LC-MS/MS. However, the results are reported in different units so they are difficult to compare. The quantitative results from ELISA are expressed as AGE kilounits/100 g food (Uribarri et al., 2010) while the results from LC-MS/MS are expressed as concentrations, e.g. mg/kg protein (Hull et al., 2012) or mg/kg food (Assar et al., 2009; Zhang et al., 2011). Therefore, only the relative content of AGEs may be compared between the two methods. Results from different methods have been compared in a few studies and similar results have generally not been reported (Ahmed et al., 2005; Henle, 2008; Koschinsky et al., 1997). As an example, a cola soft drink was analyzed by ELISA resulting in a relatively high AGE content compared to other soft drinks (Koschinsky et al., 1997). When analyzed with LC-MS/MS it has not been possible to reproduce these high concentrations of AGEs (Ahmed et al., 2005). Besides possible matrix problems with the ELISA method, reasons for these differences could also be that the ELISA method was not specific to single AGEs, but to undefined browning products in general. This hypothesis is supported by the report of values obtained with a more CML-specific ELISA method where the AGE content in cola was only five times higher than other soft drinks (Uribarri et al., 2010) as opposed to the previously reported 20 times higher values (Koschinsky et al., 1997).

It has been shown that the sole use of ELISA does not give satisfying results (Henle, 2008). For example, according to values obtained with ELISA, butter and olive oil should contain several hundredfold higher amounts of CML compared to the crust of whole wheat bread (Goldberg et al., 2004; Uribarri et al., 2010), but such high amounts of amino acid products in lipid samples seem unlikely (Henle, 2008). The results from ELISA also indicate that the AGE levels in olive oil are 24 times higher than in cow's milk and that levels in butter are twice as high as in olive oil. This 48-fold difference between butter and milk was compared with UPLC-MS/MS results, showing similar concentrations in butter and milk (0.37 and 0.30 mg CML/kg food, respectively). It was suggested that a matrix effect could have led to these conflicting results (Assar et al., 2009).

3.2. Hydrolysis of samples

To measure AGEs using an instrumental method such as HPLC the free form is required. This means that AGEs in peptides and proteins must be released prior to analysis. This is done by hydrolyzing the peptide bonds, thereby releasing free amino acids. Be-

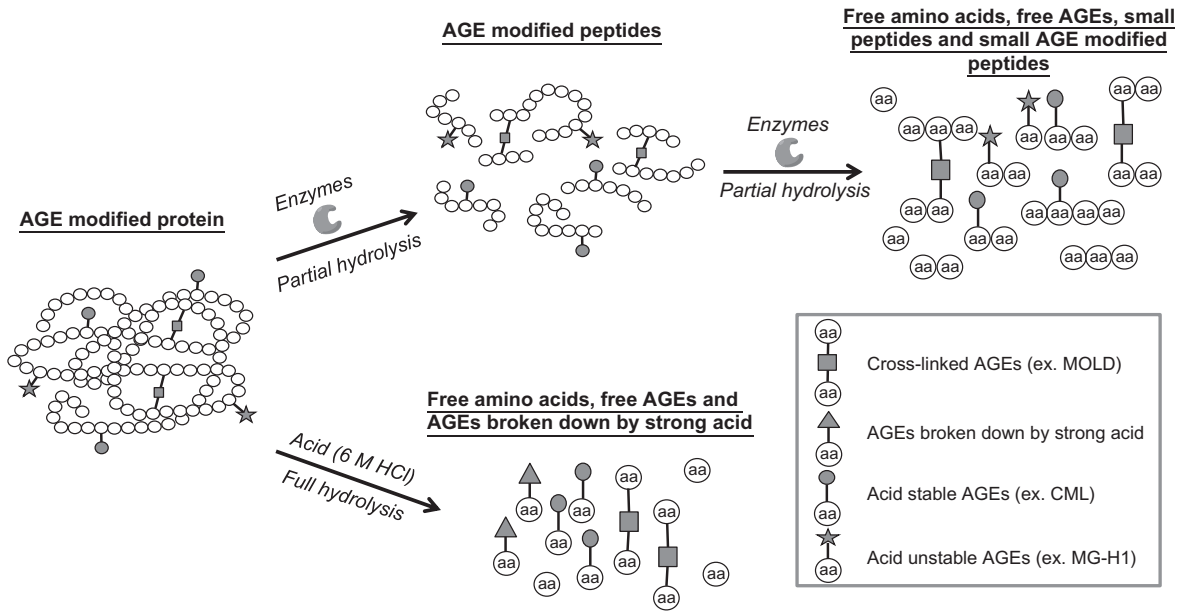

Fig. 4. Overview of the hydrolysis of an advanced glycation endproduct (AGE) modified protein. Depending on the method used, different products will be formed. Acid hydrolysis is most effective, but it will also break down AGEs, which are not stable to strong acid. Enzymatic hydrolysis, on the other hand, will probably not hydrolyze all peptide bonds and the result will be a mixture of peptides and amino acids, with and without AGE modifications.

Table 2
Enzymes of interest for future development of enzymatic hydrolysis of food for AGE analysis.

Proteases	Organism	Activity
Alcalase[a] (subtilisin)	*B. licheniformis*	Serine endopeptidase, broad specificity, pH 7–10.5
Savinase, Everlase, Esperase[a] (subtilisin)	*B. clausii*, *B. lentus*	Serine endopeptidase, broad specificity, pH 8–11
Protamex[a]	*B. licheniformis* *B. amyloliquifaciens*	Serine both endopeptidase and exopeptidase activities, pH 5–7
Neutrase[a]	*B. amyloliquifaciens*	Neutral, metallo endopeptidase, broad specificity, pH 5.5–7.5
Flavourzyme[a]	*Aspergillus oryzae*	Aminopeptidase, both endopeptidase and exopeptidase activities, pH ~7
Purafact[b] (subtilisin)	*B. lentus*	Serine endopeptidase, broad specificity, pH 10
Maxacal[b]	*Bacillus* sp.	Serine endopeptidase, broad specificity, pH 8–11
Maxatase[b] (subtilisin)	*Bacillus* sp.	Serine endopeptidase, broad specificity, pH 7–10
Protex 6L[b]	*B. licheniformis*	Serine endopeptidase, broad specificity, pH 7–10
Protex 7L[b]	*B. amyloliquifaciens*	Neutral metallo endopeptidase, broad specificity, pH 7–10
Optimase[b] (subtilisin)	*B. licheniformis*	Serine endopeptidase, broad specificity, pH 7–8.5

[a] Novozymes.
[b] Dupont Genecor.

fore hydrolysis the HMW AGEs are isolated from a sample by one of various methods, including precipitation of the protein in 20% trichloroacetic acid, Folch extraction, or ultrafiltration (Ames, 2008a). The protein hydrolysis can either be done in strong acid or by proteolytic enzymes (Fig. 4).

The classical way to perform acid hydrolysis is to heat the protein with 6 M hydrochloric acid for about 24 h at 110 °C in a sealed vessel, which is the preferred method reported in the AGE literature (Delatour et al., 2009). Acid hydrolysis is the easiest, least expensive, and most reliable procedure compared to enzymatic hydrolysis. The disadvantage, however, is that it can only be used for AGEs that are stable to these harsh conditions (Fig. 4). For the compounds that are not stable, such as hydroimidazolones and pyrralines, enzymatic hydrolysis could be an alternative (Ames, 2008a). Enzymatic hydrolysis is carried out with proteases. The proteases can be divided into two groups: endopeptidases that cleave the peptide bonds within the protein and exopeptidases that cleave the peptide bonds from the end of the protein. In order to obtain a high degree of hydrolysis, it is often necessary to use a combination of endo- and exopeptidases. In 1976, a cocktail of enzymes was used to cleave peptide bonds without cleaving any other amide bonds. The cocktail consisted of pepsin, pronase E, prolidase, and aminopeptidase (Schmitz et al., 1976). Since then, this cocktail has been used multiple times with small changes in conditions for different purposes. This enzyme cocktail has also been used to evaluate the extent of lysine modification caused by the Maillard reaction (Henle et al., 1991), and later also in the quantification of AGEs (Thornalley et al., 2003). A disadvantage is that it is unlikely to work for foods in which a lot of cross-linking has occurred, such as heavily processed food (Fig. 4). This is due to blockage of cleavage sites by modified arginine and lysine residues as well as to inhibition of the proteases by some glycation adducts (Thornalley, 2005). Trypsin cleaves lysine and arginine residues at their C-terminals within the peptide chain, but the cleavage cannot take place if the side chain of the lysine or arginine residue is modified (Ames, 2008b). These challenges with enzymatic hydrolysis can lead to an underestimation of AGE content. Acid and enzymatic hydrolysis have been compared in samples of raw and roasted almonds. The results indicated that the enzymatic hydrolysis (with the cocktail of proteases mentioned above) would result in only 70% of that of acid hydrolysis (Zhang et al., 2011). This might be

even lower for other types of foods with a higher degree of cross-linking.

Enzymes which release cross-linked AGEs have also been investigated (Glomb and Pfahler, 2001). The enzymes were proteinase K, carboxypeptidase Y, peptidase, pronase E, and aminopeptidase. The last three of these are the same as in the protease cocktail mentioned before, and these were also the ones found to be the most efficient. The combination of the enzymes gave a 63% release of GOLD compared to acid hydrolysis. Compared to the protease cocktail mentioned before, this combination was 2–3 times more effective (Glomb and Pfahler, 2001).

It is now possible to engineer proteins and thereby design enzymes for specific tasks. For example, most of the commercial detergent proteases are subtilisins, which are serine endopeptidases. They all have very broad specificity and differ primarily in temperature and pH optimum (Antrim et al., 2003). Some of the enzymes that could be of interest for the future development of enzymatic hydrolysis of food are shown in the Table 2 (Antrim et al., 2003; Gupta et al., 2002; Maurer, 2004). Protein hydrolysis is also widely used in the food industry for multiple purposes, such as elimination of allergenicity, production of flavors, detoxification, and improvement of nutritional quality (Nchienzia et al., 2010). Proteases used in this area might, therefore, also be of interest for AGE analyses or removal. It might also be possible to obtain complete hydrolysis by a system of immobilized proteases. This has been used in other areas to achieve complete hydrolysis with recoveries close to 100% (Fountoulakis and Lahm, 1998).

4. Dietary AGEs

4.1. Levels of AGEs in different foods

A large database of different food items and their AGE contents has been created by measuring CML with ELISA (Goldberg et al., 2004; Uribarri et al., 2010). In general the reported CML contents are correlated with corresponding levels of MG-derivatives (Uribarri et al., 2010). High values were found in processed meats and meat-substitutes, as well as in foods with a high content of fat and protein - all food products that are considered to belong to a Western-type diet. As described in Section 2 and 3, the estimation of the AGE content in different foods based on a single marker and/or a single method can lead to underestimation or to overestimation of AGE content in different food items, as exemplified by the cases of soft drinks, butter, and olive oils, with an overestimation of AGE contents (Assar et al., 2009). Another example is meat, where estimation by CML alone would lead to underestimation, because meat is rich in arginine. In order to evaluate the AGE content, markers of AGEs derived from both lysine and arginine must be included. Because of the limitations of the analytical approaches available the current quantitative information about the total AGE content in various foods and other complex biological matrices must be regarded as inaccurate.

A broad range of other AGEs, besides CML, have been detected in food. Lysine modifications of up to 10–20% are found, in special cases even up to 70%, during the processing of milk (Finot et al., 1981; Henle et al., 1991). However, these AGE modifications are often the early MRPs, e.g. the Amadori compounds. More advanced AGEs, such as CML, accounting for only 3–10% of the Amadori compounds, have been found in milk and other foods (Drusch et al., 1999). Another example is the sparse quantitative information existing about AGE derived from arginine residues in foods. The arginine-derived compound, ornithinoimidazolinone (δ-N-(5-methyl-4-oxo-5-hydroimidazol-2-yl)-L-ornithine), is found only at low levels in milk products but is found in greater concentrations in bakery products. This might lead to underestimation of the content of AGEs in bakery products compared to milk (Table 1). However, in a product such as coffee, ornithinoimidazolinone seems to be even more important, and probably a more useful marker for AGEs than CML. Up to 30% of arginine is modified to imidazolinone during coffee roasting (Henle et al., 1994). Another arginine derivative, pentosidine, was observed in the much lower range of 5–10 mg/kg protein in roasted coffee and up to 35 mg/kg protein in some bakery products (Henle et al., 1997).

Following its first isolation from model systems, an acid labile pyrrole derivative of lysine, pyrraline, has been quantified in several foods like milk, bakery products, and pasta using amino acid analysis or reversed phase-HPLC after enzymatic hydrolysis. The concentrations found ranged from 150 mg/kg protein in sterilized milk up to 3700 mg/kg protein in bread crusts (accounting for 15% of the lysine derivatization), indicating that pyrraline represents one of the quantitatively dominating AGEs in foods (Henle, 2003; Henle et al., 1998).

Data on the content of cross-linked AGEs in foods are limited due to the analytical challenges with hydrolysis of the AGE-modified proteins. Lysine dimers resulting from the reaction between two lysine side chains and two molecules of GO, MG, or 3-DG, namely GOLD, MOLD or DOLD (Fig. 2), respectively, were found in enzymatic hydrolysates of bakery products in the mg/kg range together with crosslinks between arginine and lysine (GODIC, MODIC, DODIC). While the aminoketose, fructoselysine, accounted for more than 90% of the observable lysine modification (Henle, 2003), MODIC has been found in up to 150 mg/kg in bakery products while GODIC and DODIC were between 10 and 50 mg/kg protein. This indicates that just like pentosidine, these amino acid derivatives may not contribute significantly to cross-linking of food proteins (Henle, 2003). The concentrations of MODIC and GODIC were found to be 5–10-fold higher than those of the corresponding imidazolium compounds, MOLD and GOLD. This establishes MODIC and GODIC as the major food protein cross-links derived from MG and GO, respectively (Biemel et al., 2001). The protein-bound 1,4-bis(5-amino-5-carboxy-1-pentyl)pyrazinium radical cation, CROSSPY, has been found in wheat bread crust, roasted cocoa, and coffee beans (Liedke and Eichner, 2002); however, its quantitative contribution to the dietary intake has not been estimated.

Knowledge of well-defined reactive dicarbonyls in food is scarce. Small amounts of MG and GO originating from enzymatic processes can be found in fermented foods such as yoghurt, wine, and beer (Marceau and Yaylayan, 2009; Weigel et al., 2004). Additionally, recent findings of measurable amounts of MG and 3-DG in a large range of food items with reversed phase-HPLC have been reported (Degen et al., 2012). Also, GO, MG, and 3-DG have be found in high concentrations in carbonated soft drinks sweetened with high fructose corn syrup. High fructose corn syrup is used as a sweetener and contributes significantly to the intake of α-dicarbonyl compounds from beverages (Lo et al., 2008).

4.2. AGE markers

Although numerous model studies dealing with isolation and structural elucidation of many possible lysine and arginine derivatives have been published, the number of compounds that have unambiguously been identified and quantified in processed foods remains surprisingly low (Henle, 2005). Quantification by either a single chosen marker, or an overall non-specific estimation by measuring fluorescence or color, are the most frequent methods used to establish the content in food or other biological materials. The choice of marker is very important for the overall estimation of the AGE content. Many AGEs are unstable and might degrade before or during measurements due to conditions such as acidity, making their quantification difficult. One example is the Amadori

products of lysine, which are quantified indirectly as the more stable furosine after acidic degradation. If the Maillard reaction progresses further, oxidative degradation of the Amadori products leads to AGEs, such as CML, CEL, and pentosidine, all of which are more acid-stable. A limitation of the present data on the content of AGEs in foods is the reliance on CML (Goldberg et al., 2004; Uribarri et al., 2010) and furosine (Erbersdobler and Somoza, 2007) for the estimation of total AGE contents. Both CML and furosine have limitations as general AGE markers. Furosine is formed by acid hydrolysis of Amadori products of lysine making it impossible to distinguish between different precursors (Henle, 2005), while CML can originate from lipid oxidation as well as glycation (Fu et al., 1996), resulting in an overestimation of glycation reactions in foods with a high fat content (Krause et al., 2003).

Several important AGEs have been chemically synthesized. In most syntheses of CML the final product was isolated as the corresponding chloride salt (Ahmed et al., 1986; Csuk et al., 2009; Delatour et al., 2006; Glomb and Monnier, 1995; Matsutani et al., 1979; Pashikanti et al., 2010). The synthetic routes proceed either *via* reductive amination of glyoxylic acid with an N^{α}-protected lysine, (Csuk et al., 2009; Delatour et al., 2006) or *via* alkylation of an N^{α}-protected lysine with haloacetic acids (Ahmed et al., 1986; Glomb and Monnier, 1995; Grunwald et al., 2006; Matsutani et al., 1979). However, these syntheses suffer from low yields and/or cumbersome purification procedures that generally only allow for synthesis of CML on a milligram scale. Recently, we (Andersen et al., 2012) and another research group (Csuk et al., 2009) reported methods where CML was synthesized on a gram scale, which would make it possible to produce CML for exposure studies. These methods apply peptide chemistry methods to provide free CML as the pure zwitterion in a crystalline form. Also MG-derived hydroimidazolones have been synthetized. Three different isomers, MG-H1, MG-H2, and MG-H3 exist of which MG-H1 is the major form *in vivo* (Ahmed et al., 2002). This has been synthesized in varying amounts ranging from 50 to 800 mg (Hellwig et al., 2011; Henle et al., 1994; Klöpfer et al., 2010). Recently, preparative-scale synthetic routes that afford access to all three of the MG-derived hydroimidazolones, as both amino acids and peptide conjugates, have been reported (Wang et al., 2012).

A range of other AGEs have also been synthesized in small scale, including pentosidine (Liu et al., 2010; Rosenberg and Clark, 2012; Visentin et al., 2010; Yokokawa et al., 2001), pyrraline (Henle and Bachmann, 1996; Nakayama et al., 1980), GOLD (Visentin et al., 2010), MOLD (Visentin et al., 2010), argpyrimidine (Al-Abed et al., 1996; Glomb et al., 2001), CEL (Ahmed et al., 1997), GO-derived hydroimidazolones (Thornalley et al., 2003), GODIC (Lederer and Klaiber, 1999), and MODIC (Lederer and Klaiber, 1999).

Finally, peptides have been synthesized on a small scale where CML, CEL, MG-H1, MG-H2, and MG-H3 have been incorporated (Gruber and Hofmann, 2005). Development of peptide-bound AGE syntheses will also allow the synthesis of labeled compounds that can be quantified by LC-MS/MS and traced in the body. Larger-scale synthesis of well-defined HMW AGEs has not yet been reported. Such products would allow highly controlled feeding studies to be conducted that could be used to elucidate the exact biological effects of single AGE-modified proteins.

4.3. Exposure to AGEs from food

The amount of AGEs consumed in a conventional diet has been claimed to be quantitatively greater than the total amount of AGEs present in plasma or tissues based on chromatographic methods (Henle, 2003). The exposure to other AGEs than CML has been evaluated in several cases. For heat-processed foods, such as heated milk, bakery products, and coffee, consumption of protein-bound amino acid derivatives of the Maillard reaction leads to an exposure of 1500–4000 μmol/day for Amadori compounds and 100–300 μmol/day for AGEs, such as pyrraline and CML (Henle, 2003). The average total dietary exposure to AGEs in adults has been calculated to be around 16,000 AGE kU/day (Uribarri et al., 2005) when the estimation was based on ELISA. A diet rich in heat-processed food, grilled or roasted meat, or other highly processed foods, especially with high sugar contents, would lead to a high exposure to AGEs exceeding 20,000 kU/day (Uribarri et al., 2007a). However, it is possible to reduce the exposure to dietary AGEs by substituting high AGE dietary sources, such as highly processed full-fat cheeses and meat, with foods low in AGEs, such as fish, grains, low-fat milk products, fruits, and vegetables (Goldberg et al., 2004). Dietary exposure to MG and 3-DG has been estimated to be 5–20 mg/day and 20–160 mg/day, respectively, calculated from data on MG and 3-DG contents in 173 food items measured by reversed phase-HPLC (Degen et al., 2012).

Generally, the exposure estimations are often based on calculation from a single marker or in rare cases a couple of markers, which is a major limitation, since there is a considerable variation in the contents of individual AGEs in different foods. Therefore, reported exposures of total AGEs from the diet can so far only be regarded as estimates.

5. Absorption and bioavailability

It was reported from early animal studies that MRPs are at least partially absorbed, and that LMW MRPs are absorbed to a higher degree than HMW MRPs (Finot and Magnenat, 1981). The absorption and bioavailability of a range of mildly modified/glycated protein products (i.e. early MRPs) such as fructoselysine (Erbersdobler and Faist, 2001; Foerster et al., 2005; Hultsch et al., 2006), fructoseleucine (Sgarbieri et al., 1973), fructosetryptophan (Sgarbieri et al., 1973), and lactuloselysine (Schwenger et al., 2006), have later been investigated more thoroughly (Faist and Erbersdobler, 2001; Finot, 2005). Studies of the absorption and bioavailability of AGEs are, however, more scarce. Early investigations of the more advanced MRPs led to the identification of CML as a compound of exogenous origin excreted in rat urine (Liardon et al., 1987). Since then bioavailability, metabolic fate, and excretion of CML and other AGEs have been investigated in different rat models and in humans.

5.1. Absorption

The intestinal absorption of ^{14}C labeled AGEs in rats was around 10% within 72 h with a peak at 6–12 h after feeding with AGEs in the form of ^{14}C-labeled glucose reacted with ^{125}I-labeled proteins (He et al., 1999). A large part of the absorbed AGEs were apparently still bound to peptides as determined from ^{125}I-colabeled metabolites. Total AGEs in this study was also determined by lysozyme affinity giving a quite similar absorption profile (He et al., 1999). The absorption of AGEs into the circulation in humans measured by a non-specific ELISA method was also estimated to be about 10% of ingested AGEs (Koschinsky et al., 1997). Recent recovery estimates of AGEs in the urine from healthy adolescents indicate a higher absorption of CML after intake of diets with both low and high amounts of AGEs (Delgado-Andrade et al., 2012).

LMW and HMW AGEs have different absorption rates with a slower and less efficient absorption of HMW AGEs, compared to LMW AGEs (Finot and Magnenat, 1981). HMW AGEs need to be degraded by gut proteases before the LMW products are liberated. The bioavailability of the partially degraded HMW AGEs will depend on the size of the associated peptide, type of diet, gut environment, and duration of their presence in the gut. Heat-induced changes in proteins can decrease their susceptibility to degradation by gastrointestinal enzymes, and protein and mineral bioavail-

ability have been shown to be influenced negatively by a heat-treated diet (Delgado-Andrade et al., 2011; Garcia et al., 2009; Seiquer et al., 2006). Similar phenomena could potentially also affect liberation of AGEs from heat-denatured proteins.

Free CML is most probably absorbed by simple diffusion rather than transported across the epithelium (Grunwald et al., 2006). However, absorption of CML, CEL, and MG-H1 in dipeptides is mainly carried out by peptide transporters, especially PEPT1 (Hellwig et al., 2011), as is also the case for pyrraline (Geissler et al., 2010; Hellwig et al., 2009).

5.2. Distribution

The distribution of AGEs has not been extensively studied so far. However, due to their water soluble and amphoteric properties, it would be expected that the LMW AGEs can be more readily distributed to extracellular and intracellular compartments after absorption than HMW AGEs. The *in vivo* distribution of CML and CEL after an intravenous injection in rats showed a temporary accumulation in the liver (Bergmann et al., 2001), indicating that they may have high affinity to some specific hepatic proteins. In the study of ^{14}C labeled AGEs, it was observed that 60% of the absorbed AGEs were bound in liver and kidney after 72 h, but radioactivity was also observed in lung, heart, and spleen indicating more global distribution and tissue binding (He et al., 1999). The tissue binding seems mainly to affect proteins since serum from rats treated with AGEs was able to cross-bind added test peptides or proteins leading to HMW aggregates (He et al., 1999). This would indicate that only a minor fraction of absorbed AGE-peptide fragments are available for excretion whereas a large fraction of AGE-peptide fragments bind non-specifically to proteins in the body, especially in liver and kidney. The nature of the high affinity of peptide-bound AGEs to certain proteins and the turnover of these adducts has not been reported.

5.3. Metabolism

AGEs would not be expected to be typical substrates for enzyme systems involved in detoxification by phase 1 and 2 enzymes. The highly water-soluble AGEs in particular may not be substrates for the phase 1 enzymes in the fatty membranes of the endoplasmic reticulum. Most AGEs also lack typical side groups for phase 2 coupling reactions, except acidic groups for esterification. Induction of phase 2 enzymes by HMW CML has been reported, but the control measurements in the study varied so much that the results seem questionable and the study should be repeated (Wenzel et al., 2002). Only few studies on AGE metabolism exist and none of them dealt with the reactive AGE-peptides formed by degradation of dietary AGE-protein complexes. The extensive reactivity of AGE-peptides towards proteins is probably not mediated by enzyme-activation since it also takes place readily *in vitro*. Co-administration of aminoguanidine inhibited the tissue binding *in vivo* of labeled AGE-peptides in rats and aminoguanidine also inhibited *in vitro* protein-binding of AGE-peptides isolated from rat or human sera (He et al., 1999; Koschinsky et al., 1997). When radio-labeled pentosidine was administered intravenously to rats, 20% was recovered intact in the urine, the remainder being metabolized or changed by unknown processes (Miyata et al., 1998). No further identification of the metabolic products has been performed to date.

5.4. Excretion

For the same reasons that LMW AGEs are rapidly absorbed, they should also be readily cleared by glomerular filtration and excreted with relatively short half-lives. In accordance with these expectations the renal clearance of free CML and CEL after an intravenous injection in rats was rapid with over 87% detected in the urine after 2 h (Bergmann et al., 2001). It has been reported from studies in rats that only 29% of CML could be recovered in urine and 22% in feces after 10-days on a feed containing high levels of HMW CML (Somoza et al., 2006). Limited absorption of free CML from its protein-bound form or slow excretion of peptide-associated CML could explain this finding. When radioactively-labeled free pentosidine was given intravenously to rats a total of 27% and 83% radioactivity was recovered in the urine within 1 and 72 h, respectively (Miyata et al., 1998). After feeding rats by gavage with a reaction product of ^{14}C-glucose with ^{125}I-labeled ovalbumin, excretion of only around 2% of labeled AGEs into the urine was observed. This corresponds to about one third of the absorbed fraction (He et al., 1999). Similarly, after intravenous infusion of ^{14}C-glucose or ^{125}I-labeled AGE peptides it was found that only about 30% was recovered in the urine, again underlining the extensive tissue binding (He et al., 1999). In general this indicates a high excretion rate of the free LMW AGE compounds and a comparatively short time in which they interact with functional proteins in the body of healthy individuals. However, peptide-bound AGEs seem to have comparatively higher affinity for proteins leading to extensive tissue retention. Despite these findings in animal models only a few studies have investigated the elimination of well-defined LMW or HMW AGEs in humans.

The renal excretion of AGEs (measured with a non-specific ELISA method) has been estimated to be about 30% of the absorbed amount in healthy subjects, decreasing to levels as low as 5% in renal disease patients (Koschinsky et al., 1997). When well-defined amounts of LMW pyrraline and pentosidine in selected food items were specifically investigated in humans (Foerster et al., 2005) large amounts of free pyrraline and pentosidine were recovered in the urine, 50% and 60%, respectively. In contrast, when food with HMW pentosidine was consumed only 2% was recovered in urine (Foerster et al., 2005). Urinary excretion rates in healthy adolescents after intake of a low or a high CML diet have been reported to be 24% and 15% of dietary intake respectively (Delgado-Andrade et al., 2012).

In conclusion, the available information regarding absorption, distribution, metabolism, and excretion of AGEs is scarce. The available data indicate that the absorption is highly dependent on whether AGEs are present in protein-bound form or not. The free AGEs may be relatively quickly absorbed, biotransformed, and excreted; however, there is a high affinity of the peptide-bound LMW AGEs to the liver and kidneys. In contrast, HMW AGEs may not be very extensively absorbed due to insufficient degradation by gastrointestinal enzymes, and the bioavailability and further fate may depend on factors such as their exact structure, host diet, gut environment etc. Knowledge about the fate of dietary HMW AGEs and their degradation products formed in the gut is particularly scarce.

6. Mechanism of action

AGEs are known to induce effects within the body by two separate mechanisms: structural deformation or cross-linking of body proteins, and interaction with AGE receptors. The structural deformation or cross-linking of body proteins has mainly been related to the increased endogenous production of AGEs in diabetes and to the comorbidities of diabetes (Baynes and Thorpe, 1999). AGE cross-linking with proteins depends on both the sugar concentration and the turnover rate of body proteins. Long-lived proteins are therefore more often modified by AGEs (Brownlee, 1995). The proteins collagen and low-density lipoprotein (LDL) are also sensitive to AGE cross-linking, resulting in increased arterial stiffness

and decreased uptake by LDL receptors (Zieman and Kass, 2004). AGE cross-linking to lens proteins induces functional changes, for example in lens crystallins (Bucala and Cerami, 1992), while AGE cross-linking in renal tissues increases the thickening of the basement membrane (Ahmed, 2005). In general the accumulation of AGEs in the different organs seem to be involved in diabetic complications, including those of the retina, kidneys, nerves, and atherosclerotic plaques (Goh and Cooper, 2008). AGEs have a potential role in protein aggregation related to amyloidosis. High levels of argpyrimidine have been observed in protein aggregates in familial amyloidosis cases but not in disease-free controls indicating an important role of MG in pathogenic protein aggregation (Gomes et al., 2005). Similar mechanisms have been investigated in relation to a range of neurodegenerative disorders, including Alzheimer's disease, as reviewed elsewhere (Li et al., 2012; Miranda and Uteiro, 2010). An important mechanism in AGE-related toxicity and disease may therefore relate to a high protein affinity of some AGEs and their capacity to cause aggregation of certain protein structures.

One of the main mechanisms of action of AGEs may be via AGE-sensitive receptors. These include a receptor for AGEs (RAGE), oligosaccharyl transferase complex protein 48 (OST-48 or AGER1), 80 K-H protein (AGER2), galectin-3 (AGER3), and some scavenger receptors (Thornalley, 1998). The AGE receptors are expressed in a wide range of cells, e.g. monocytes, macrophages, endothelial cells, adipocytes, and podocytes. AGEs can also bind to lysozyme and lactoferrin (Thornalley, 1998). Among the AGE binding proteins, RAGE and AGER1 seem to be the most important, and in particular RAGE has been thoroughly investigated (Han et al., 2011; Ramasamy et al., 2011; Schmidt et al., 2000).

6.1. RAGE

RAGE is a cell surface receptor and a member of the immunoglobulin superfamily first isolated from bovine lung endothelial cells (Neeper et al., 1992). Investigation of its distribution found RAGE to be expressed in a wide range of tissues, including the vasculature, endothelium, smooth muscle cells, neural tissue, and mononuclear cells (Brett et al., 1993). The activation of RAGE induces vascular cell dysfunction, but whether RAGE indeed interacts with AGEs is under much debate (Heizmann, 2007; Ramasamy et al., 2007; Thornalley, 2007). Especially, because RAGE has other known ligands *in vivo*, including calcium-binding S100 proteins (Heizmann, 2007), high-mobility group box 1 protein (HMGB1/amphoterin), and β-amyloid (Thornalley, 1998). RAGE seems important in development of disease as studies with RAGE-deficient mice have demonstrated protection from diabetic complications (Bucciarelli et al., 2002; Soro-Paavonen et al., 2008; Thallas-Bonke et al., 2013). RAGE may also be directly involved in amyloidosis and Alzheimers disease (Maslinska et al., 2011; Wang et al., 2013). Different variants of RAGE exist, including a soluble variant (sRAGE) consisting of only the extracellular domain. Due to its structure, sRAGE cannot propagate signaling events, but rather contributes to AGE clearance (Yan et al., 2010).

Activation of RAGE induces oxidative stress and inflammation with a large degree of redundancy. RAGE regulates transcription factors, such as nuclear factor kappa B (NF-κB), activator protein 1, and forkhead box protein O4, via various signal transduction cascades, such as mitogen-activated protein kinases (MAPK), c-Jun N-terminal kinases, extracellular signal-regulated protein kinases 1 and 2, Janus kinase/signal transducers and activators of transcription, cell division control protein 42 homolog-Rac, toll-interleukin 1 receptor domain containing adaptor protein and myeloid differentiation primary response protein 88, and NADPH oxidase (Fig. 5) (An et al., 2011; Harja et al., 2008; Huang et al., 2001; Huttunen et al., 1999; Lander et al., 1997; Mahali et al., 2011; Sakaguchi et al., 2011; Wautier et al., 2001; Yeh et al., 2001). It has also been speculated that RAGE might exert its effects by down-regulating enzymes in the glyoxalase system, which would lead to decreased protection against protein glycation caused by carbonyl stress (Thornalley, 2007).

The dispute about AGE-RAGE interaction is the result of conflicting reports. AGEs are in general considered ligands for RAGE (Ramasamy et al., 2008; Schmidt et al., 1994, 1999; Thornalley, 1998), but it has also been reported that AGEs do not induce an inflammatory response by interaction with RAGE (Buetler et al., 2011, 2008; Fa et al., 2006; Valencia et al., 2004). There could be several interacting factors causing this discrepancy, including a lack of sufficient distinction between binding and non-binding AGEs, contamination of AGE preparations by endotoxins, and differences in the amount of AGE modifications in the proteins used for the studies. An example is the interaction between protein-bound CML and RAGE, which has been observed by some (Kislinger et al., 1999) but later rejected by others (Buetler et al., 2008; Fa et al., 2006). The discrepancy may be related to the protein–sugar incubations used to produce CML. These may have led to multiple AGE modifications in the proteins, where CML is only one among many. In consequence, the activation of RAGE may not be due to a CML-RAGE interaction, but to binding by some of the other glycated protein modifications (Buetler et al., 2008). As CML is often used as an overall marker of AGEs, a clear distinction between different AGEs in relation to receptor interaction is of great importance and studies with chemically well-defined AGEs are needed. The problem with endotoxin contamination has also been debated. Even low endotoxin concentrations in AGE preparations stimulate an inflammatory response. Studies have shown how an inflammatory response induced by AGEs could not be reproduced in a strict endotoxin-free environment (Buetler et al., 2011; Reznikov et al., 2004). Also the amount of AGE modifications on the proteins is of relevance in the discussion of AGE-RAGE interactions, especially when extrapolating results from *in vitro* studies to AGE-RAGE interaction *in vivo*. The procedures for AGE preparations lead to highly modified proteins i.e. 15–40% of the lysine or arginine residues are modified in the proteins (Buetler et al., 2008). This is in sharp contrast to the *in vivo* physiological modification of proteins where only 1–3% of lysine residues are modified in long-lived proteins among healthy individuals (Bucala and Cerami, 1992). The *in vivo* affinity of AGEs for RAGE might, therefore, be lower than *in vitro* studies indicate. The only exception is highly modified AGE-proteins in heat-treated foods, which interact *in vivo* with exposed cells in the gastrointestinal tract. However, since the expression of RAGE in the gastrointestinal tract may be generally low (Brett et al., 1993), the consequences of AGE-RAGE interaction in this region seem limited.

Finally, the interaction between AGEs and RAGE seems to depend on the molecular size of the AGE compounds. When comparing affinity of LMW (free or <30 kDa) and HMW CML binding to RAGE, only the HMW CML interacts with RAGE (Kislinger et al., 1999; Penfold et al., 2010; Xie et al., 2008). This is important to note, because the dietary HMW AGEs generated during cooking are partly degraded in the intestine and only absorbed as LMW AGEs (either free or bound to peptides). A subsequent incorporation of free AGEs into proteins in the body seems unlikely, and it is therefore questionable that dietary AGEs are able to interact directly with RAGE *in vivo*. On the other hand it has been reported that circulating HMW AGEs are increased with high AGE diets (Birlouez-Aragon et al., 2010) providing the possibility that an indirect mechanism is involved where dietary AGEs induce endogenous AGE formation thereby activating RAGE. The literature within this area has focused on protein-bound AGEs (mainly albumin) and not on dietary AGEs, probably because the endogenous AGEs are protein-bound. Only a few

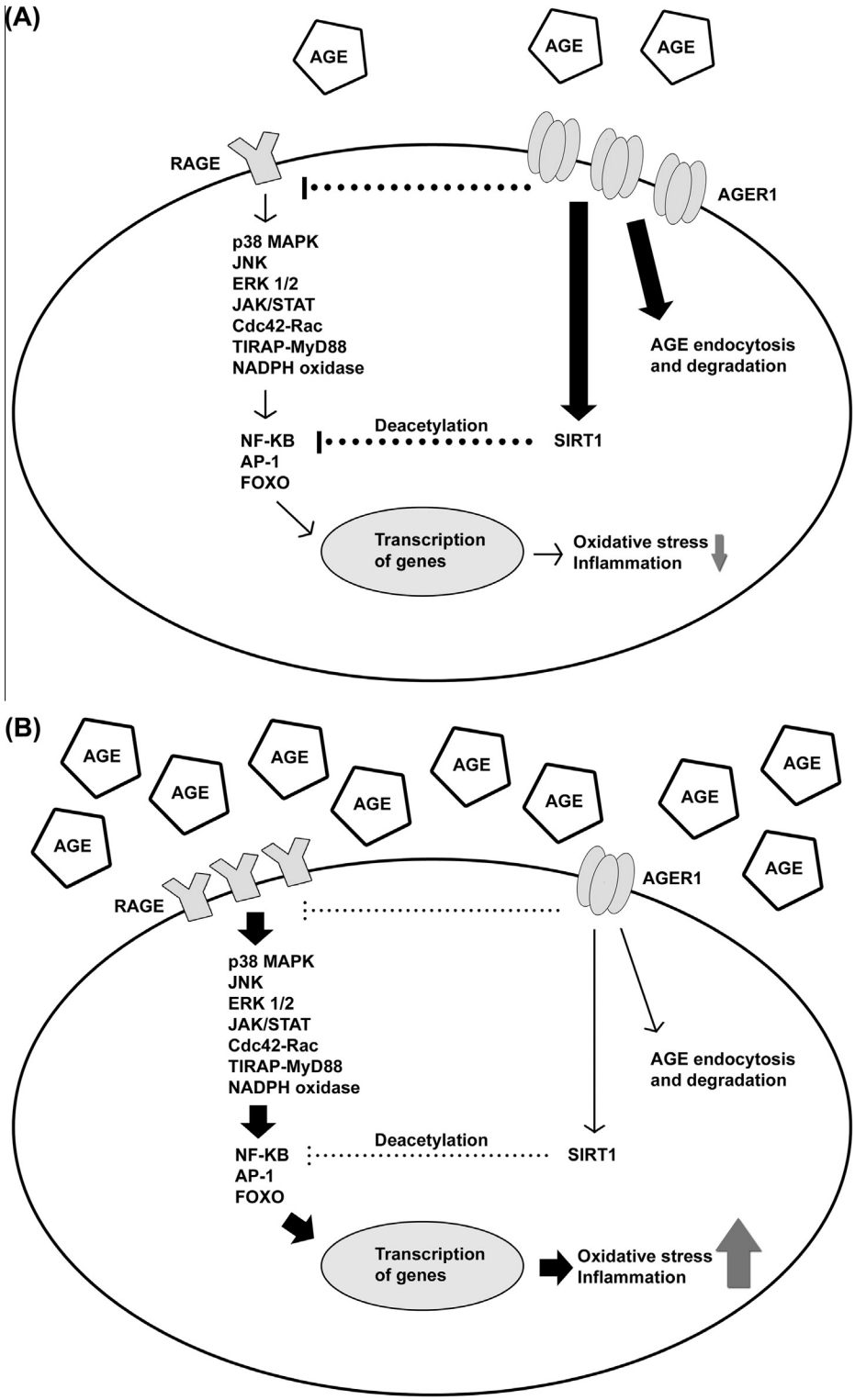

Fig. 5. Scheme of AGE interaction with RAGE and AGER1 in conditions with different AGE burdens. (a) In conditions with a low AGE burden, the expression of RAGE is down-regulated while the expression of AGER1 is up-regulated. The RAGE signaling pathways leading to activation of transcription factors NF-κB, AP-1, and FOXO and consequently transcription of genes related to oxidative stress and inflammation are inhibited by AGER1 and SIRT1. This means an overall lower degree of oxidative stress and inflammation caused by AGEs. Besides inhibiting RAGE signaling pathways, AGER1 mediates degradation of AGEs. (b) In conditions with a prolonged high AGE burden, RAGE is up-regulated leading to increased oxidative stress and inflammation. The prolonged high AGE burden leads to down-regulation of AGER1 that, therefore, cannot exert strong inhibitory effects on RAGE signaling or reduce AGE levels. *Abbreviations*: AGE = advanced glycation endproduct; AGER1 = AGE receptor 1; AP-1 = activator protein 1; Cdc42-Rac = cell division control protein 42 homolog-Rac; ERK 1/2 = extracellular signal-regulated protein kinases 1 and 2; FOXO = forkhead box protein O subclass; JAK/STAT = Janus kinase/signal transducers and activators of transcription; JNK = c-Jun N-terminal kinases, NADPH = nicotinamide adenine dinucleotide phosphate; NF-κB = nuclear factor kappa B; p38 MAPK = p38 mitogen-activated protein kinases; RAGE = receptor for AGE; SIRT1 = sirtuin-1; TIRAP-MyD88 = toll-interleukin 1 receptor domain containing adaptor protein and myeloid differentiation primary response protein 88.

studies have focused on thermally generated AGEs in foods in relation to RAGE activation, but none of them accounted for the degradation of AGE-proteins in the intestine (Somoza et al., 2005; Zill et al., 2003, 2001).

Adverse effects of a high AGE/high fat diet in RAGE-deficient mice are limited compared with wild type mice (Tikellis et al., 2008), while expression of RAGE can be influenced by the diet in wild type mice. The expression of RAGE increases in a range of different organs, including liver, kidney, spleen, heart, vascular tissue, skeletal muscle, and adipose tissue in animals fed a high AGE diet compared to animals fed a low AGE diet (Cai et al., 2007, 2008b, 2012; Harcourt et al., 2011; Lin et al., 2003). The addition of the precursor MG to the drinking water also leads to an increased expression of RAGE in rats (Sena et al., 2012). Up-regulation of RAGE due to a high AGE burden leads to increased transcription of factors involved in inflammation and oxidative stress (Fig. 5b). The picture is, however, ambiguous, as a higher RAGE expression is not always observed after feeding a high AGE diet (Sato et al., 2009; Tan et al., 2010). It is still interesting that certain high AGE diets might be able to increase the expression of RAGE. This is surprising as dietary AGEs are absorbed as free or peptide-bound AGEs, which we would not expect to interact with RAGE. Incorporation of the absorbed LMW AGEs into proteins in the body and subsequent interaction with RAGE seems an unlikely explanation. The ability of certain LMW AGE structures to form protein aggregates could be involved since aggregation and RAGE activation seem to be coupled phenomena (Wang et al., 2013). It is also possible that the absorption of reactive dicarbonyls, which increase carbonyl stress in plasma and promote successive formation of endogenous HMW AGE, could result in increased expression of RAGE.

6.2. AGER1

AGER1 is a type I transmembrane protein that is believed to facilitate AGE turnover by mediating uptake, degradation, and removal of AGEs (Thornalley, 1998; Vlassara and Striker, 2011). AGER1 was first identified as a macrophage scavenger receptor by mediating endocytosis of AGE-modified proteins (Li et al., 1996; Vlassara et al., 1985, 1986; Yang et al., 1991). More recent data from a mesangial cell line confirmed that AGER1 is involved in AGE turnover. Endotoxin-free radiolabeled AGE-BSA was used to assess binding, uptake, and degradation of AGE-BSA compared to radiolabeled BSA (Lu et al., 2004). In transgenic mice overexpressing AGER1, *in vivo* turnover of plasma and tissue AGEs was increased compared to wild type mice (Torreggiani et al., 2009).

Besides enhancing AGE removal, AGER1 has been shown to negatively regulate signals induced by AGE-RAGE interaction and, thus, contribute to the body's defense against AGE toxicity (Fig. 5), a mechanism recently reviewed elsewhere (Vlassara and Striker, 2011). The mechanisms by which AGER1 counteracts RAGE-induced oxidative stress and inflammatory actions are by suppressing NF-κB activity and MAPK phosphorylation (Cai et al., 2012; Lu et al., 2004). Upstream of MAPK, AGER1 also suppresses the epidermal growth factor receptor and the Shc/Grb2/Ras pathway (Cai et al., 2006). AGER1 inhibits AGE-induced Ser36 phosphorylation of the Shc isoform $p66^{shc}$ and activation of NADPH oxidases, thereby preserving cellular resistance to oxidative stress (Cai et al., 2008a, 2010).

AGER1 also seems to exert its functions via the NAD-dependent deacetylase sirtuin-1 (SIRT1) (Cai et al., 2012; Uribarri et al., 2011). SIRT1 has regulatory effects on insulin and adipokine signaling as well as anti-inflammatory effects (Liang et al., 2009). SIRT1 is in many conditions regulated in a similar way to AGER1, and an AGE-induced suppression of SIRT1 is overruled by overexpression of AGER1 (Vlassara and Striker, 2011). Further research on AGER1 and SIRT1 will clarify the importance of this interaction.

As with RAGE, the expression of AGER1 can also be influenced by the diet in a range of organs, including liver, kidney, spleen, heart, vascular tissue, skeletal muscle, and white adipose tissue. Both higher (Lin et al., 2003) and lower AGER1 expression (Cai et al., 2007, 2008b, 2012) have been reported after feeding mice a high AGE diet compared to a low AGE diet. These differences could very well be due to the duration of the studies and the type of animal model, as the study that reported an up-regulation of AGER1 lasted only 2 months and was conducted in diabetic mice (Lin et al., 2003), whilst the other studies were longer-term and in healthy wild type mice (Cai et al., 2007, 2008b, 2012). In healthy humans AGER1 expression in peripheral blood mononuclear cells (PBMC) correlates with plasma and urine concentrations of AGEs (Vlassara et al., 2009). It has been speculated that the role for AGER1 in the body's defense against AGE depends on the duration of AGE exposure, i.e. AGER1 is down-regulated after extensive, long-term exposure to AGEs. The consequence is a compromise of the body's innate defenses (Fig. 5) (Cai et al., 2007; Vlassara et al., 2009; Vlassara and Striker, 2011). This is in line with attenuated expression of AGER1 in humans (He et al., 2001) and rodents (He et al., 2000) that have increased AGE accumulation and concomitant complications of diabetes.

7. Effect of dietary AGEs on disease

7.1. Animal studies

Low versus high AGE diets have been investigated in rodents in relation to the development of both type 1 (T1D) and type 2 (T2D) diabetes and their complications. It has been demonstrated in rodent models of T1D that long-term feeding with diets low in AGEs prevented T1D in non-obese diabetic mouse offspring exposed to AGEs *in utero* or through lactation (Peppa et al., 2003b). Insulin secretory defects and β-cell death have been reported after feeding rats a high AGE diet (Coughlan et al., 2011). Feeding through 11 weeks with glycated casein and soy protein (highly modified in their lysine residues) did not affect the concentration of blood glucose or oxidative stress in streptozotocin-treated diabetic Wistar rats (Chuyen et al., 2005). Long-term feeding with diets low in AGEs improved insulin sensitivity in *db/db* mice (Hofmann et al., 2002), a rodent model of T2D. In wild type mice a combined high AGE and high fat diet has been shown to induce insulin resistance and T2D (Sandu et al., 2005), but such clear effects were not observed with a high AGE and standard fat diet (Hofmann et al., 2002), suggesting that the combination of AGEs and a high fat diet was the most detrimental. A limitation in most of these studies is lack of an exact assessment of the AGE contents in the diets.

Some studies that have focused on the development of insulin resistance and oxidative stress have used MG-modified BSA as a means of exposure to AGEs. After feeding wild type mice this MG-modified BSA diets for 6 months, a causal relationship between the supplementation with the MG-BSA preparation and markers of oxidative stress was established (Cai et al., 2008b). A recent study reported insulin resistance in four generations of mice receiving MG-BSA (Cai et al., 2012). Both of these studies avoided the unspecific heated foods containing other potentially harmful compounds as well as loss of nutrients by heating the diet, thus investigating "pure" effects of the MG-reacted protein. The MG-BSA was dialyzed to avoid that any unreacted MG could confound the study. The studies with MG-BSA resulted in significant effects on markers of oxidative stress and insulin resistance (Cai et al., 2008b, 2012). Also unreacted MG absorbed from the diet can lead

to increased carbonyl stress, and concomitantly to increased formation of endogenous AGEs. This is supported by the observation of increased formation of AGE cross-linking in mice when administering MG (Golej et al., 1998). When MG was added to the drinking water in rodents, worsening of endothelial dysfunction, oxidative stress, inflammation, insulin resistance, and increased blood pressure were observed (Ankrah and Appiah-Opong, 1999; Guo et al., 2009; Sena et al., 2012; Vasdev et al., 1998). More studies with chemically synthesized, well-characterized AGEs are needed to clarify if AGEs are indeed the responsible components in heat-treated food, and, furthermore, to differentiate between the different AGEs, i.e. reactive dicarbonyl precursors and the various final AGEs. Chemical synthesis of AGEs with higher yields is progressing and should be used in future experimental studies.

With regards to complications of diabetes, several different animal models have been used to examine the role of dietary AGEs in the development of kidney disease. In diabetic mouse models, there has been reports of both protective (Zheng et al., 2002) and disparate effects (Tan et al., 2010) of diets low in AGEs in development of diabetic nephropathy. In remnant kidney models in rats, proteinuria increased during feeding with high AGE diets (Feng et al., 2007; Sebekova et al., 2003, 2005). Furthermore, high AGE diets were shown to accelerate progression of renal fibrosis (Feng et al., 2007). In addition, in a mouse model of obesity, renal impairment developed when high AGEs and a high fat diet were combined (Harcourt et al., 2011).

With regards to the macrovascular complications of diabetes, the development of atherosclerotic lesions was attenuated in diabetic apolipoprotein E (apoE)-deficient mice fed a low AGE diet compared to apoE-deficient mice on a high AGE diet (Lin et al., 2003). Similarly, in non-diabetic apoE-deficient mice on a low AGE diet a reduction of excessive neointimal formation in the lesions after arterial injury has been observed (Lin et al., 2002). Interestingly, impaired wound healing has also been found to be improved with a diet low in AGEs (Peppa et al., 2003a).

Age-related metabolic changes and lifespan has also been investigated in long-term animal models with dietary AGEs. It has been found that a high AGE diet led to an increase in age-related insulin resistance, oxidative stress, and renal dysfunction and ultimately reduced lifespan compared to a low AGE diet (Cai et al., 2007). In another study, it was tested if beneficial effects of a calorie restricted diet could be due to a restricted intake of AGEs and it was concluded that restricted AGE intake could be one of the determinants of the well-known beneficial effects of calorie restriction (Cai et al., 2008b). A methodological problem with this study, as with most AGE research in general, is the loss of heat-sensitive nutrients in the high AGE diet during autoclaving/heat-treatment. This seems especially important when it is a lifelong, 40% calorie-restricted diet because the intake of micronutrients compared to a regular diet is already low without the autoclaving. A long-term or lifespan marginal deficiency of heat-sensitive micronutrients would be crucial for health and could cause similar effects to those reported in the study.

Direct extrapolation of results from animals to humans can be problematic, as rodents unlike humans are not used to eating heat-treated foods, whether they are bread crusts (as in Sebekova et al., 2003, 2005) or a regular animal diet that has been heated beyond autoclaving (as in Sandu et al., 2005). Furthermore, heating induces a range of other processes in the food, e.g. degradation of heat sensitive nutrients, which can be problematic, especially when feeding the animals severely heat-treated diets for very long periods of time or even during their whole lifespan.

Table 3
Human single meal studies with dietary AGEs.

Study	Design	Population	Test meals	Results
(Negrean et al., 2007)	Crossover meal test up to 6 h	20 T2D patients (M/F)	Low AGE meal (2750 kU AGE): steamed/boiled chicken breast, potatoes, and vegetables High AGE meal (15,100 kU AGE): fried/broiled chicken breast, potatoes, and vegetables	↓ FMD and reactive hyperemia after high AGE meal compared to low AGE meal ↑ TBARS, circulating E-selectin, ICAM-1, VCAM-1, and MG-derivatives after high AGE meal compared to low AGE meal → circulating glucose, TG, cholesterol, insulin, CRP, fibrinogen, TNF-α, IL-6, and CML between low and high AGE meal
(Stirban et al., 2007)	Crossover meal test up to 6 h	19 T2D patients (M/F)	Low AGE meal (2750 kU AGE): steamed/boiled chicken breast, potatoes, and vegetables High AGE meal (15,100 kU AGE): fried/broiled chicken breast, potatoes, and vegetables High AGE meal + benfotiamine	↓ Circulating adiponectin after high AGE meal compared to baseline → Circulating adiponectin after low AGE meal and after high AGE meal + benfotiamine
(Stirban et al., 2008a)	Crossover meal test up to 6 h	20 T2D patients (M/F)	Low AGE meal (2750 kU AGE): steamed/boiled chicken breast, potatoes, and vegetables High AGE meal (15,100 kU AGE): fried/broiled chicken breast, potatoes, and vegetables	↓ Circulating leptin after high AGE meal compared to low AGE meal ↑ Urinary CML after high AGE meal compared to low AGE meal
(Uribarri et al., 2007b)	Single meal test up to 1.5 h	23 T1D patients, 21 T2D patients, and 10 healthy subjects (M/F)	High AGE beverage (1800 kU AGE): prepared from glucose and caffeine-free Coca-Cola light	↓ FMD in both diabetic and healthy subjects ↑ Circulating PAI-1 and CML in both diabetic and healthy subjects → Percent change between diabetic and healthy subjects → Circulating VCAM-1 and glucose
(Schiekofer et al., 2006)	Crossover meal test up to 2 h	9 Healthy subjects (M)	Low AGE meal (447 pmol CML/mg casein): casein heated with sorbitol High AGE meal (1294 pmol CML/mg casein): casein heated with glucose	→ Circulating CML and mononuclear NF-κB activation between low and high AGE meal

Abbreviations: AGE = advanced glycation endproduct; CML = N^{ε}-carboxymethyl-lysine; CRP = C-reactive protein; F = female; FMD = flow-mediated dilation; ICAM-1 = intercellular adhesion molecule 1; IL-6 = interleukin-6; IL-8 = interleukin-8; M = male; MG = methylglyoxal; NF-κB = nuclear factor kappa B; PAI-1 = plasminogen activator inhibitor-1; TBARS = thiobarbituric acid reactive substances; TG = triacylglycerol; TNF-α = tumor necrosis factor α; T1D = type 1 diabetes; T2D = type 2 diabetes; VCAM-1 = vascular cell adhesion molecule 1; ↑ = increase; ↓ = decrease; → = no difference.

Table 4
Human intervention studies with dietary AGEs.

Study	Design	Population	Test diets	Results
(Vlassara et al., 2002)	2-wk crossover study ($n = 11$)	6 T1D and 17 T2D patients (M/F)	Prepared meals with calculated AGE content based on table values. Same energy and macronutrient content Low AGE diet: 3670 kU AGE/d High AGE diet: 16,300 kU AGE/d	2-wk study: ↓ Urine AGEs, circulating AGEs, AGE-modified LDL, AGE/creatinine, VCAM-1, and mRNA TNF-α after low AGE diet compared to high AGE diet → BW, BP, circulating glucose, fructosamine, cholesterol, TG, and CRP
	6-wk parallel study ($n = 13$)			6-wk study: ↓ Circulating AGEs, MG-derivatives, AGE-modified LDL, CRP, VCAM-1, glucose, BW, and PBMC TNF-α after low AGE diet compared to high AGE diet → BP, circulating fructosamine, cholesterol, and TG
(Cai et al., 2004)	6-wk parallel study	6 T1D and 18 T2D patients (M/F)	Prepared meals with calculated AGE content based on table values. Similar energy and macronutrient content Low AGE diet: 3670 kU AGE/d High AGE diet: 16,300 kU AGE/d	↓ LDL glycation and oxidation and vascular toxicity via redox-sensitive MAPK activation after low AGE diet compared to high AGE diet
(Uribarri et al., 2011)	4-mo parallel study	18 T2D patients (M/F)	Low AGE diet: instructions to modify cooking time and temperature (AGE intake decreased by 50%) High AGE diet: usual diet	Diabetic subjects: ↓ Circulating CML, MG-derivatives, 8-isoprostanes, insulin, HOMA, leptin, PBMC TNF-α, NF-κB acetylation, and mRNA RAGE after low AGE diet compared to high AGE diet ↑ Circulating adiponectin, mRNA AGER1, and mRNA SIRT1 after low AGE diet compared to high AGE diet → HbA_{1c}
		18 Healthy subjects (M/F)		Healthy subjects: ↓ Circulating CML, MG-derivatives, 8-isoprostanes, PBMC TNF-α, and mRNA RAGE, after low AGE diet compared to high AGE diet → Circulating insulin, HOMA, leptin, adiponectin, HbA_{1c}, PBMC NF-κB acetylation, mRNA AGER1, and mRNA SIRT1
(Uribarri et al., 2003b)	4-wk parallel study	18 Non-diabetic patients with renal failure (M/F)	Low AGE diet (5500 kU AGE): instructions to boil, poach, stew, and steam High AGE diet (17,000 kU AGE): instructions to roast, broil, and oven fry Differences in protein, total fat, and saturated fat content between diets	↓ Circulating CML, MG-derivatives, CML-LDL, CML-apoB, dialysate CML, and dialysate MG-derivatives after low AGE diet compared to high AGE diet → Peritoneal dialysate volume inflow, peritoneal dialysate fluid glucose inflow, and peritoneal glucose load
(Peppa et al., 2004)	4-wk parallel study	18 Non-diabetic patients with renal failure (M/F)	Low AGE diet (5500 kU AGE): instructions to boil, poach, stew, and steam High AGE diet (17,000 kU AGE): instructions to roast, broil, and oven fry Differences in protein, total fat, and saturated fat content between diets	↓ Circulating CRP and PAI-1 after low AGE diet compared to baseline ↓ Circulating VCAM-1 and TNF- α after low AGE diet compared to high AGE diet
(Vlassara et al., 2009)	4-wk parallel study ($n = 9$)	9 Kidney disease patients (M/F)	4-wk study: Prepared meals with calculated AGE content based on table values Low AGE diet: 8000 kU AGE High AGE diet: 12,000 kU AGE	4 wk study (kidney disease patients): ↓ Circulating CML, 8-isoprostane, and PBMC TNF-α after low AGE diet compared to high AGE diet ↑ PBMC mRNA AGER1 after low AGE diet compared to high AGE diet → Circulating MG-derivatives, VCAM-1, glucose, TG, HDL, LDL, BW, BP, creatinine clearance, PBMC mRNA RAGE, and mRNA $p66^{shc}$,
	4-mo parallel study ($n = 40$)	40 Healthy subjects (M/F)	4-mo study: Low AGE diet (10,200 kU AGE): instructions to boil, poach, stew, and steam High AGE diet (20,600 kU AGE): usual diet	4-mo study (healthy subjects): ↓ Circulating CML, MG-derivatives, 8-isoprostane, VCAM-1, PBMC TNF-α, mRNA AGER1, mRNA RAGE, and mRNA $p66^{shc}$ after low AGE diet compared to high AGE diet → Circulating glucose, TG, HDL, LDL, BW, BP, and creatinine clearance

(*continued on next page*)

Table 4 (*continued*)

Study	Design	Population	Test diets	Results
(Birlouez-Aragon et al., 2010)	4-wk crossover study	62 Healthy subjects (M/F)	Prepared meals with small differences in energy and nutrient content Low AGE diet: 2.2 mg CML/d High AGE diet: 5.4 mg CML/d	↓ CML in plasma proteins, urine CML, circulating total cholesterol, HDL cholesterol, TG, n-6 fatty acids, insulin, HOMA, and ubiquinol after low AGE diet compared to high AGE diet ↑ Circulating n-3 fatty acids, vitamin C, and vitamin E after low AGE diet compared to high AGE diet → CML feces, circulating LDL cholesterol, malondialdehyde, AOP, glucose, fructosyllysine, and HbA_{1c}
(Harcourt et al., 2011)	2-wk crossover study	11 Healthy overweight subjects (M)	Prepared meals with calculated AGE content based on table values. Similar in energy and nutrient content Low AGE diet: 3302 kU AGE High AGE: 14,090 kU AGE	↓ urine CML, 8-isoprostanes, albumin/creatinine ratio, circulating cystatin C, and MCP-1 after low AGE diet compared to high AGE diet ↑ Circulating CML and MIF after low AGE diet compared to high AGE diet → BW, body fat, urine albumin, circulating creatinine, cholesterol, glucose, IL-6, CRP, NF-κB, and sRAGE

Abbreviations: AGE = advanced glycation endproduct; AGER1 = advanced glycation endproduct receptor-1; AOP = antioxidant power of the plasma; apoB = apolipoprotein B; BP = blood pressure; BW = body weight; CML = N^{ε}-carboxymethyl-lysine; CRP = C-reactive protein; F = female; HbA_{1c} = glycosylated hemoglobin; HDL = high-density lipoprotein; HOMA = homeostatic model assessment; IL-6 = interleukin-6; LDL = low-density lipoprotein; M = male; MAPK = mitogen-activated protein kinase; MCP-1 = monocyte chemotactic protein-1; MG = methylglyoxal; MIF = macrophage migration inhibitory factor; NF-κB = nuclear factor kappa B; PAI-1 = plasminogen activator inhibitor-1; PBMC = peripheral blood mononuclear cells; RAGE = Receptor for advanced glycation endproducts; SIRT1 = sirtuin-1; sRAGE = soluble receptor for advanced glycation endproducts; TG = triacylglycerol; TNF-α = tumor necrosis factor α; T1D = type 1 diabetes; T2D = type 2 diabetes; VCAM-1 = vascular cell adhesion molecule 1; ↑ increased; ↓ decreased; → no difference.

As already detailed, the feeding of animals with well-defined HMW and LMW AGE preparations and AGE precursors would seem to be the most important next step in the use of animal models for elucidation of the bio-kinetics and biological effects of dietary AGE.

7.2. Human studies

An overview of human single meal and longer-term intervention studies with low versus high AGE diets is given in Tables 3 and 4. All studies of the health effects of lowering dietary AGEs that have been published to date (to the best of our knowledge) are included in the tables. Two identified dietary studies investigated other aspects of a high AGE diet (antioxidant effects of HMW melanoidins and protein digestibility) and are therefore irrelevant in the present context and were consequently not included in the tables (Dittrich et al., 2009; Seiquer et al., 2006). Two studies that investigated effects of AGEs on mineral bioavailability are also omitted as irrelevant (Delgado-Andrade et al., 2011; Garcia et al., 2009).

7.3. Diabetes patients

In epidemiological studies, serum concentration of AGEs has been positively associated with both T1D (Berg et al., 1998, 1997; Chiarelli et al., 1999; Hwang et al., 2005) and T2D (Aso et al., 2000; Kilhovd et al., 1999; Tan et al., 2002, 2004). The associations were related to the severity and the progression of diabetes and complications, i.e. microvascular complications (Aso et al., 2000; Chiarelli et al., 1999; Hwang et al., 2005; Makita et al., 1991; Miura et al., 2003; Wagner et al., 2001; Wautier et al., 2003), macrovascular complications (Aso et al., 2000; Kilhovd et al., 1999; Kilhovd et al., 2007), and an increase in markers of inflammation and endothelial dysfunction (Nakamura et al., 2008; Tan et al., 2002, 2004). Despite many reports showing associations, not all studies agree (Busch et al., 2004, 2006; Schwedler et al., 2002). Dietary AGEs also contribute to the burden of AGEs in the body, and there is a correlation between dietary AGE intake and serum concentration of AGEs (Chao et al., 2010; Uribarri et al., 2003a). Dietary AGEs also correlate with plasma markers of inflammation and oxidative stress, both of which are risk factors for diabetes (Chao et al., 2010).

The first study on adverse effects of AGEs in T1D and T2D patients contained both a 2-week crossover study and a 6-week parallel study (Vlassara et al., 2002). In both studies, inflammatory markers decreased on the low AGE diet compared to the high AGE diet. In a related 6-week parallel study, modifications of LDL were investigated (Cai et al., 2004). LDL in the low AGE group was less glycated and oxidized compared to LDL in the high AGE group. Moreover, LDL isolated from the high AGE group increased vascular toxicity in human endothelial cells via activation of redox dependent MAPK (Cai et al., 2004).

The beneficial effects of an AGE-restricted diet have been confirmed in a recent study from the same research group (Uribarri et al., 2011). Plasma concentrations of inflammatory markers and leptin decreased, and insulin sensitivity and adiponectin concentrations increased, in patients with T2D after 4 months on the AGE restricted diet. Changes in both leptin and adiponectin have been reported postprandially following a high AGE meal in T2D patients (Stirban et al., 2008a, 2007). These changes in leptin/adiponectin ratio suggest a possible involvement of adipose tissue in AGE metabolism, since both leptin and adiponectin are important adipose-derived hormones related to appetite and energy metabolism. In the same study the expression of RAGE in PBMC decreased with the low AGE diet, while expression of AGER1 and SIRT1 increased (Uribarri et al., 2011). The short-term regulation of leptin

and adiponectin differs from their typical long-term regulatory effects. The authors suggest that a condition of oxidative stress after the high AGE meal lead to decreased adipokine secretion (Stirban et al., 2008a, 2007). It is also possible that these changes in leptin and adiponectin reflect a postprandial change in insulin sensitivity. A high AGE meal has also been shown to induce postprandial impairment of vascular function and increase markers of endothelial dysfunction (Negrean et al., 2007; Stirban et al., 2008b; Uribarri et al., 2007b) compared to a low AGE meal.

7.4. Kidney disease patients

In epidemiological studies, serum concentration of AGEs has been positively associated with both diabetic and non-diabetic kidney disease (Kratochvilova et al., 2011; Nakamura et al., 2009; Schwedler et al., 2002; Sebekova et al., 2001b; Wagner et al., 2001). Dietary AGEs also correlate with serum concentrations of AGEs in kidney disease patients (Uribarri et al., 2003a). This accumulation of AGEs in kidney disease patients was found to be related to an increased endogenous AGE formation (Henle and Miyata, 2003), as well as reduced renal clearance of AGEs (Koschinsky et al., 1997). Intervention studies in patients with kidney disease revealed that a 4-week low AGE diet reduced AGE burden and AGE modifications in circulating proteins, inflammatory markers, and oxidative stress (Peppa et al., 2004; Uribarri et al., 2003b; Vlassara et al., 2009). Despite the small numbers (9–18 subjects in a parallel design) significant beneficial effects of a low AGE diet were reported. PBMC expression of RAGE was reduced while PBMC expression of AGER1 increased after the AGE-restricted diet (Vlassara et al., 2009). In a healthy low AGE control group in the same study, the expression of both RAGE and AGER1 decreased. Based on the role of AGER1 in AGE metabolism, it was concluded that suppression of AGER1 levels in kidney disease patients indicates compromised innate defenses and/or that AGER1 is down-regulated as a consequence of the high AGE burden (Vlassara et al., 2009).

7.5. Healthy individuals

In healthy individuals, serum concentration of AGEs was positively associated with age (Uribarri et al., 2007a; Vlassara et al., 2009), insulin resistance (Tahara et al., 2012; Tan et al., 2011; Uribarri et al., 2007a), oxidative stress (Vlassara et al., 2009), and cardiovascular disease mortality (Kilhovd et al., 2005). The fact that there are associations between serum concentration of AGEs and risk factors for disease in healthy individuals suggests a possible role of AGEs in the etiopathogenesis of diabetes and cardiovascular disease. Similar to patients with diabetes and chronic kidney disease, dietary AGE intake correlates with serum concentration of AGEs in healthy individuals, i.e. individuals eating large amounts of AGEs have correspondingly higher serum concentrations of AGEs compared to individuals eating restricted amount of AGEs (Uribarri et al., 2007a; Vlassara et al., 2009). In vegetarians, plasma concentrations of AGEs have been reported to be higher compared to omnivores on a traditional Western diet (Krajcovicova-Kudlackova et al., 2002; Sebekova et al., 2001a). Based on food-analysis data from ELISA, this could be regarded as opposite of what would be expected (Uribarri et al., 2010), however based on LC-MS results, this outcome would be predicted (Henle, 2008); that is, a high AGE diet would be composed quite differently, depending on the analytical database used, again underlining the need for resolving fundamental analytical issues in this field.

Another interesting finding is that plasma concentration of AGEs is inversely associated with obesity in children in spite of insulin resistance, oxidative stress, and inflammation (Sebekova et al., 2009). An inverse association between serum concentration of AGEs and fat mass is also seen in adults (Semba et al., 2011). This could be due to accumulation of AGEs in adipose tissue (Cai et al., 2012), which again suggests a role for adipose tissue in AGE metabolism, as discussed in Section 7.3. It could also be due to changes in the regulation of AGE formation similar to that seen for production of reactive oxidative species in some obese individuals (Hopps et al., 2010).

Beneficial effects of a low AGE diet in healthy individuals have been reported, but compared to diabetes patients in the same study, fewer markers were affected by the intervention (Uribarri et al., 2011). A 4-month intervention with a low AGE diet in healthy individuals resulted in beneficial effects on markers of oxidative stress and inflammation similar to those seen after a 4-week intervention in patients with kidney disease (Vlassara et al., 2009). Two other dietary AGE intervention studies have been conducted with healthy subjects (Birlouez-Aragon et al., 2010; Harcourt et al., 2011). In the first study, intake of a low AGE diet for 4 weeks resulted in reductions in cholesterol levels (total and high-density lipoprotein), triacylglycerol levels, and insulin resistance and increased plasma concentrations of long-chain n-3 fatty acids, vitamin C, and vitamin E compared to a high AGE diet (Birlouez-Aragon et al., 2010). However, the high AGE diet in this study was higher in energy, fat, and carbohydrate and lower in vitamin C, compared to the low AGE diet. The effects of a highly heat-treated diet, such as in this study, cannot be directly related to the AGE content. However, there was no correlation between the intake of energy, fat, or carbohydrate and the risk factors in this study, indicating a possible effect of AGEs on the outcome. The other study focused on renal function; a low versus a high AGE diet was tested in healthy overweight and obese subjects in a 2-week crossover intervention study (Harcourt et al., 2011). Renal function and the inflammatory markers, monocyte chemoattractant protein-1 and macrophage migration inhibitory factor, improved with the low AGE diet, compared to the high AGE diet. Insulin sensitivity also improved over the 2-week period (Barbora de Courten, unpublished observation).

Two acute meal studies with healthy individuals have also been conducted (Schiekofer et al., 2006; Uribarri et al., 2007b). One study found no difference in postprandial NF-κB activation between a low AGE and a high AGE meal (Schiekofer et al., 2006), and the other study found that an oral high AGE challenge affected flow-mediated dilation and plasminogen activator inhibitor 1 concentrations (Uribarri et al., 2007b).

The choice of study designs and diets are an important discussion. In some studies, instructions on cooking methods were given to the subjects without any meal plans (Peppa et al., 2004; Uribarri et al., 2011, 2003b; Vlassara et al., 2009), while in other studies foodstuffs were handed out together with a specific meal plan (Harcourt et al., 2011) or prepared meals were handed out (Birlouez-Aragon et al., 2010; Cai et al., 2004; Vlassara et al., 2002, 2009). The low and high AGE diets have to be similar in energy and nutrient content to be able to differentiate between effects of high AGE diet as opposed to effects of high energy or high fat diet, which can both influence the risk factors for diabetes and metabolic parameters. Some of the studies did not control for the energy and/or macronutrient content (Birlouez-Aragon et al., 2010; Peppa et al., 2004; Uribarri et al., 2003b). In general, controlled settings in relation to both energy and macro- and micronutrients are essential, as physiological endpoints are often influenced by these factors.

8. Effects of heated foods or AGEs?

Many of the studies cited so far used more or less well-controlled changes in cooking methods to increase AGEs in the food. Other processes, besides the formation of AGEs, also take place in

food during cooking. It is well-known and described in the literature that heating of food induces degradation and oxidation of heat-sensitive compounds, including vitamins and other bioactive compounds (Dhuique-Mayer et al., 2007; Klopotek et al., 2005; Vikram et al., 2005). A high versus low AGE diet made by differences in heat treatment will, therefore, have dissimilar content of such compounds, and this has also been confirmed when it has been measured in intervention studies (Birlouez-Aragon et al., 2010). This is a problem, because effects of high AGE diets cannot be directly related only to the AGE content. It cannot be ruled out that a lower content of a range of heat-sensitive nutrients in the diet, e.g. vitamin C, E, and thiamine, could also contribute to these negative effects. Accordingly, AGE levels in body fluids might be markers of the inflammatory and oxidative burden. For example, marginal thiamine deficiency has been shown to increase both markers of oxidative stress and of reactive dicarbonyls (Depeint et al., 2007; Shangari et al., 2005) and vitamin B6 can also affect AGE formation (see Section 2.8).

Furthermore, extensive heat processing of food can generate Maillard-derived anti-nutritional and toxic compounds (Friedman, 1992; Perez-Locas and Yaylayan, 2010). Such compounds include acrylamide (Gokmen and Senyuva, 2012; Tareke et al., 2002), heterocyclic aromatic amines (Skog et al., 1998), and 5-hydroxymethylfurfural (Janzowski et al., 2000; Murkovic and Pichler, 2006), all of which are suspected carcinogens. Thus, simply referring the effects of a less heat-treated diet to effects of AGEs is problematic; the consequences of cooking for the concentrations of AGEs as well as other heat-derived compounds are not tested in the majority of the dietary AGE studies. Only one study has reported the content of acrylamide and 5-hydroxymethylfurfural and they were found to be significantly higher in the high AGE diet (Pouillart et al., 2008). Endpoints investigated in relation to these heat-generated compounds are most often related to their carcinogenic actions (Abraham et al., 2011; Sugimura et al., 2004; Tritscher, 2004), which does not seem to be comparable to the investigated endpoints in the dietary AGE studies. Nevertheless, this shows there is a large range of potentially harmful compounds generated by heat and points to the essential problem with identifying the active compounds. Harmful effects of high AGE diets cannot be directly related to the AGE content. Studies with well-defined compounds outside a complex food matrix (e.g. synthetically produced AGEs) are needed to identify individual effects. Moreover, AGEs are often investigated and discussed as a whole, even though they are a large and heterogeneous group of compounds. The heterogeneity of AGEs makes it difficult to conclude which of these compounds are biologically active and exert which specific effects *in vivo*. Based on the few animal studies conducted so far with well-defined AGEs (Cai et al., 2008b, 2012), MG-modifications in HMW AGEs seem to be of importance. Also, absorption of reactive dicarbonyls from the diet may induce endogenous AGE formation. This is indicated by increased AGE accumulation in MG-exposed rats (Sena et al., 2012) and by an increased CML content of plasma proteins after a highly heat-treated diet intervention in humans (Birlouez-Aragon et al., 2010). In order to confirm specific biological effects of the various AGEs, feeding experiments have to be conducted with well-defined AGEs in well-characterized LMW and HMW forms.

Within the large range of MRPs, not only AGEs have been identified, but also compounds with potential beneficial effects have been described (Silvan et al., 2006). Melanoidins have been associated with health benefits in some studies (Morales et al., 2012; Somoza, 2005; Wang et al., 2011), and antioxidative properties of MRPs have been observed in a human intervention study (Dittrich et al., 2009). The formation of potentially harmful and beneficial MRPs is often observed within the same context, which makes the distinction between different effects of separate MRPs crucial and accentuates the need to understand the underlying mechanisms. Again, this emphasizes the need to study single AGEs separately to distinguish their possible harmful effects from effects (harmful or beneficial) caused by other heat generated compounds in the diet.

The actual exposure to AGEs in the dietary studies has often been calculated from table values based on an immunosorbent assay using anti-CML antibodies and given in arbitrary AGE units (Goldberg et al., 2004; Uribarri et al., 2010), rather than measured with chromatographic methods. The problems with this approach have been discussed in Section 3; however, it is important to underline that in several of the human dietary AGE studies, this method has been used to determine AGE exposure, making the actual exposure scenario uncertain. Potentially harmful effects of the cooking method are nevertheless still relevant and valid, but again it cannot be concluded from these studies that they are caused directly by AGEs.

Many compounds in our diet have adverse as well as beneficial effects, and in an overall varied diet, the importance of potentially adverse effects of dietary AGEs might be neglected. AGEs are often found in connection with a typical Western diet high in fat and heat-treated foods and, consequently contribute to the overall health profile of this type of diet as one of many dietary risk factors. When taking the whole diet and lifestyle into account, the question is whether AGEs single out as major contributors or disappear in the crowd. For some high risk groups, such as diabetes patients, AGEs might be of greater importance than for the healthy population. For this population group in particular the prevention of AGE formation in the diet, inhibitors of their action in the body and enhancers of their degradation are important nutritional and pharmaceutical targets for disease prevention.

Based on the discussion above, a diet restricted in AGEs has been shown to have beneficial effects in healthy individuals, but the effects cannot be finally attributed to the AGE contents *per se*. The potential for inhibition of the actions of AGEs may therefore have even wider implications. Based on the current evidence, individuals with diabetes and/or kidney disease seem to be the population groups deriving most benefit from an AGE-restricted diet and potentially from inhibition of AGE-formation and its associated actions in the body.

9. Conclusions and perspectives

AGE research in food and nutrition-related diseases has progressed considerably within the last 20 years, but it is facing obstacles that need to be overcome in order to advance further. These challenges to the research community include mainly three areas, namely agreeing what constitutes AGEs, finding methods for accurately measuring AGEs, and understanding the relationship between AGE exposure and biological effects.

The many different processes leading to formation of AGEs are complex and not fully understood. This complexity and diversity of the AGE formation pathways leads to many possible compounds defined as AGEs. Within this broad concept, consensus about a distinction between "early" and "advanced" glycation endproducts is lacking. For example, MRPs or the term 'glycotoxins' are sometimes used interchangeably with AGEs, whereas other times these terms are used only when referring to the early reaction products. Also a universal definition of HMW and LMW AGEs is lacking. The distinction between HMW and LMW AGEs is often used to discriminate protein-bound AGEs from peptide-bound or free AGEs. However, when using the term, MRPs, the HMW compounds can also be aggregated endproducts, such as melanoidins. The reactive dicarbonyls, which are AGE precursors, are also a matter of debate, as they are often considered AGEs although they are indeed precur-

sors and not endproducts. Different uses of all these concepts have led to confusion in the literature, especially when measuring AGE exposure and investigating their biological effects. It is suggested that carbonyl precursors and carbonyl stress is treated as distinct from those of the early reaction products and also from the effects of their reaction endproducts, the AGEs. Moreover, a clear distinction between the effects of free LMW AGEs, peptide-bound AGEs, and HMW protein-bound AGEs should be pursued.

AGEs can be measured with both instrumental and immunochemical methods, but their quantification is hampered by technical challenges due to their structural diversity and by our lack of consensus on what constitutes AGEs. Analysis of identical food items have resulted in large differences in their reported AGE content depending on analytical method, with fat-rich foods and soft drinks as the extreme examples. Immunoassays are widely used in the literature and have the advantage that HMW and LMW AGEs can be measured within the same assay. Immunoassays are, however, potentially unspecific and limited to measuring a few AGEs, most often only CML. The use of CML as a marker of AGE formation in food has led to the development of a commonly used database containing CML content of several hundred food items. However, the disagreement between results from this database and other methods clearly points out the considerable challenges still remaining with analysis of AGEs. Another challenge is the lack of both HMW and LMW AGE standards. Only a limited number of compounds are available commercially, and large amounts for feeding experiments would currently be very costly. A range of well-defined free and bound AGE compounds are needed alongside exact analytical tools in order to obtain a clearer picture of actual exposures and cause-and-effect relationships.

In experimental animal and human studies, diets high in AGEs have been shown to affect inflammatory markers, and in observational studies dietary AGEs are strongly associated with late complications in diabetes. However, almost all studies have been carried out with heat-treated food which does not unambiguously point to AGEs. A few animal studies have shown clear adverse effects of well-defined MG-BSA indicating that MG-derived modifications may be of central importance. AGEs bind different proteins in the body, among which some are receptors, e.g. RAGE and AGER1. The impact of any interaction with receptors, however, is not clear as only HMW AGEs seem to bind to RAGE. Peptide-bound AGEs have not yet been tested. It is therefore uncertain whether dietary AGEs are able to interact with RAGE, or if such interaction is limited to endogenously formed AGE. In the latter case, it might be the dietary or endogenously formed AGE precursors, for example reactive dicarbonyls, that are of most significance. Reactive dicarbonyls are found in ordinarily consumed foods, but knowledge of absorption and bioavailability is scarce and further investigation of their importance for endogenous AGE formation should be carried out. The interaction between AGEs and the receptors is not similar for all AGEs, and some AGEs seem not to bind to the receptors at all, regardless of molecular weight. The concept of specific AGE receptors can, therefore, be partially misleading. Nonetheless, it seems that there is a distinction between the receptors with a pro- and an anti-inflammatory effect. RAGE is the most studied pro-inflammatory receptor and AGER1 the most studied anti-inflammatory receptor. There seems to be an interaction between these receptors illustrated by a sort of biological switch, which contributes to initiation and inhibition of low-grade inflammation. This possible switch might be an important drug target in future research on inflammatory diseases.

The effect of cooking on inflammation and other markers of diabetes risk seems clear and diets cooked in such a way that less AGE is formed may have a considerable health impact in dietary prevention of diabetes and especially in prevention of diabetes complications. Other potential targets for prevention include inhibitors of AGE-forming Maillard processes in food processing and development of inhibitors of AGE-protein aggregate formation in the human body as well as enhancers of their degradation.

Overall, the concept of AGEs in food and health seems highly important but needs better definitions at the analytical, molecular, and biological level. The concept also needs support by synthesis of better chemical standards for quantitation of LMW and HMW AGEs and development of standard methods for measuring the overall biological effects related to different specific AGEs. Last but not least, despite large advances in understanding the effects of AGEs in the body, unequivocal evidence that dietary AGEs are directly responsible for the biological effects currently associated with AGEs in the human diet is still lacking.

10. Conflict of Interest

The authors declare that there are no conflicts of interest.

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