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Review

Dietary advanced glycation end products – a risk to human health? A call for an interdisciplinary debate

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Physiological consequences resulting from protein-bound Maillard compounds in foods must be discussed carefully. This was the idea behind the debate, which is put for discussion by the papers by Sebekova and Somoza, who argued for the motion that dietary advanced glycation end products (AGEs) are a health risk, and by Ames, who provided evidence against the motion. In this two excellent reviews, numerous arguments based on papers published in high-impact journals are given for each of the opinions. The fact that no final conclusion can be drawn, may reflect the need for a more comprehensive examination of this issue in the future. For a deeper understanding of biological consequences resulting from heated foods, the relationships between well-defined biological effects and well-characterized chemical structures must be studied. Prerequisite for this is profound chemistry – pure compounds, exact concentrations, and unambiguous analytical techniques. A real "risk assessment" is much too complex than to leave it up to one discipline alone. It must be a comprehensive and interdisciplinary approach, joining the resources of biology, medicine, and chemistry.

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This article provides an introduction to "Dietary AGEs are a risk to human health".
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1 The benefit of cooking

The consistent and purposeful use of fire by *Homo erectus* probably began by 400 000 years ago and was definitely an important milestone for hominid survival and development [1]. It is most likely, that our ancestors soon after its invention also used fire for cooking and roasting of food (Fig. 1). Cooked food has much better hygienic quality, and due to chemical reactions during heat treatment, heated foods are much better digestible, have an increased nutritional value, and can be stored longer. Most of all, however, it simply may taste better, due to the formation of numerous reaction products resulting predominantly from Maillard reactions.

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Abbreviations: AGEs, advanced glycation end products; **RAGE,** receptor for AGEs

Nowadays, heat treatment is an indispensable prerequisite in order to obtain safe and high-quality food products. The risk resulting from foods which have not been sufficiently heat treated may be realized from the fact that foodborne diseases by the bacterial pathogens *Salmonella* and *Listeria* account for more than 1500 deaths in the USA *per* year [2]. Furthermore, we may not forget that bovine spongiform encephalopthie (BSE), coming up in the UK in 1986, was induced by feeding meat and bone meal products prepared *via* modified mild heat treatment conditions, thus enabling the infectious prions to survive the manufacturing process.

2 The impact of cooking on nutritional quality

Although the phenomenon that foods turn brown during heating is probably known since the discovery of fire, it took until the years around 1912, when the French biochemist Louis-Camille Maillard [3] reported the first systematic studies, indicating that reactions between amino acids and

Figure 1. Fire and the Maillard reaction – a historical coincidence? (Cartoon licensed by CartoonStock.com.)

reducing sugars are the chemical basis for the formation of brown substances, the so-called melanoidins. Based on the fundamental work of Amadori (1929), Heyns (1953), Hodge (1953) [4 – 6], and numerous others, it is today generally accepted that the "Maillard reaction" is a series of subsequent and parallel reactions, that can occur simultaneously, influenced by each other as well as by milieu parameters [7]. First observations that heat treatment may also have a negative impact on the nutritional quality of proteins were made in the early years of the 20th century [8]. With respect to possible antinutritive aspects due to Maillard reactions, studies in the 1950s and 1960s focused on the question, whether industrial processes or home-cooking as well as long-term storage of foods may extensively modify lysine and arginine residues in proteins [9 – 10]. The pioneering observation that Amadori products of lysine are not used as lysine source after digestion shed light on a new side of the Maillard reaction, making this reaction responsible for a negative impact of food processing on food quality [11]. The quantification of "blocked" or "not available" lysine became an important parameter for assessing the influence of heat treatment on the biological value of food proteins [12]. Main research in the field of the Maillard reaction throughout the 1960s to 1990s, however, was dealing with this complex series of reactions from the view of carbohydrate chemistry. Numerous low-molecular weight compounds have been identified, including important intermediates to clarify pathways of carbohydrate degradation and formation of aroma compounds [13]. Within the last 20 years, food research in the field of Maillard chemistry turned to a new point of interest. Studies on protein modifications were motivated by the observation that amino acid derivatives resulting from the Maillard reaction may also occur *in vivo*. With the identification of HbA_{Ic}, a nonenzymatically glycosylated variant of hemoglobin, in the blood of diabetic patients [14] it was found that nonenzymatic reaction pathways known from food processing are also followed *in vivo* (referred to as "nonenzymatic glycosylation" or "glycation"). "Advanced glycation end products" (AGEs) were found to increase during aging and diabetes, and were directly linked to the pathophysiology of several diseases like cataract, atherosclerosis, and uremia [15, 16].

During the last years, several amino acid derivatives have been identified, and some of them were unambiguously quantified in foods [7]. It cannot be overlooked that only little information is available today concerning the physiological handling of such dietary glycation products. From proteins glycated with radioactive glucose, only low absorption rates were measured in feeding studies either for "early" as well as for "advanced" stages of modification [17]. Similar results were found for studies with human volunteers. For orally administered early Amadori products, urinary excretion was about 3% [18 – 20]. Resorption of certain advanced glycation compounds such as pyrraline or free pentosidine, however, is high, as demonstrated by the observation that nearly all peptide-bound pyrraline or free pentosidine supplied with the diet can be found as free amino acid in the urine [19, 21].

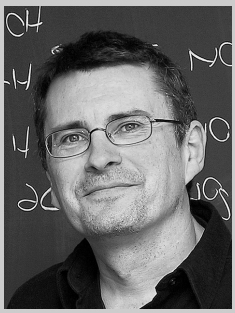
3 Biological activity of dietary AGEs – two sides of a medal?

Starting with reports in the mid 1980s of the 20th century, the formation of AGEs was linked to consequences of diabetes [22] and later on to biological disorders such as cataract or diabetic nephropathy [23, 24]. Artificially prepared "AGE-proteins" were found to initiate a range of cellular responses *in vitro*, including stimulation of monocyte chemotaxis, secretion of cytokines and growth factors from macrophages and endothelial cells, and proliferation of smooth muscle cells [15]. Concerning molecular mechanisms responsible for cell activation by AGEs, a specific receptor designated "RAGE" ("receptor for AGEs") gained particular interest [36]. Since its first description, a myriad of papers has been published showing that binding of ligands to RAGE results in activation of the proinflammatory transcription factor nuclear factor-kappaB (NF-κB) and subsequent expression of NF-κB-regulated cytokines [37, 38]. RAGE-AGE interaction thus may trigger cellular dysfunction in inflammatory disorders. Based on this findings, RAGE is discussed as a target for drug development [39], although the structures of possible RAGE-ligands still have not been identified. Nowadays, it is generally accepted that AGEs are an important class of uremic toxins, although there is virtually no information about defined structure-activity relationships documenting the "toxic" effect of individual compounds in physiological concentrations [15, 25].

In line with this discussion, it was not a surprise that questions arose concerning the intake of dietary AGEs *via* the daily food and their possible (patho)physiological role [26]. From the quantitative point of view, the amount of specific amino acid derivatives ingested with meals from certain heated foods farly exceed the total amount of AGEs in the human body. In this context, it was proposed that serum AGE levels can be influenced by a diet containing AGEs, and the term "glycotoxins" was created in order to express that dietary glycation products may represent a risk factor in diabetic and uremic patients [27]. Indeed, spectacular reports showed that a high-AGE diet may lead to an increase in inflammatory markers [28], and concrete dietary recommendations were published in order to minimize health risks by avoiding heated foods [29]. On the other hand, however, these studies must be discussed carefully due to considerable limitations in the analytical techniques used. 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 hemodialysis patients, it was found that increased AGEs are not linked to mortality [30]. On a cellular level, it was found that defined AGEs do not bind to RAGE, the prominent receptor for AGEs, and do not induce inflammatory signals, thus arguing against a uniformly role of AGEs in cellular activation [31, 32]. Furthermore, there may even be a "chemoprotective" role of individual dietary AGES due to antioxidative properties or by inhibiting tumor cell growth [33 – 35].

4 Conclusion

Physiological consequences resulting from protein-bound Maillard compounds in foods must be discussed carefully. This was the idea behind the debate, which is put for discussion by the papers by Sebekova and Somoza, who argued for the motion that dietary AGEs are a health risk, and by Ames, who provided evidence against the motion. In this two excellent reviews, numerous arguments based on papers published in high-impact journals are given for each of the opinions. The fact that no final conclusion can be drawn, may reflect the need for a more comprehensive examination of this issue in the future. For a deeper understanding of biological consequences resulting from heated foods, the relationships between well-defined biological effects and well-characterized chemical structures must be studied. Prerequisite for this is profound chemistry – pure compounds, exact concentrations, and unambiguous analytical techniques. A real "risk assessment" is much too complex than to leave it up to one discipline alone. It must be a comprehensive and interdisciplinary approach, joining the resources of biology, medicine, and chemistry.



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