Editorial

Are dietary AGEs/ALEs a risk to human health and, if so, what is the mechanism of action?

Pioneer work by Anthony Cerami, Vincent Monnier and John Baynes showed in the 1980s that long living proteins are chemically modified by sugars in the human organism. This process is not mediated by enzymes and thus leads to a great variety of reaction products of which only a few have been structurally identified so far. Some years later, the term advanced glycation end-products (AGEs) was created which summarizes all possible adducts formed from sugars and proteins, independent of their structure. In the meantime, it is well established that the formation of AGEs is correlated not only with ageing, but also with the development of several diseases, such as diabetes or uremia. Furthermore, there is growing evidence that AGEs, although present in low concentrations, affect complications related to these diseases, for example cataract or atherosclerosis. The pathological activity may be caused by structural changes in the AGE-modified proteins leading to different physiological behavior. Additionally, pathological processes may be mediated by receptors which bind to specific AGEs. In this context, the best characterized receptor is RAGE, the receptor for advanced glycation end-products, which was first described by David Stern and Ann-Marie Schmidt. RAGE, which is a multiligand receptor, has important tasks under physiological conditions. However, it also binds to specific AGE structures, and, if present at higher levels, it leads to an inflammatory imbalance.

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It has also become clear in the last decades that proteins are modified *in vivo* not only by sugars, but also by many other carbonyl compounds; for example short chain dicarbonyl metabolites, such as methylglyoxal, efficiently bind to proteins. Likewise, carbonyl compounds derived from lipid oxidation, such as glyoxal or 4-hydroxynonenal, are important precursors, leading to structures similar to AGEs. To make a distinction between the origin of the protein adducts, the term advanced lipid oxidation products (ALEs) was created, covering adducts formed from lipid oxidation products. Interestingly, some products, such as N^{ε}-carboxymethyllysine (CML) can originate from both sugars and lipid oxidation products. Thus, ALEs build a fascinating link between lipid oxidation and protein glycation, two non-enzymatic processes responsible for the disturbance of the physiological balance, but which were previously considered to be separate entities.

In the last couple of years, the question about the role of dietary AGEs in human health arose. For about hundred years it has been well known that many heated food stuffs contain very high levels of AGEs, also known as Maillard products. AGE-rich food products are, for example, coffee, heated milk products, bread crust or dark beer. Dietary AGEs ingested in a regular Western diet should by far exceed endogenously formed AGE levels. Consequently, dietary AGEs should interfere with physiological processes in a similar way as observed for AGEs formed during the state of disease. On the other hand, Maillard products have been a fundamental part of our diet for thousands of years, suggesting that the human organism developed mechanisms to cope with detrimental Maillard components. Although (or because) excellent work on this topic has been published in the last couple of years, there is still a highly controversial debate on the health implications of dietary AGEs.

On this basis, a workshop was organized by Nestlé, bringing together leading scientists in this field where controversial opinions were aired on three major issues of dietary AGEs:

1. Dietary AGEs are a risk to human health
2. Dietary ALEs are a risk to human health
3. Dietary AGEs and ALEs interact with RAGE

Each motion was first introduced by a chairman and then supported and opposed by two speakers. The workshop was organized as a satellite event of the COST Action 927 Meeting "Thermally Processed Foods: Possible Health Implications", which was covered in Issue 4/2007 of Molecular Nutrition and Food Research.

In the current issue of MNF, the pros and cons of each motion are summarized by the speakers Katerina Sebekova (for motion 1), Jennifer Ames (against motion 1), Joseph Kanner (for motion 2), John Baynes (against motion 2), Ann-Marie Schmidt (for motion 3) and Claus Heizmann (against motion 3). Furthermore, the topics are introduced

by short reviews from the chairmen, Thomas Henle, Vincent Monnier and Paul Thornalley, who also summarize the exciting discussions which followed each motion.

The role of dietary AGEs in human health were certainly not solved during the workshop, but the nine reviews in this issue of Molecular Nutrition and Food Research bring together the state of knowledge in this field, critically commented by experts working on these questions.

One important point which we learnt from the workshop is that we must have a differentiated view on AGEs and Maillard products. Terms such as "Maillard products", "AGEs" and "ALEs" are essential to handle the complex network of reactions between carbonyl compounds and amines. However, these terms are also conducive to forgetting that AGEs comprise many different structures with different bio-availability, metabolism and harmful as well as beneficial effects in the human organism.

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Guest Editor

