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Review

Five years of research on health risks and benefits of Maillard reaction products: An update

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When the COST Action 919 started to investigate the role of melanoidins in food and health in 1999, the chemical structures of dietary melanoidins were poorly defined and hardly anything was known about structure-specific health effects of this chemical class. In addition, the degradation of melanoidins in the gut and their absorption and function or that of any of their degradation products had not yet been reported. In the past five years, results from *in vitro* studies demonstrated that at least some of the dietary melanoidins are degraded by intestinal microorganisms, possibly influencing their growth rate. The absorption and excretion rates of individual Maillard reaction compounds and melanoidin structures have been investigated in animal studies. These studies show that at least 30% of the ingested dose of low-molecular-weight compounds are absorbed. Structure-specific health-promoting effects of newly identified compounds have been described by means of their antioxidant and chemopreventive activity in cell culture investigations as well as in animal feeding studies and human trials. Harmful effects of dietary melanoidins have been investigated in the context of their ability to promote glycation reactions *in vivo*, which are involved in the progression of several diseases, such as diabetes mellitus, cardiovascular complications, and Alzheimer's disease. Toxicological studies were performed showing that melanoidin structures can not be classified as potent dietary mutagens or genotoxins. Thus, substantial knowledge on the health effects of melanoidins has been gained within COST Action 919. But still, further studies are needed to distinguish between chemically identified harmful and health-beneficial melanoidins.

Keywords: Antioxidative effects / Cancer / Chemoprevention / Glycation / Melanoidins / Metabolic transit / Microbial degradation / Review

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Abbreviations: AGEs, advanced glycation end products; **GST**, glutathione-*S*-transferase; **HAA**, heterocyclic aromatic amine; **HMW**,

1 Introduction

The Maillard reaction is a series of reactions between proteins and carbohydrates. In foods, these reactions occur during storage at room temperature, as well as during cooking, with the rate of reaction accelerating as temperature increases. As virtually all foods contain both proteins and carbohydrates, Maillard reaction products (MRPs) are present in the daily diet in considerable amounts. The results of early-stage Maillard reactions are the so-called "Amadori products", whereas, when higher temperatures are applied for longer times, advanced brown-pigmented MRPs, termed "melanoidins", are formed. Predominantly MRPs provide the characteristic color and aroma of cooked foods,

like bread crust, and are the main determinants of the consumer's quality-oriented food choice. Next to the sensory properties, health aspects, such as food safety, the content of health-promoting nutrients, and the nutritional value of foods, are the main quality criteria of foods. The heat-induced formation of putative harmful compounds formed in the course of Maillard reactions, like heterocyclic aromatic amines [1] or acrylamide [2], give rise to the question whether MRPs are tasty but toxic. From an evolutionary perspective, humans have been cooking on a daily basis for a relatively short period of about 40 000 years. In the Darwinian sense, it seems questionable whether humans have adapted to a broad range of chemically different MRPs which are formed during widely varying processing technologies. On the other hand, Maillard reactions also originate in the human body, where the rate of chemical reactions is lower due to the lower temperature. The MRPs formed from endogenous carbohydrates and proteins might be similar but also different from those formed in heat-treated foods. Thus, metabolic adaptation to endogenously formed MRPs seems likely and a classical biotransformation through xenobiotic, chemopreventive enzymes is hypothesized [3 – 5].

The formation of MRPs *in vivo* has been of recent growing interest, particularly in relation to the progression of diabetes and aging. It is thought that the cross-linking between long-lived proteins, such as collagen, and carbohydrates generates advanced glycation end products (AGEs) at advanced stages of the Maillard reactions, contributing to tissue degeneration [6]. Although the human body is not defenseless, since at least some of the AGEs are recognized and endocytosed by macrophages [7] or degraded by enzymes [8], the key question is whether dietary MRPs or melanoidins can pose risks to the vascular system and kidneys resulting in the progression of diabetes or ageing. If so, a diet of raw, non-cooked food might increase longevity. To answer this question, the chemical structures and the mode of action of MRPs, melanoidins, and AGEs are important to know. Owing to the scarce information available about structure-specific effects of dietary MRPs and melanoidins, neither in foods nor a in the human body, a European Cooperation in the field of Scientific and Technical Research (COST) was initiated to investigate the formation of MRPs and the brown-colored melanoidins, in particular in processed foods and in model systems, and, moreover, to study their metabolic transit pathways and their structure-specific physiological effects. In this review, work is presented which was done on the health effects of melanoidins within the past five years of Working Group V of the COST Action 919, entitled "Melanoidins in food and health" (Table 1). In the described experiments, MRPs or melanoidins, either prepared from standardized model systems using, *e.g.*, heated glucose-glycine, or glucose-casein mixtures, or isolated from heated foods, were investigated for their health effects (Fig. 1).

Table 1. Results obtained on health effects of MRPs and melanoidins within COST 919

Health effect	Main results obtained
Effects on gut health	Model melanoidin mixtures stimulate the growth of health-beneficial bacteria in the gut [9, 10]. Model melanodins bind to HAAs and may subsequently decrease the absorption rate of HAAs [13].
Effects on the chemopreventive potential	Induction of chemopreventive enzymes in *in vitro* and *in vivo* systems by model and food melanoidin mixtures [5, 11, 26, 27] as well as by novel, chemically identified compounds [28, 29, 30].
Effects on the antioxidant capacity	Inhibition of lipid peroxidation by model melanoidin mixtures in isolated hepatocytes [37]. Increased antioxidant capacity in the plasma of humans after administration of food melanoidin mixtures [38].
Mutagenic and genotoxic effects	Compared to the effects of well-known mutagens, model melanoidin mixtures show negligible mutagenic and genotoxic effects in *in vitro* systems [39 – 41].
Effects on glycation reactions	Model melanoidin mixtures as well as chemically characterized compounds were demonstrated to bind to the receptor of AGEs *in vitro* [58], possibly resulting in pro-inflammatory reactions on a cellular level [57]. Intake of food melanoidins by healthy vegetarians was not associated with increased AGE levels in human plasma [61].

2 Intestinal fate of dietary MRPs and melanoidins

Significant quantities of dietary MRPs and melanoidins enter the human intestines every day, but very little is known about their metabolism therein. Neither the effects of digestive enzymes in the small intestines nor those of the bacteria in the large bowel on melanoidin degradation have been described yet. In a recent study, a roasted mixture of glucose-glycine was demonstrated to change the dynamics of large bowel bacteria [9]. After a maximum time of 24 h of incubation, the total number of anaerobes, bacteroides, clostridia, and bifidobacteria increased in a batch culture fermenter containing human fecal bacteria. Although no degradation product was identified in this study, a bacterial growth clearly indicated that gut bacteria are able to utilize melanoidins prepared from a roasted glucose-glycine mixture as energy substrates.

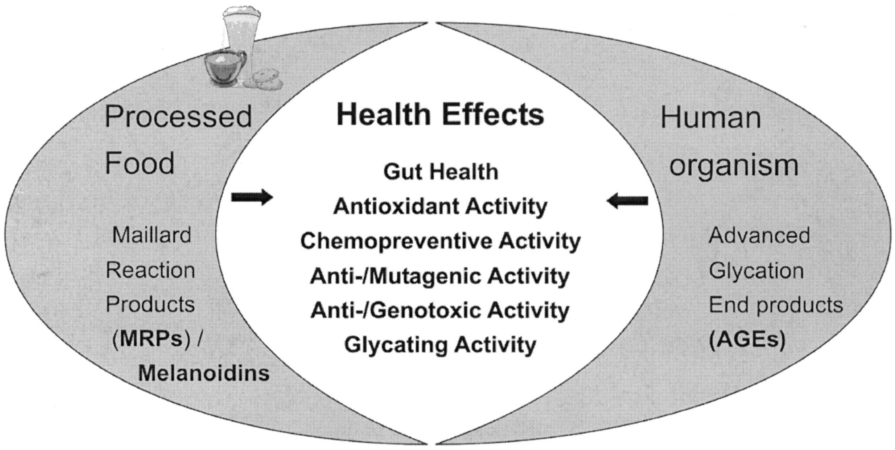

Figure 1. Interactions between food-derived MRPs and melanoidins and AGEs formed in the human body.

Microbial degradation of melanoidins isolated from a gluten-glucose mixture healed in water for 1 h was also indicated by the stimulated growth of bifidobacteria and by the production of short chain fatty acids in a fermenter containing human fecal bacteria [10]. As the stimulated growth of bifidobacteria was inhibited when gluten-glucose mixtures prepared by 2 or 3 h heating times were tested, it might be speculated that the microbial degradation is limited to less complex melanoidin structures, which are preferentially formed in the presence of water than under roasting conditions and during shorter heating times rather than during longer heat treatment at comparable temperatures [11].

The role of unabsorbed melanoidins and their degradation products on human health also remains an open question. One hypothesis is that these compounds are able to reduce the absorption of mutagens [12], such as heterocyclic aromatic amines (HAAs). HAAs have been quantified in all kinds of cooked meat and fish products, especially those cooked by frying, grilling, broiling, barbecuing, and roasting, and even in smoked foods [1]. Thus, in meat products, melanoidins may be formed and ingested in parallel with the HAAs. Interactions between melanoidins and HAAs have been reported for melanoidins either formed in a model system prepared by roasting a glucose-glycine mixture and in model systems representing the formation of coffee and meat melanoidins [13]. After enzymatic *in vitro* digestion, up to 64% of the HAAs tested, such as harman, norharman, or PhIB, were bound to melanoidins. These results suggest that HAAs could be tightly bound to melanoidins. If such binding to melanoidins largely resists digestion and absorption of HAAs from the gut, HAAs could be excreted intact without exerting any harmful physiological effects. However, the melanoidin structures which bind to individual HAAs or even other mutagens in the gut, the type of binding and the binding kinetics still have to be investigated. Binding of coffee melanoidins to Streptococcus mutans on saliva-coated hydroxyapatite beads have been demonstrated recently [14], indicating that melanoidins may also pose anti-cariogenic effects.

3 Metabolic transit of MRPs and melanoidins

The metabolic fate of melanoidins in the human body is still under investigation. Only very few key melanoidin structures have been identified so far and none of them has been investigated for its metabolic transit due to analytical and physiological limitations [15]. However, available data on the metabolism of high-molecular, protein-bound MRPs are considered to give rise to biotransformation mechanisms that may also work in the case of melanoidins.

Homma and Fujimaki [16] investigated the metabolic fate of a ^{15}N-labelled nondialysable, high-molecular-weight (HMW) melanoidin fraction in rats (Table 2). The melanoidin was prepared by refluxing equimolar amounts of glucose and ^{15}N-glycine for 7 h, followed by dialysis and lyophilization. The lyophilisate was added to a standard diet at 2% w/w and fed to rats for 6 days. Twenty-six percent of the ingested ^{15}N-labelled melanoidin was found to be excreted in the feces and 1.8% in the urine. From these results, the authors suggested that the HMW melanoidin fed to rats was absorbed, probably after some modification by intestinal enzymes and/or microorganisms, and that the entire ^{15}N-melanoidin absorbed was not excreted. Interestingly, a low-molecular-weight (LMW) fraction was hardly detected by gel chromatography in the feces of rats fed the diet containing 2% HMW melanoidin, but the melanoidin excreted had an even smaller proportion of LMW components than the original one. Therefore, it may be speculated that even the HMW melanoidin fraction in the diet was degraded into LMW fractions by intestinal microorganisms, and some of the degradates were absorbed in the intestines.

The first experiments on the digestion and utilization of severely heat-treated proteins were carried out by Valle-

Table 2. Metabolic transit data on melanoidins in rats

Authors	Protein-sugar model compound	Heat treatment of protein-sugar compound	Way of application	Percentage of ingested radioactivity excreted *via*		
				air	urine	feces
Homma and Fujimaki [16]	Glucose + ^{15}N-lysine	Reflux heating, 7 h	Orally, 6 days	Not determined	1.8%	26%
Valle-Riestra and Barnes [17]	glucose + egg white ^{14}C-lysine	120°C, 60 min	Orally, 3 weeks	10%	3%	74%
Finot and Magnenat [18]	Casein + ^{14}C-glucose LMW	100°C, 90 min	Orally, single dose	7.8%	27%	61%
Finot and Magnenat [18]	Casein + ^{14}C-glucose HMW	100°C, 90 min	Orally, single dose	1.8%	4.3%	87%
Finot and Magnenat [18]	Glycine + ^{14}C-glucose HMW	100°C, 90 min	Orally, single dose	1.5%	1%	93%

Riestra and Barnes [17]. The authors prepared ^{14}C-labelled eggs by injecting laying hens with ^{14}C-L-lysine. The radioactive egg white was autoclaved at 120°C for 60 min either in the presence or absence of glucose to obtain either dark-browned protein containing melanoidins or heat-damaged carbohydrate-free protein. Rats fed on the browned protein excreted about 3% of the ingested radioactivity in the urine and about 74% in the feces, which was three and two times more than that excreted by rats fed on the glucose-free ovalbumen. In contrast, the $^{14}CO_2$ expired by the rats fed the carbohydrate-free protein was three times higher than in rats fed the browned protein. This was explained by an absorption mechanism of the melanoidins or their metabolites, which could not be utilized and were therefore excreted in the urine.

Finot and Magnenat [18] extensively studied the metabolic transit of LMW and HMW fractions of melanoidins in rats by oral administration of a heated casein-^{14}C-glucose mixture. For the isolated LMW melanoidins below 10 000 Da, 61% were excreted in the feces, while 27% were excreted in the urine. Since the radioactivity remaining in the carcass was very low, it appears that pre-melanoidins are not utilized or retained in the body in considerable amounts. For the HMW melanoidins (>10 000 Da) isolated from the casein-^{14}C-glucose mixture, 87% of the ingested radioactivity was excreted in the feces and 4.3% in the urine [18], indicating that HMW melanoidins are absorbed to a much lesser extent than LMW compounds.

Metabolic transit studies on chemically characterized LMW MRPs have been performed on protein-linked fructoselysine [19], casein-N$^{\varepsilon}$-carboxymethyllysine [20], or free compounds such as lactuloselysine [21], pyrraline [22], and N$^{\varepsilon}$-carboxymethyllysine [23]. All these studies showed that at least LMW components of melanoidins or their intestinal degradation products are absorbed in quantities up to about 30%. The daily intake of melanoidins does, therefore, increase the concentration of endogenously circulating compounds formed from nonenzymatic glycation products in heat-treated foods. As accumulation of these structural analogues of MRPs, termed AGEs, in tissues and blood compartments is associated with the progression of various diseases, the analysis of AGEs in blood or urine samples of healthy volunteers in relation to their intake of heat treated foods was a prevailing aim of human studies published in the recent literature and also performed in the framework of COST Action 919. The question which of the melanoidin metabolites are absorbed, metabolized and, thus, likely to cause health effects still has to be answered but the present results clearly indicate that at least their LMW components are absorbed and are biologically active.

4 Health effects of MRPs and melanoidins

Health effects of melanoidins can be categorized into primary effects, which are attributed to a structure specific action, *e.g.*, inhibition/activation of intestinal enzymes, and secondary effects, which are based on interactions with other nutrients. The most important secondary health effect of heat-treated proteins is the loss of bioavailable amino acids destroyed in the Maillard reaction. This effect can easily be corrected by an appropriate dietary supplement of amino acid(s) or protein(s) [3]. Primary health effects, in contrast, have to be investigated using chemically characterized compounds, but lacking the chemical structures of the majority of melanoidins, no distinct structure-based health effect had been described before this COST Action 919 started. Therefore, chemical identification and characterization of food-derived MRPs or melanoidin structures were mandatory for the investigation of the physiological effects. The other prerequisite was to determine what kind of structure-specific physiological effect MRPs and melanoidins exert *in vivo*. Once a distinct *in vivo* effect is scientifically based, it can serve as a biomarker for biologically active MRPs and melanoidins.

5 Effect on MRPs and melanoidins on xenobiotic, chemopreventively active enzymes

With respect to a structure-specific action, the modulation of xenobiotic enzyme activities was selected as one basis for the research carried out within this COST Action 919. The tested hypothesis was whether compounds that are pri-

marily formed in severely heat-treated foods, namely advanced MRPs and melanoidins, are recognized by the organism as xenobiotics.

Xenobiotics are classified as compounds that are not formed endogenously and which require detoxifying mechanisms to protect the organism from harmful effects. Moreover, these detoxifying mechanisms contribute to the chemopreventive potential [24]. Most chemopreventive, nonendogenously formed agents act through enzyme systems by modulating Phase I and Phase II enzymes. Phase I metabolic transformations include reduction, oxidation, and hydrolytic reactions while Phase II transformations generally act through conjugation reactions of the parent xenobiotics or of Phase I metabolites. The conjugation reactions facilitate transport and enhance elimination of the inactive compounds *via* the renal and biliary routes [25]. Current data suggest that the balance between the Phase I carcinogen-activating enzymes and the Phase II detoxifying enzymes is critical for determining an individual's risk for cancer. Human deficiencies in Phase II enzyme activity, specifically glutathione-*S*-transferase (GST), have been identified and associated with increased risk for colon cancer [24].

Induction of Phase I enzymes, in contrast, is not clearly associated with health risks or benefits. Although these enzymes also contribute to the metabolization and excretion of exogenous toxins, in many of the enzymatic reactions catalyzed by, for example, the NADPH cytochrome *c*-reductase (CCR) activity, putatively harmful xenobiotic radicals are formed. An increased Phase I enzyme activity is not necessarily regarded as health promoting. Therefore, a decreased Phase I enzyme activity associated with an increased Phase II enzyme activity is regarded as most effective in contributing to the chemopreventive potential.

By means of *in vitro* experiments in human intestinal Caco-2 cells exposed to a glucose/glycine melanoidin model system and the corresponding LMW (< 10 000 Da) or HMW (> 10 000 Da) fractions, a decreased enzyme activity for CCR and GST was demonstrated [26]. Considering the different yields of 30% and 10% for the LMW and HMW fractions, respectively, the total amount of the LMW fraction present in the glucose/glycine model is obviously more active in modulating the selected enzyme activities. Similar to these results, GST activity was also decreased by 8% and 9% following the cells' exposure to a nondialysed glucose/casein melanoidin model and its HMW (> 10 000 Da) fraction [11]. Although these results strongly indicate a sum of different effects on CCR and GST activities mediated by various reaction products formed during heat treatment of the glucose/glycine and glucose/casein models, LMW compounds were demonstrated to be more effective than HMW compounds.

In order to investigate whether food-derived MRPs and melanoidins affect the CCR and GST activity, the enzyme modulating effects of water-soluble fractions isolated from roasted malt were investigated. In Germany, for example, an average daily intake of 0.5 L beer by adults would correspond to a total amount of about 40 g of malt per day ingested with the habitual diet. The substantial amounts of MRPs and melanoidins in roasted, dark-colored malts, are formed during kiln-drying from germination-derived carbohydrates and amino acids. Melanoidin fractions of different molecular weights prepared from roasted malt by hot water extraction followed by gel filtration chromatography were demonstrated to modulate the CCR and GST activity in human intestinal Caco-2 cells. Again, the LMW fraction of 10 kDa was most effective in enhancing the CCR and the GST activity (+ 122% and + 33% *vs.* control, respectively) [27].

In summarizing the results obtained from the experiments on melanoidin model systems as well as malt melanoidins, it becomes obvious that any interpretation of CCR and GST enzyme-modulating effects mediated by MRPs and melanoidins was strongly limited by the lack knowledge about chemically defined compounds. The first study, in which a melanoidin structure showing xenobiotic enzyme-modulating effects was identified and characterized, was performed on bread crust [28]. Different solvent fractions isolated from bread crust, crumb, and flour were tested for their CCR and GST enzyme modulating activity and for their antioxidant activity *in vitro.* In these experiments, the antioxidant activity was also investigated, since for various dietary antioxidants it has been demonstrated that they bind to an antioxidant responsive element resulting in the specific, monofunctional induction of Phase II enzymes [25]. In the study of Lindenmeier *et al.* [28], the highest antioxidative potential was demonstrated for the dark-brown, ethanol solubles of the crust, whereas corresponding crumb and flour fractions showed only minor activity. The bread crust and, in particular, the ethanolic crust fraction induced a significantly elevated GST activity and a decreased CCR activity compared to control cells and compared to crumb-exposed cells. These results clearly demonstrate that CCR and GST activities were modulated by thermally generated MRPs or melanoidins in such a way as to be interpreted as a protective functional parameter of an antioxidant activity. Antioxidant screening of MRP model mixtures, followed by structure determination, revealed a protein-bound pyrrolinone reductonyl-lysine, abbreviated as pronyl-lysine, as the most powerful antioxidant predominantly formed in bread crust (62.2 mg/kg), but present at very low concentrations in bread crumb (8.0 mg/kg). Exposing Caco-2 cells for 48 h to either synthetically pronylated albumin or to purified pronyl-glycine, significantly increased Phase II GST activity by 12% or 34%, respectively, while CCR activity was decreased. Thereby, it was demonstrated for the first

time that, at least in Caco-2 cells, "pronylated" proteins as part of bread crust melanoidins and as synthetic compound do act as monofunctional inducers of GST, serving as a functional parameter of an antioxidant, chemopreventive activity *in vitro* [28]. Although feeding studies with pronylglycine are still lacking, the GST-inductive effect of bread crust has been demonstrated in an animal trial on rats [29].

Another key chemopreventive compound formed during heat-treatment was identified in roasted coffee [30]. Solvent fractionation, followed by multiple-step ultrafiltration revealed that the polar coffee compounds with molecular masses below 1 kDa show the major inhibitory effect on the *in vitro* peroxidation of linoleic acid as well as the predominant chemopreventive enzyme modulating activity on the CCR and the GST in human intestinal Caco-2 cells. The chemical structures of the most active antioxidants and chemopreventive compounds *in vitro* were, then, identified to be 5-chlorogenic acid as the most powerful antioxidant, whereas strong chemopreventive effects on the GST activity were found for *N*-methylpyridinium ions. This Phase II inductive effect of coffee beverage and *N*-methylpyridinium ions was confirmed by results obtained from an animal feeding trial on rats. Surprisingly, feeding of *N*-methylpyridinium also resulted in an increased total antioxidant capacity in the plasma [30]. The data indicate that the antioxidant activity demonstrated for *N*-methylpyridinium in biological systems is different from that in foods, possibly due to the formation of effective metabolites *in vivo*.

To study the antioxidant activity of compounds inducing xenobiotic enzymes is of particular interest since for various dietary antioxidants it has been demonstrated that they bind to an antioxidant responsive element resulting in the specific, monofunctional induction of Phase II enzymes, such as GST [25].

6 Antioxidant activity of melanoidins

From many of the *in vitro* studies carried out within Working Group V of this COST Action 919, there is supporting evidence for an antioxidant activity of melanoidin structures modeling food conditions [31–36]. Also in cell culture experiments on rat hepatocytes, the protective effect of melanoidins prepared from a roasted glucose-glycine mixture on lipid peroxidation and protein oxidation induced by adriamycin in hepatocytes has been shown [37]. However, the question arises whether those compounds also act as antioxidants in the human body, after intestinal metabolization, absorption and, possibly, *in vivo* transformations.

In humans, the consumption of unfiltered coffee, containing bioactive diterpenes, was reported to increase the plasma concentration of glutathione [38]. In this study, 22 volunteers consumed five cups of coffee per day for 1 week and maintained their usual diet. At the end of this period, plasma hydroperoxide levels were not changed but the plasma content of the antioxidant glutathione increased by 16% upon coffee consumption. Although the number of animal studies as well as human trials performed to investigate the antioxidant activity of dietary melanoidins *in vivo* are limited and further studies aimed at answering this question are imperatively needed, the broad range of antioxidant actions demonstrated in *in vitro* studies gives rise to possible health benefits from antioxidative melanoidin structures.

7 Mutagenic and genotoxic properties of MRPs and melanoidins

Diet has been associated with differences in cancer rates in human populations for many years. Although the exact causes of cancer from the diet have yet not been adequately explained, a wide series of potent chemicals that cause mutagenic events in bacteria and cancer in animals has been identified. Among these substances, HAAs are well known to be formed in heated foods from the reaction between free amino acids, monosaccharides, and creatinine [1]. The question whether, and if so, which dietary MRP or melanoidin structure pose an increased cancer risk in humans is still under investigation. As genotoxic compounds can act at various levels in the cell causing gene, chromosome, or genome mutations, a range of genotoxicity assays are designed to detect these different types of mutations in various biological test systems, including bacterial strains, human intestinal cells, or lymphocytes. Most of the data available in the literature report mutagenic or genotoxic effects of different mixtures of MRPs or melanoidins. Brands *et al.* [39] have shown that in the bacterial *Salmonella typhimurium* strain T100, heated sugar-casein systems exhibit mutagenic activities which were strongly related to the type of sugar. Among monosaccharide-casein systems, ketose-casein mixtures, like those prepared from fructose and tagatose, showed a remarkably higher mutagenicity compared with their aldose isomer-casein systems, respectively those of glucose and galactose. Disaccharide-casein systems showed no mutagenic activity (lactose) or a lower mutagenic activity (lactulose) than their corresponding monosaccharides.

Taylor *et al.* [40] investigated complex melanoidin fractions prepared by roasting a mixture of glucose and glycine for their genotoxic activity. This reaction mixture as well as its dialyzed LMW and HMW fractions showed no genotoxicity, neither in the AMES test, in the Vitotox test, nor in the micronucleus test, despite being tested at concentrations much higher than those of naturally found in food products. Another comprehensive study on the genotoxicity and mutagenicity of melanoidins isolated from a roasted glu-

cose-glycine model revealed similar results by applying the AMES test in the *Salmonella typhimurium* strains TA98 and TA102 [41]. But a significant increase in the formation of sister chromatid exchange (SCE) rates in human lymphocytes after exposure to concentrations of 0.05% and 0.1% was observed for LMW and HMW water-soluble melanoidin fractions. However, this genotoxic effect of water-soluble melanoidins was still much weaker compared to that of typical genotoxins. Also, the results were obtained from an *in vitro* system which might be different from *in vivo* conditions, in which completely different melanoidin structures may circulate in the blood steam after intestinal degradation, absorption, and endogenous metabolization.

Antimutagenic properties of MRP or melanoidin mixtures have been noted by Kim *et al.* [42] and are attributed either to the inhibition of mutagen absorption [12] or to the inhibition of mutagen activation through enhanced detoxification of reactive intermediates [4, 5, 43]. Another *in vitro* study reported an inhibition of tumor cell growth and microtubule assembly by chemically characterized MRPs formed from carbohydrates under household heating conditions [44]. Herein, the Maillard-type chromophores 2-(2-furyl)methylidene-4-hydroxy-5-methyl-2*H*-furan-3-one, 4-(2-furyl)-7-[(2-furyl)methylidene]-2-hydroxy-2*H*,7*H*,8a*H*-pyrano-[2,3-*b*]-pyran-3-one and 3-hydroxy-4[(*E*)-(2-furyl) methylidene]methyl-3-cyclopentene-1,2 dione inhibited the growth of human tumor cells in the low micromolar range, causing tumor cell cycle arrest and apoptosis induction.

Heat-treated foods have played an important role in human nutrition since *Homo habilis* began to use fire [45]. Up to now, highly genotoxic effects of foods containing a mixture of various MRP or melanoidin structures seem unlikely to pose an evolutionary disadvantage for humans, although individual compounds formed during heat treatment of foods may have these effects, such as HAAs. But as the majority of dietary MRPs and melanoidins, as well as their intestinal degradation, absorption or endogenous metabolism are still unknown, the risk assessment remains unfeasible.

8 Effects of dietary MRPs and melanoidins on *in vivo* glycation and their medical consequences

The Maillard reaction also proceeds in the body at homeostatic concentrations of glucose, resulting in the formation and accumulation of AGEs. The potential importance of the complex, late-stage Maillard processes to age- and diabetes-related changes in the mechanical properties of vascular tissues was first recognized by Monnier and Cerami in the early 1980s [46, 47].

The ability of AGE-modified proteins to form protein–protein crosslinks in collagen *in vivo* is a key determinant in the pathogenesis of the reduced vascular and myocardial compliance observed with aging and diabetes, but also plays a role in the progression of associated complications, such as nephropathy or retinopathy [48 – 50] as well as in Alzheimer's disease [51]. Diabetes-associated hyperglycemia may not only lead to protein-glycation but also to the formation of DNA-glycation adducts. One of these adducts, *N*(2)-(1-carboxyethyl) deoxyguanosine (CEdG), is a major nonenzymatic glycation product of DNA. When the effect of CEdG modification on plasmid DNA topology was evaluated, a time-dependent decrease of supercoiled plasmid-DNA was observed in parallel to the increase of CEdG adducts [52]. In this study, the glycated DNA showed a 6-fold increase in mutation frequency after transfer into *Escherichia coli* cells, suggesting that a defined DNA glycation reaction forming the AGE CedG may lead to DNA damage *in vivo*. On the other hand, protective effects of melanoidins from polyphenol-free Spanish sweet wines on copper-induced DNA damage have been described in isolated calf thymus DNA [53]. Although these affects have been attributed to the antioxidative effects of melanoidin compounds, chemical identification of the antioxidant melanoidin structure is still necessary to balance the promoting or preventing effects on DNA damage.

Similar to AGEs, the formation of proteins modified by lipids, named ALEs (advanced lipoxidation end-products), is also catalyzed by hyperglycemia and oxidative stress and may also pose an increased risk for diabetic complications [54].

The pathophysiological significance of AGEs stems not only from their ability to modify the functional properties of proteins, but also from their interaction with cells *via* AGE-binding proteins or AGE receptors. The cellular interactions of AGEs are mediated through a specific receptor for AGEs (RAGE) on cell surfaces [55]. AGE interaction with cellular RAGE results in receptor activation and receptor-mediated release of superoxide anions and pro-inflammatory cytokines [55, 56]. For example, in tissue cultures on calf epithelial lens cells, studies revealed a significant increase in lipid peroxidation products in the cell culture medium after irradiation and treatment with glycated proteins [57]. Besides the endogenously formed AGEs, dietary melanoidin structures present in bread crust and coffee have also been shown to act as RAGE ligands and to activate major signal transduction pathways *in vitro* [58].

The first human trial to study whether dietary MRPs or melanoidins increase the endogenous load of AGEs was conducted by Koschinsky *et al.* [59]. The authors fed a single meal of egg whites, cooked with (termed as "AGE-diet") or without (termed as "Control-diet") fructose to either

healthy subjects or patients with diabetes mellitus. Interestingly, in both experimental groups, the AGE-diet, but not the Control-diet produced distinct elevations of serum AGE-levels, analyzed as AGE immunoreactivity by ELISA. In diabetics with renal failure symptoms, the renal excretion of dietary ingested AGEs was markedly reduced as compared to healthy subjects and, furthermore, correlated inversely with the degree of albuminuria as a marker of impaired kidney function. From these results, the authors concluded that dietary restriction of food MRPs may reduce the burden of MRPs in diabetic patients and possibly improve the prognosis of the disease. More recently, the same research group of Vlassara *et al.* [60] demonstrated that the intake of dietary MRPs in diabetics promote the formation of pro-inflammatory mediators, leading to tissue injury. Although restriction of dietary AGEs suppressed these effects, it is still not clear (i) which of the dietary MRP or melanoidin structures activate pro-oxidative and pro-inflammatory pathways after their absorption and (ii) whether the healthy organism can compensate for pathophysiological effects.

The first question is difficult to answer because of analytical limitations due to the complex HMW structures of melanoidins. For human trials, the diet has often been analyzed for its content of total AGEs by applying an ELISA assay specific for glycated serum albumin. Although this test might serve as a rough indicator for the content of glycated proteins in human plasma, the chemical structures of individual dietary MRPs or melanoidins still remain unknown. The importance of this question becomes clearer when another human trial is considered in which the intake of a diet high in severely heat-treated foods by healthy volunteers did not result in elevated levels of endogenous AGEs, nor in impaired renal function, compared to the intake of diets rich in less severely heat-treated items, such as fruits and vegetables [61]. Human trials on chemically characterized MRP or melanoidin structures are still lacking, and even animal feeding studies are scarce. Only in one study, in which a novel melanoidin structure, pronyl-lysine, was identified, a chemically defined melanoidin was demonstrated to exert a strong structure-specific antioxidant activity and to induce chemopreventive enzymes in a cell culture model on human intestinal cells [28]. These results support a health-promoting activity of pronyl-lysine rather than potential harmful effects, although pronyl-lysine and also bread crust were shown to act as RAGE ligands in the same cell culture model [58]. Probably, MRP or melanoidin binding to RAGE on a cellular level does not necessarily result in an increased load of pro-oxidants in tissues and plasma of healthy people. Diabetes mellitus associated with a broad range of complications, such as vascular diseases, retinopathy, and an impaired renal function, might be a pathophysiological state in which compensatory mechanisms of the healthy organism are no longer working sufficiently. An impaired renal function, in particular, has been suggested to result in increased endogenous AGE loads due to a restricted AGE excretion with the urine [62]. This has been shown in the rat remnant kidney model having an impaired kidney function [63], but also in diabetic mice [64]. Under these pathophysiological conditions, the dietary intake of at least some of the MRP or melanoidin compounds should be carefully monitored. But still, the majority of diabetic complications result from the vast increase in blood glucose and it then may be more important to regulate blood glucose than to worry excessively about avoiding dietary MRPs. Whether the intake of severely heat-treated foods contribute the AGE-associated reactions in Alzheimer's disease has not been investigated so far, but has been hypothesized by Muench [65].

9 Conclusions

In summary, the health effects of dietary MRPs and melanoidins have been intensively studied in the frame of COST Action 919 (Working Group V). The results obtained for intestinal degradation, and respective implications for gut health, absorption, and further health effects, such as antioxidant activity, chemopreventive activity, and antimutagenic activity, clearly demonstrate that at least some of the dietary MRPs and melanoidins are health-promoting, while others may be not. The challenge for future studies is the chemical characterization of harmful and beneficial compounds for their structure-specific health effects and the optimization of food processing technologies for a selective formation of health beneficial MRPs and melanoidins.

10 References

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