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Review

Dietary advanced lipoxidation products as risk factors for human health – a call for data

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This article provides an introduction to "Dietary ALEs are a risk to human health".
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The debate of whether advanced lipoxidation end products (ALEs), and for that matter, advanced glycation end products (AGEs) are detrimental for health is of paramount importance for two reasons. If endogenously formed ALEs represent a health risk, then lifestyle changes such as weight loss to prevent diabetes or pharmacological interventions might be needed to decrease their burden. On the other hand, if dietary ALEs and their precursors have biologically detrimental properties, then major changes in food processing technique and consumption might be necessary. A trade-off would be expected: in the former instance, major changes in lifestyle are notoriously difficult to achieve and chronic consumption of pharmacological agents that scavenge ALE precursors would likely have some side effects, as previously reported in clinical studies with aminoguanidine [1, 2]. On the other hand, decreasing the food content of AGEs/ALEs may hamper the organoleptic properties of foods and thus severely affect the quality of life. Thus, before contemplating any anti-ALE/AGE intervention comprehensive data on the expected risk/benefit ratio will be needed. It should be noted that the same arguments might be applicable to ALEs and AGEs out of the belief that it might be very difficult to separate the two, *e.g.*, for carboxymethyl-lysine (CML) [3]. This, however, is not applicable to exogenous sources of ALEs, since it should be relatively easy to produce ALE poor foods by decreasing the fat content prior to processing. Similarly, hyperglycemia in diabetes is not necessarily associated with hyperlipidemia, although both glucose and fatty acids can be a source of reactive oxygen species [3]. Thus, a debate focusing primarily on risk factors stemming from ALEs can be reasonably treated as a separate entity from AGEs, especially since analytical techniques are sufficiently advanced to measure specific ALEs and their precursors.

Joseph Kanner presents a number of arguments supporting the view that food-borne ALEs are risk factors to human health. These include (i) epidemiological studies showing that a typical Western diet rich in fat is a known risk factor for atherosclerosis, (ii) the fact that such diets are rich in oxidized lipids which appear postprandial in chylomicrons, (iii) evidence that several oxidized lipids have profound biological effects, such as impaired forearm vasodilation (a measure of available nitrous oxide) following the intake of meals rich in oxidized fat, (iv) the ability of the gastrointestinal tract to further oxidize lipids, and (v) the ability of hydroperoxides to destroy other important defense mechanisms in food such as vitamins. Additional, though indirect support for a role of lipid oxidation in atherosclerosis and perhaps cancer comes from epidemiological studies showing that higher fruit and vegetable consumption is associated with lower incidence of cardiovascular disease and cancer [4], and that dietary polyphenols can inhibit lipid peroxidation product (LPO) formation. Dr. Kanner concludes that ALEs indeed represent a risk to human health.

On the contrary John Baynes advances a number of arguments supporting the notion that ALEs do not represent a significant risk to human health. He first makes the point that it might be very difficult to separate effects related to the presence of ALEs *per se*, *vs*. those stemming from their more toxic and reactive precursors, such as the hydroperoxides. Regarding the toxicity of reactive compounds, he also argues that high reactivity does not necessarily imply toxic-

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Abbreviations: AGE, advanced glycation end product; **ALE,** advanced lipoxidation end product

ity or damage under physiological conditions because the compounds are often present in small concentrations. In addition, the organism has powerful defense mechanisms to neutralize and eliminate the reactive compounds that include oxidoreductases, nucleophilic trapping agents, glutathione dependent enzymes, and a sharp decrease in the enzymatic digestibility of highly modified food proteins, thereby limiting their potential toxicity. Other protective mechanisms include the high turnover and therefore repair rate of gut epithelial cells, and the presence of powerful hepatic and renal detoxification mechanisms. Concerning the proinflammatory effects of foods rich in AGEs/ALEs, Baynes notes that inflammation is a part of the physiological response to food intake, and that studies on exposure to foods artificially enriched with high quantities of ALEs are therefore difficult to interpret. For all those reasons he also suggests that extrapolation of existing data implicating ALE toxicity to healthy populations is not warranted, especially since it is not clear whether any observed effect is indeed attributable to ALEs *vs*. AGEs that are simultaneously present in cooked foods.

What can one conclude from the diametrically opposed views concerning the health risk imparted by the consumption of ALE or AGE rich foods? Intuitively, it is difficult to argue that daily consumption of a balanced diet containing moderate amounts of ALEs and AGEs, coupled with simultaneous avoidance of calorie excess and sedentary lifestyle, would be deleterious to a healthy human being. Indeed, major gains in mean life expectancy have been made in recent years in Western populations in spite of moderate changes in the composition of the diet and increase in sedentary lifestyle. *Vice versa*, it is not difficult to accept the notion that diets rich in ALEs and LPOs might be deleterious to individuals susceptible to accelerated atherosclerosis, or those whose health is compromised by chronic metabolic disorders such as diabetes, glucose intolerance, end stage renal disease, or immune suppression and chronic inflammatory bowel disease such as Crohn's disease and ulcerative colitis. While specific nutritional guidelines already exist for each of these conditions, except for atherosclerosis scanty data are available on the nature and biomedical impact of dietary ALEs and AGEs.

The pioneering studies of Vlassara *et al.* [5] clearly illustrate the feasibility of studying the effects of variable AGE content in food on clinical parameters in a well-defined subset of human beings, such as diabetics. Paradoxically, however, the interpretation of the data is fraught with ambiguities. For example, the study revealed that a 6 wk long treatment with AGE-poor *vs* AGE-rich diet resulted in lower cytokine release in the former group. However, in spite of careful measures to ensure identical food intake, there was 40% lower fasting blood glucose and a 2.3% drop in body weight in the low compared to high AGE group, suggesting that the AGE-poor diet had an anorectic effect. Unfortunately, several independent studies have shown that decreasing the body weight or glycemia was associated with lower plasma cytokine levels [6, 7]. As suggested by Baynes, the even more difficult question to be addressed is whether increase in the cytokine plasma content is deleterious or whether the organism can adapt by down-regulating cell signals. A partial answer to this dilemma comes from studies showing that chronic elevation of serum TNFα and other cytokines is thought to participate in the development of metabolic syndrome in obese patients [8].

While the study of the impact of food ALEs/AGEs is expected to be readily approachable in well-defined subsets of high-risk groups, much more difficult and no less important will be the study ALEs and AGEs as risk factors for colon cancer in healthy populations in whom its incidence increases sharply with age. As pointed out by Kanner, the concentration of ALEs/LPOs could reach micromolar concentrations, possibly exerting profound genotoxic effects. In individuals with certain cancer susceptibility genes [9], mutations might arise that suppress apoptosis, thus favoring clonal expansion and invasion of the cancer cell. Sustained proinflammatory effects by AGE/ALE mediated RAGE activation would be a perfect recipe for enhanced carcinogenesis and metastasis [10]. However, the logistics of such studies is expected to be very challenging, since it would optimally require genotyping and comprehensive determination of ALE/AGE composition in the diet. At the present time the relationship between lipid content, and presumably ALE content, in the diet and colon cancer is not convincing and controversial [11]. This may in part reflect the fact that the food questionnaires utilized in such studies did not take processing techniques into consideration. On the other hand, the complex interplay between procarcinogenic and anticarcinogenic properties of foods constituents and human genetics may statistically mask effects that are clearly carcinogenic in genetically predisposed individuals. As Bruce Ames once concluded, even vegetables and fruits contain similar amounts of natural procarcinogens and anticarcinogens, making it very difficult to single out dietary culprits of cancer [12].

Finally, little has been said by either of the debators of the critical role of bioavailabilty, biodistribution, and catabolism of dietary ALEs and AGEs, all of which may influence their systemic or tissue-specific toxicity. Studies by Ebersdobler, Henle, Vlassara [5, 13, 14] and others have documented various degrees of absorption of Amadori products, carboxymethyl-lysine and other dietary AGES in the human and rodent [13, 14]. However, only few studies on this question are available for ALEs.

In sum, the above debate has only revealed the tip of the iceberg. It calls for a vast expansion of research into the chemistry, biology, bioavailability, and clinical relevance of AGEs/ALEs as risk factors to human health. Similarly, a "Maillardomic" approach in which individual genetic susceptibility to selected ALEs/AGEs will have to be determined.

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