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Protein-bound advanced glycation endproducts (AGEs) as bioactive amino acid derivatives in foods

Review Article

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Summary. The Maillard reaction or nonenzymatic browning is of outstanding importance for the formation of flavour and colour of heated foods. Corresponding reactions, also referred to as ''glycation'', are known from biological systems, where the formation of advanced glycation endproducts (AGEs) shall play an important pathophysiological role in diabetes and uremia. In this review, pathways leading to the formation of individual protein-bound lysine and arginine derivatives in foods are described and nutritional consequences resulting from this posttranslational modifications of food proteins are discussed.

Keywords: Lysine – Arginine – Amadori products – Furoylmethyl amino acids – Nonenzymatic browning – Glycation – Metabolic transit

Chemistry of Maillard reactions

Historical aspects

The phenomenon that foods turn progressively brown during heating is probably known since the discovery of fire more than 300.000 years ago. Although several attempts were made to explain this nonenzymatic browning in relation to changes of amino acids and reducing sugars (Ling, 1909), it took until the years around 1912, when the French biochemist Louis-Camille Maillard (Maillard, 1912) reported the first systematic studies, indicating that amino acids and reducing sugars undergo complex reactions during heating, finally leading to the formation of brown substances, the so-called melanoidins, via condensation, elimination and other degradadation mechanisms. Based on the fundamental work of Amadori (1929), Heyns (1953), Hodge (1953) and numerous others, it is today generally accepted that the ''Maillard reaction'' is a series of subsequent and parallel reactions, which for reasons of clarity can be divided into three ''stages'', designated ''early'', ''advanced'' and ''final'' Maillard reaction, being aware that all reactions can occur simultaneously, influenced by each other as well as by milieu parameters (Ledl and Schleicher, 1990; Friedman, 1996).

The ''early stage''

The first stable reaction products which are formed during the ''early stage'' after condensation between an amino group of amino acids, peptides or proteins and the carbonyl group of a reducing carbohydrate and subsequent rearrangement are the so-called Amadori products (Fig. 1). In the case of protein-containing foods, the ε-amino group of lysine represents the primary target for an attack by carbohydrates, leading to N-ε-ketosyllysine derivatives **1** to **4** (Ledl and Schleicher, 1990; Friedman, 1996). Amadori products of free amino acids have been detected in various foods like dried fruits and vegetables (Eichner, 1982), beer (Wittmann and Eichner, 1989) or honey (Sanz et al., 2003). The fact that such reactions also occur under physiological conditions was demonstrated with the identification of the hemoglobin variant HbA_{IC}, in which the N-terminal valine residue has reacted with glucose to N-α-fructosylvaline (Rahbar et al., 1969). The reliable quantification of Amadori products in foods or physiological samples is difficult, as they are destroyed during conventional acid hydrolysis of proteins, thus making it impos-

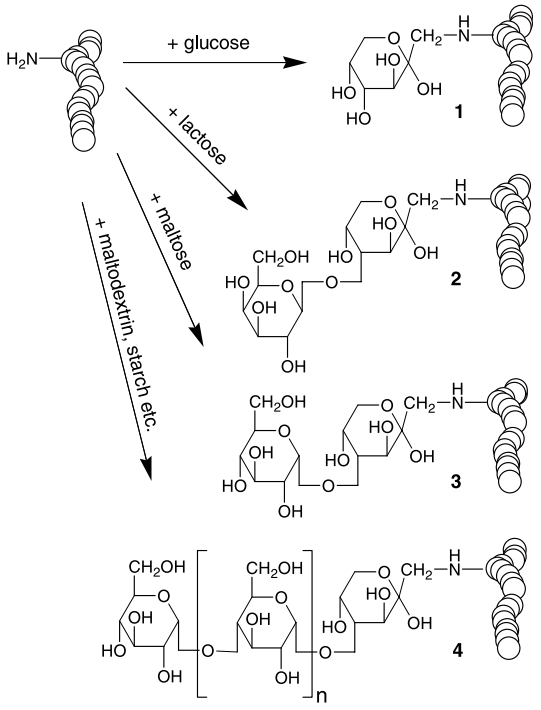

Fig. 1. Formation of Amadori products (aminoketoses) from the reaction of protein-bound lysine with glucose (to N-ε-fructosyllysine **1**), lactose (to N-ε-lactulosyllysine **2**), maltose (to N-ε-maltulosyllysine **3**) or maltodextrin/starch (resulting in protein-bound oligo/olysaccharides **4**)

sible to detect them with routine amino acid analysis (Erbersdobler and Bock, 1967; Finot et al., 1968). However, it was found that controlled acid hydrolysis of Amadori products leads to the formation of defined degradation products, among which the furoyl derivatives **5** are formed in reproducible amounts under defined conditions (Fig. 2) (Finot and Mauron, 1972; Krause et al., 2003). The corresponding derivative of N-ε-fructoselysine, namely furosine, is widely used as a parameter for assessing the extent of the early Maillard reaction mainly in milk products (Finot et al., 1981; Erbersdobler et al., 1987; Resmini et al., 1992; Henle et al., 1995). Depending on time and temperature during heating or storage, up to 70% of lysine initially present in proteins may react to the Amadori product (Finot et al., 1981). Recently, corresponding furoylmethyl derivatives of Amadori products of free amino acids are reported as indicators for heat

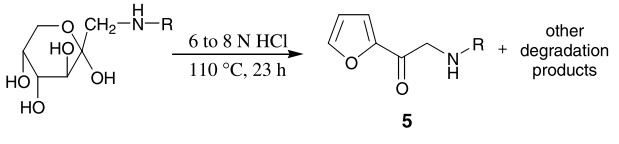

Fig. 2. Degradation of Amadori products (a fructosyl amino acid shown) to furoylmethyl amino acids 5 during acid hydrolysis

treatment of juices, dehydrated foods or honey, respectively (Dolores del Castillo et al., 1999; Sanz et al., 2001, 2003). From the analytical point of view, it furthermore must be realized that foods may contain several kinds of reducing saccharides, thus leading to a certain number of possible Amadori products derived from mono- and oligosacccharides (compounds **1** to **4** in Fig. 1). Whereas glucose represents the main sugar under physiological conditions, foods mainly contain disaccharides like maltose or lactose in addition to oligo- and polysaccharides. With the exception of milk products, for which the separation of lactuloselysine and fructoselysine was reported (Moeller et al., 1977; Henle et al., 1991), there is up to now no information on the content of individual Amadori products resulting from various carbohydrates in foods. Data for peptide-bound Amadori products of lysine published are mainly based on an indirect quantification as furosine after acid hydrolysis, thus making it impossible to distinguish between different precursors.

Advanced Maillard reactions: formation of 1,2-dicarbonyls

The Amadori products – although fairly stable in foods with low water activity – may undergo several degradation reactions during severe heating or prolonged storage, leading to the formation of 1,2-dicarbonyls (Fig. 3), among which 3-deoxyglucosulose **6** (Anet, 1960), 1-deoxyglucosulose **7** (Ishizu et al., 1967; Glomb and Pfahler, 2000), methylglyoxal **8** and glyoxal **9** (Thornalley, 1996) may represent the most important structures. Detailed discussions of possible reaction mechanisms, which include enolization, elimination of water as well as retroaldolization reactions, can be found in the literature (Weenan, 1998). It is noteworthy that 1,2-dicarbonyls are also formed from reducing carbohydrates without involvement of amines, a process commonly called ‘‘caramelization’’ (Hoellnagel and Kroh, 1998). Studies concerning the formation and the amount of individual 1,2-dicarbonyls in complex foods are rare, probably due to difficulties in analytical characterization of this labile intermediates in complex matrices. 1,2-Dicarbonyls are generally quantified after derivatization with compounds like orthophenylenediamine and subsequent RP-HPLC or GLC. It is noteworthy to mention that such derivatization reactions may significantly influence the amount of carbonyls (Glomb and Tschirnich, 2001). Based on such analytical approaches, low amounts of glyoxal and methylglyoxal have been quantified in food items like coffee, wine or beer (Rodrigues et al., 1999). Very recently, honey was

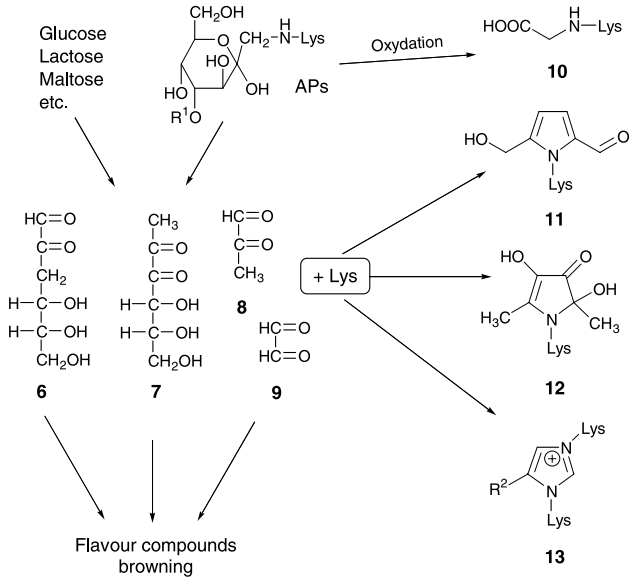

Fig. 3. Degradation of Amadori products (APs) and reducing carbohydrates to the 1,2-dicarbonyls 3-deoxyglucosulose **6**, 1-deoxyglucosulose **7**, methylglyoxal **8** and glyoxal **9**. The 1,2-dicarbonyls can further react to low molecular flavour compounds or brown polymers, or they can react with protein-bound lysine. N-ε-carboxymethyllysine **10** (CML), pyrraline **11**, pronyllysine **12** or the lysine dimers **13**, designated GOLD (R = H), MOLD (R = CH_3) or DOLD [R = CH_2–$(CHOH)_2$–CH_2OH)], were quantified in foods. *Lys*, lysyl

found to contain relatively high amounts of 3-deoxyglucosulose (Weigel et al., 2004).

Besides degradation of carbohydrates or Amadori products, 1,2-dicarbonyls may also be formed under oxydative conditions from the Schiff base, the initial condensation product of a reducing carbohydrate and an amino compound, via the so-called Namiki pathway (Hayashi and Namiki, 1980). Methlyglyoxal can arise from degradation of triosephospahates (Phillips and Thornalley, 1993). Furthermore, lipid peroxydation shall represent a source for glyoxal (Fu et al., 1996). The quantitative contribution of individual mechanisms for the formation of 1,2-dicarbonyls in foods is hardly known. One study by Berg and van Boekel (1994) showed that during heating of milk, the degradation of lactose via lactulose to dicarbonyls is quantitatively more important compared to the degradation of the Amadori product lactuloselysine. Further investigations are necessary in order to obtain profound information about the extent of 1,2-dicarbonyl formation in foods. Although formed in relatively low amounts compared to the starting carbohydrate, this dicarbonyls on one hand represent major precursors for the formation of low-molecular heterocyclic compounds, among them important flavour compounds (Fig. 3). On the other hand, dicarbonyls are highly reactive for reactions with proteins, leading to the formation of peptide-bound amino acid derivatives in the ''final stages'' of the Maillard reaction.

From advanced to final Maillard reactions: formation of end products

During prolonged heating or storage, lysine and arginine side chains of proteins may react with 1,2-dicarbonyls to form stable peptide-bound amino acid derivatives as ''endproducts'' of the Maillard reaction. For such reaction products resulting from Maillard reactions *in vivo*, the term ''advanced glycation endproducts'' (AGEs) can be found in the literature since the mid 1980ies (Brownlee et al., 1984). Although numerous model studies have been published, dealing with isolation and structure elucidation of a large number of possible lysine and arginine derivatives which may form during food processing or under physiological conditions, the number of compounds which have unambigously been identified and quantified in processed foods remains quite low (Fig. 3). The first amino acid derivative of the advanced Maillard which was detected in foods accounting for 3 to 10% of Amadori products was N-ε-carboxymethyllysine **10** (CML) (Hartkopf and Erbersdobler, 1994; Drusch et al., 1999). CML is predominatly formed from oxidative cleavage of Amadori products, but other mechanisms are also possible (Ahmed et al., 1986; Fu et al., 1996). Following its first isolation from model systems (Nakayama et al., 1980), an acid labile pyrrole derivative of lysine, namely pyrraline **11**, which is formed from the reaction of the ε-amino group of lysine and 3-deoxyglucosulose, was quantified in several foods like milk or bakery products and pasta using amino acid analysis or RP-HPLC after enzymatic hydrolysis (Henle and Klostermeyer, 1993; Henle et al., 1994a; Resmini and Pellegrino, 1994; Rufian-Henares et al., 2004). Concentrations found ranged from 150 mg/kg protein in sterilized milk up to 3700 mg/kg protein in bread crusts, indicating that pyrraline represents one of the quantitatively dominating AGEs in foods. A new lysine derivative designated pronyllysine **12**, resulting from lysine side chains and acetylformoin, was detected and quantified in amounts of around 60 mg per kg in the crust and 6 mg/kg in the crumb of bread (Lindenmeier et al., 2002; Lindenmeier and Hofmann, 2004). Lysine dimers (compounds **13** in Fig. 3) resulting from the reaction between two lysine side chains and two molecules of glyoxal, methylglyoxal or 3-deoxyglucosulose, namely GOLD, MOLD or DOLD, respectively, were found in enzymatic hydrolysates of bakery products in the mg

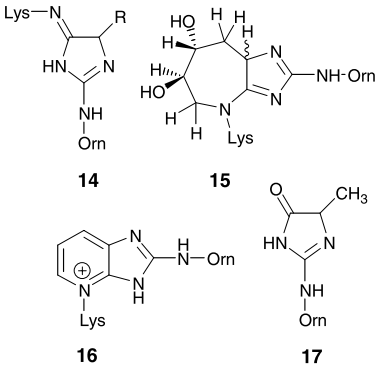

Fig. 4. Arginine derivatives of the advanced Maillard reaction, which have been quantified in foods. GODIC (R = H), MODIC (R = CH_3) and DODIC [(R = CH_2–$(CHOH)_2$–CH_2OH)] **14**, glucosepan **15**, pentosidine **16**. The imidazolinone **17** was the first arginine derivative detected in foods and represents the direct precursor for MODIC. *Orn*, ornithyl; *Lys*, lysyl

per kg range together with crosslinks between arginine and lysine (Fig. 4), which were named as GODIC, MODIC, DODIC (compounds **14**) and glucosepan **15** (Biemel et al., 2001). Pentosidine **16**, a crosslinking amino acid, initially identified in hydrolyzates of human collagen, was found in very low amounts in several foods (Henle et al., 1997). This results point to the fact that nonenzymatic oligomerization of food proteins, which is well known to occur in the coarse of the Maillard reaction (Henle et al., 1996; Lauber et al., 2001), may be due to a large number of individual crosslinks formed during Maillard reactions.

In addition to lysine, the guanidino side chain of arginine is a target for modification by 1,2-dicarbonyls. The acid labile imidazolinone **17** (Fig. 4) resulting from the reaction between peptide-bound arginine and methylglyoxal was quantified in alkali-treated bakery products and coffee (Henle et al., 1994b) where it accounts for a substantial degree of arginine derivatisation. Compound **17** can react with a lysine side chain, resulting in the crosslink MODIC **14** (R = CH_3). In addition to imidazolinones, which may represent the major form of arginine derivatization in foods, argpyrimidine **18** (Fig. 5), a reaction product formed from two molecules of methylglyoxal and the guanidino side chain or arginine, was detected as free amino acid in beer (Glomb et al., 2001). As argpyrimidine was originally found in biological samples (Shipanova et al., 1997), the formation of this compound as peptide-bound derivative in foods is likely.

Several other amino acid derivatives (Fig. 5) resulting from Maillard reactions in food resembling systems have been detected, but not yet quantified unambigously as peptide-bound compounds, like oxalic acid monolysylamide **19** (OMA) (Hasenkopf et al., 2001) or the aminoreductone **20** (Pischetsrieder et al., 1998). The propylimidazolinone-ornithine **21** (PIO) was found to be specific for the reaction of arginine with C5-dicarbonyls resulting as exclusive degradation products of disaccharides with 1,4-glycosidic linkages (Mavric et al., 2004). PIO therefore may represent the main form of arginine derivatization in oligosaccharide-containing foods like milk. Furthermore, Krause et al. (2004) proved that the α-amino termini of peptides are modified by 1,2-dicarbonyls to peptide-bound pyrazinones **22**, a new class of fluorescent AGEs, which may have quantitative importance in heated peptide-containing foods as well as *in vivo*.

In recent years, significant progress was made in understanding the formation of coloured peptide-bound Maillard compounds, generally summarized as ''melanoidins'' (Ledl and Schleicher, 1990). Complex structures involving lysine and arginine have been isolated from browning mixtures consisting of carbohydrates or their degradation products, respectively, and casein as model protein, and were assayed for their contribution to the colour of browning systems (Hofmann, 1998a, 1998b)

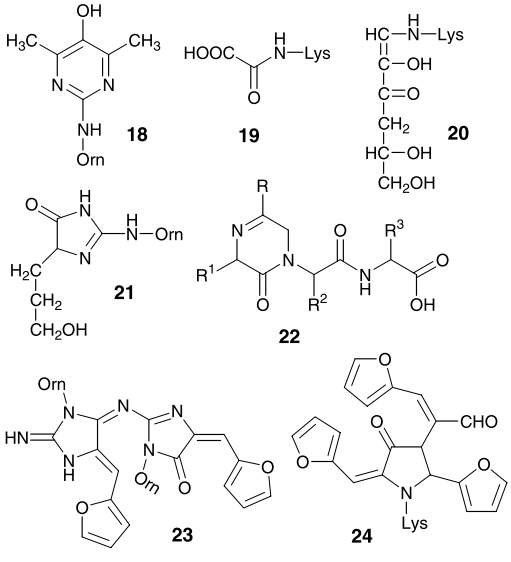

Fig. 5. Candidates for protein-bound amino acid derivatives, not yet quantified in foods: Argpyrimidine **18**, oxalic acid monolysylamide **19** (OMA), lysine aminoreductone **20**, N-δ-[5-(3-hydroxypropyl)-4-oxo-imidazolon-2-yl]-L-ornithine **21** (PIO); peptide-bound pyrazinones **22** resulting from the reaction of N-termini of peptides with glyoxal (R = H) or methylglyoxal (R = CH_3), respectively (R^1, R^2 and R^3 represent side-chains from amino acids); coloured compounds (S,S)-1-[4-(acetylamino)-4-carboxy-1-butyl]-2-imino-4-[(Z)-(2-furyl)methylidene]-5-{2-[1-[4-(acetylamino)-4-carboxy-1-butyl]-4-[(E)-(2-furyl)methylidene]-5-oxo-1,3-imidazol-2-inyl]}azamethylidene-1,3-imidazolidine **23** (BisArg) and (S)-2-amino-6-{4-[(E)-1-formyl-2-(2-furyl)ethenyl]-5-(2-furyl)-2-[(E)-(2-furyl)methylidene]-2,3-dihydro-3-oxo-1H-pyrrol-1-yl}-hexanoic acid **24**. *Orn*, ornithyl; *Lys*, lysyl

(compounds **23** and **24** in Fig. 5). Although not yet identified or quantified in browned foods, this compounds stand for a new class of Maillard reaction products, giving new insights into the phenomenon of nonenzymatic browning on a molecular level.

Taking together the data available for the presence of protein-bound Maillard compunds in foods, it can roughly be calculated that with a conventional diet, about 1000 to 2000 μmole of Amadori products and about 100 to 150 μmole of advanced reaction products, mainly CML and pyrraline, are consumed per day, with bakery products representing the major ''source'' of amino acid derivatives (Henle, 2003).

Nutritional and biological aspects

Lessons from Maillard reactions in vivo

With the identification of the hemoglobin variant HbA_{IC} it was demonstrated that the Maillard reaction does also occur *in vivo*. To distinguish this reaction mechanisms from enzymatic glycosylation, the term ''glycation'' was introduced (Ledl and Schleicher, 1990). The quantification of HbA_{IC} in the blood of diabetics today is an important tool in clinical chemistry for long-term control of blood glucose (Cohen et al., 1999). Following the discovery of HbA_{IC}, several other proteins have been found to contain nonenzymatically modified amino acids (Miller et al., 1980; Vlassara et al., 1981), but biological implications resulting from glycation reactions initially remained open. In the mid 80s, reports were published linking the formation of AGEs to consequences of diabetes (Brownlee et al., 1984). It was found that AGE content in plasma and tissues correlates with biological disorder like cataract or diabetic nephropathy (Abraham et al., 1989; Makita et al., 1991). Furthermore, it was found that ''AGE-proteins'', generally prepared by incubation of proteins like serum albumin (Lu et al., 1998) or β_2-microglobulin (Miyata et al., 1991) in the presence of high concentrations of glucose, initiate a range of cellular responses, including stimulation of monocyte chemotaxis, secretion of cytokines from macrophages, proliferation of smooth muscle cells and production of vascular endothelial growth factor (VEGF) from endothelial cells (Miyata et al., 1991; Lu et al., 1998; Sakata et al., 2000; Henle and Miyata, 2003). Accumulation of AGEs is predominantly observed in uremic patients, where plasma levels for pentosidine or CML may far exceed those in diabetic or healthy subjects (Makita et al., 1991; Takahashi et al., 1996). Whether this is due to impaired renal clearence of AGE-modified proteins or impaired enzymatic detoxification of dicarbonyl precursors, which may lead to ''carbonyl stress'', is under debate (Sugiyami et al., 1998). It is generally accepted that AGEs are an important of uremic toxins (Raj et al., 2000; Schwenger et al., 2001; Henle and Miyata, 2003).

Evidence for a pathophysiological role of glycation reactions was also derived from the detection of specific receptors capable for binding AGEs (Thornalley, 1998). Among them, a specific receptor designated ''RAGE'' (''receptor for AGEs'') gained particular interest (Stern et al., 2002; Chavakis et al., 2004). RAGE is a multiligand transmembrane receptor of the immunoglobulin superfamily, which is expressed at low levels in normal tissues, but becomes upregulated at sites where its putative ligands accumulate. Binding of ligands to RAGE results in activation of the proinflammatory transcription factor nuclear factor-kappaB (NF-kappaB) and subsequent expression of NF-kappaB-regulated cytokines, which shall lead to perpetuated cell activation. RAGE-AGE interaction thus may initiate cellular dysfunction in inflammatory disorders (Yamagishi et al., 2003). Based on this findings, RAGE is discussed as a target for drug development (Hudson and Schmidt, 2004), although the structures of possible RAGE-ligands still have not been identified.

Metabolic handling of dietary AGEs

The fact that heat treatment may have a negative impact on the digestibility and thus on the nutritional quality of proteins was studied since the early years of the 20th century (McCollum and Marguerite, 1915). With respect to carbonyl-amine reactions, Finot et al. (1977) were the first to prove that Amadori products of lysine are not used as lysine source during digestion, thus introducing the term ''blocked'' or ''not available'' lysine, which became an important parameter for assessing the influence of heat treatment on the biological value of food proteins (Mauron, 1990). Several methods for indirect or direct quantification of a lysine blockage in foods have been published (Carpenter et al., 1989). Despite the fact that Amadori products and other peptide-bound Maillard compounds are formed during food processing, only little information is available today concerning a physiological handling of posttranslationally modified amino acids present in proteins after heating with carbohydrates. Initial studies pointed to a low resorption rate. When egg-white, which had been autoclaved in the presence of ^{14}C-glucose, was fed to rats, only 3% of the ingested

radioactivity was found in the urine and 74% in the faeces (Valle-Riestra and Barnes, 1970). Similar results for radioactively labelled proteins containing ''early'' and ''advanced'' Maillard compounds were reported by Finot and Magnenat (1981). Erbersdobler et al. (1991) were the first to perform studies with human volunteers, showing that urinary excretion of orally administered fructoselysine is about 3% and fecal excretion about 1%. The original observation of the authors that the intestinal flora may be mainly responsible for metabolism of Amadori products *in vivo* (Erbersdobler et al., 1970) was strengthened by recent characterization of a bacterial enzyme, namely fructoseamine-6-kinase, which enables E. coli and other species to metabolize Amadori products (Wiame et al., 2002). Studies in our laboratory showed that urinary excretion of furosine (as a hallmark for Amadori products) as well as of pyrraline is directly affected by the diet and can be decreased by a diet free of AGEs (Henle et al., 2000; Förster and Henle, 2003). Interestingly, whereas bioavailability of Amadori products is very low, nearly all peptide-bound pyrraline supplied with the diet can be found as free amino acid in the urine (Förster and Henle, 2003), pointing to different resorption and metabolic pathways of individual Maillard products.

With respect to the above mentioned pathophysiological role of AGEs, biological implications of dietary AGEs are currently discussed intensively. It was found that serum levels of circulating AGEs, as measured with an antibody specific for CML, can be influenced by eating egg white which was heated in the presence of fructose (Koschinsky et al., 1997). As the decrease in the immuno response after ingestion of the meal containing the browned protein was significantly slower in patients with renal failure compared to healthy subjects, speculations were made whether dietary Maillard compounds may be reactive under physiological conditions and therefore may represent a ''risk factor'' in diabetes and uremia (Koschinsky et al., 1997; He et al., 1999). The term ''glycotoxins'' was created in this context. Evidence strengthening this hypothesis was deduced from subsequent studies of the same group, in which a higher plasma CML content concomitant with a decreased insulin response was found for rats fed a diet high in AGEs (Hofmann et al., 2002). Dietary glycotoxins were found to correlate with circulating advanced glycation end product levels in renal failure patients (Uribarri et al., 2003a, 2003b). For dialysis patients on conventional diet, no correlation was found for plasma CML and inflammatory markers such as tumor necrosis factor α and C-reactive protein, but an AGE-free diet for four weeks induced a significant decrease of this markers (Vlassara et al., 2002; Peppa et al., 2004a). Authors discuss dietary AGEs as risk factors not only in diabetes, uremia or atherosclerosis (Peppa et al., 2002, 2004b), but also for healthy subjects, and recommendations for selecting food items with low amount of AGEs are given based on data bases, in which the so-called ''AGE content'' of foods has been determined with an ELISA based an anti-CML monoclonal antibody (Goldberg et al., 2004). From the analytical standpoint, however, this data collection must be handled with care, as results are published which need confirmation. For instance, fat-rich foods like butter or margarine are reported to contain highest amounts of AGEs, which seems very unlikely due to the low protein content and lack of severe heating during processing. On the other hand, foods rich in carbohydrates like bakery products are reported to contain very low AGE contents, which is in contrast to analytical data based on the use of chromatographical means (Henle et al., 1994a; Drusch et al., 1999). Prerequisite for an actual risk assessment in the near future, therefore, must be a data evaluation for individual Maillard compounds in common foods using reliable chromatographic techniques rather than screening methods like ELISA. Furthermore, we need to know more about the handling of posttranslationally modified proteins by the human body. Are such proteins proteolysed? Are the resulting amino acids resorbed, what is their biodistribution, how are they excreted? In a pioneering study, Bergmann et al. (2001) used positron emission tomography (PET) to monitor biodistribution and elimination of radiofluorinated CML. The authors found that the compound was fast distributed via the blood, followed by a rapid excretion through the kidneys. PET may be a useful tool for studying the metabolic transit of AGEs in the future.

Maillard compounds in foods – risk or benefit?

Physiological consequences resulting from protein-bound Maillard compounds in foods must be discussed carefully, as no unambigous results about defined toxicological effects of individual compounds are available yet. Furthermore, several recent reports argue against adverse effects and even discuss positive aspects resulting from consumption of browned foods. In a cross-sectional study with 312 hemodialysis patients, it was found that high serum AGEs, measured as AGE-specific fluorescence and using an ELISA for CML, are not linked to increased mortality (Schwedler et al., 2002). High plasma AGEs linked to a better survival rate may reflect a better nutritional status

of patients or may be due to a ''benefit'' caused by currently unknown AGE-effects resulting from browned foods. This results are in line with risk assessment studies for acrylamide. It was found that consumption of foods high in acrylamide and thus also high in other Maillard compounds has no measurable impact on risk of three major types of cancer (Mucci et al., 2003; Mucci et al., 2004). On a cellular level, it was found for RAGE-expressing endothelial cells as well as for human mononuclear cells that binding to RAGE of defined AGEs free of endotoxins is not sufficient to induce inflammatory signals, thus arguing against a uniformly role of AGEs in cellular activation. Furthermore, there is growing body of evidence that individual Maillard compounds in foods may even act as chemoprotective agents. Several Maillard compounds identified as constituents of melanoidins were found to inhibit tumor cell growth (Marko et al., 2002; Marko et al., 2003). *In-vitro* antioxidative properties of Maillard compounds have been described in a number of papers (e.g. Borelli et al., 2002; Dittrich et al., 2003; Shizuuchi and Hayase, 2003; Daglia et al., 2004). Pronyllysine as part of bread crust melanoidins was found to induce glutathione S-transferase (GST) activity in CaCO-2 cells, and thus could exhibit antioxidant chemopreventive activity *in vivo* (Lindenmeier et al., 2002). N-methylpridinium, a low-molecular constituent formed during roasting of coffee, increased total antioxidant capacity in the plasma of rats fed with coffee melanoidins (Somoza et al., 2003). Similar results were obained for melanoidins isolated from bakery products (Borrelli et al., 2003) and model systems (Usui et al., 2004; Jing and Kitts, 2004).

Conclusion

Although enormous progress has been made in research in the field of the Maillard reaction, basic questions from a chemical as well as biological point of view are still unresolved. Without doubt it can be stated that the reaction products we know today do only represent a minor part of the total AGEs probably present in ''browned'' foods. As most of the knowledge we have about formation of individual reaction products mainly originates from model systems, further efforts for identifying and quantifying individual compounds in complex foods using relaible analytical techniques are absolutely necessary. Comprehensive data bases as well as informations about pathways may allow food manufacturers to process their products as careful as possible in order to obtain products with minimal amounts of AGEs. On the other hand, a selective fortification of proteinaceous foods with individual compounds may be conceivable, if possible benefits of individual AGEs can be proven for biological systems. For this, however, profound understanding of the relationships between well-defined biological effects and well-characterized chemical structures are necessary. With respect to the role of AGEs *in vivo*, either due to endogenous formation or supply via foods, cell biology raises several interesting questions. It is up to the chemists to answer them.

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