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Review

Genetic variability in the RAGE gene: Possible implications for nutrigenetics, nutrigenomics, and understanding the susceptibility to diabetic complications

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Complex chemical processes called nonenzymatic glycation and glycoxidation are one of the interesting examples of potentially harmful interaction between nutrition and disease. This review summarizes factors influencing the extent of glycoxidation in health and disease and especially focuses on the role of genetic variability in "glycoxidation-related genes" in a disease and diet-related pathogenesis. Possible interaction between genetic variability in relevant loci and dietary advanced glycation end products (AGEs) is considered. As AGEs possess a wide range of chemical and biological effects, the interindividual functional variability in systems dealing with glycoxidation could have a significant nutrigenomic and nutrigenetic consequences.

Keywords: Advanced glycation end-product / Diabetes / Glycoxidation / Nutrigenetics / RAGE / Review

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Abbreviations: AGE, advanced glycation end-product; **CAD**, coronary artery disease; **CML**, carboxymethyllysine; **RAGE**, receptor for advanced glycation end-products; **ROS**, reactive oxygen species; **T2DM**, type 2 diabetes mellitus

1 Introduction

The rise in the incidence of obesity and type 2 diabetes mellitus (T2DM) over the past two decades fuelled considerably the "nature *versus* nurture" debate. So-called "complex diseases" – with classical examples of T2DM, atherosclerosis or essential hypertension – account for the best part of morbidity and mortality in populations of industrialized countries. Progress in identifying molecular causes of the majority of mono-/oligogenic diseases and the completion of the Human Genome Project strengthened a "genome-centric" view of disease pathogenesis and has led to a corresponding approach in the study of complex diseases. In fact, reality is probably far from being that simple. Genetically variably predisposed subjects gradually variably exposed to additional epigenetic and environmental factors develop clinically significant disease anytime (but often later) during their life. Although the naturists and nurturists acknowledge the importance of both influences, experimental designs very often reflect either the genetic or the environmental part of the problem but not both simultaneously [1].

Current variability in the human genome is the result of a long-lasting genetic selection which took place in circumstances quite different from our current environment; some

even doubt any changes of genetic profile since the hunter-gather period of human evolution. It is generally perceived that inheritance of a majority of complex diseases is polygenic; therefore, a cluster of interacting genes rather than a single major gene modulates disease susceptibility. Identifying such gene-gene interactions represents a major goal of current genetic research in this area. At the same time, potent gene-environment interactions (gene-diet in particular) must also be considered, since environmental changes, first of all diet and sedentary life style, undoubtedly account for the recent growing prevalence of the above-mentioned metabolic diseases.

Complex chemical processes called nonenzymatic glycation and glycoxidation are one of the interesting examples of potentially harmful interaction between nutrition and disease. The pioneering studies of Maillard almost a century ago pointed out the role of chemical interaction between sugars and proteins in food chemistry long before any pathophysiologic consequences were considered. Today, undisputable body of evidence support causal involvement of glycoxidation is in the development and/or progression of diabetes-related pathology [2], atherosclerosis [3], neurodegenerative diseases [4], and osteoarthritis [5]. In diabetes, both hyperglycemia (and hyperlipidemia) itself and hyperglycemia-driven overproduction of reactive oxygen species (ROS) contribute to increased production of endogenous advanced glycation end-products (AGEs) by nonenzymatic glycation and increased glycoxidation. Diet is believed to be the major source of exogenous AGEs.

The following review summarizes factors influencing the extent of glycoxidation in health and disease and especially focuses on the role that genetic variability in "glycoxidation-related genes" could play in the pathogenesis of diabetic complications and, eventually, in modulation of the impact of food-derived AGEs on the health. As AGEs possess a wide range of chemical and biological effects, the interindividual functional variability in systems dealing with glycoxidation could have a significant nutrigenomic and nutrigenetic consequences.

2 Formation and metabolism of AGEs, determinants of the overall extent of glycoxidation

The Maillard reaction (named after the French scientist Louis Camille Maillard) described at the beginning of the 20th century originally denoted the browning reaction between reducing sugars and amino acids during cooking. Although the series of original Maillard's articles described the process quite in detail it remained forgotten for nearly another quarter of the century before food chemistry, and much more recently medicine, finally began to recognize the significance of the nonenzymatic glycation [6]. Products formed by this reaction contribute to color, taste, and aroma of foods; moreover, it becomes increasingly evident that they also affect nutritional and toxicological properties of food. In a physiological context, Maillard reaction between sugars, α-oxoaldehydes (methylglyoxal, glyoxal, and 3-deoxyglucosone) and other sugar derivatives and proteins leads (through the early and intermediate stages) to the formation of heterogeneous moieties collectively called AGEs. The rate of reaction depends on parameters, such as temperature, pH, carbonyl/amine ratio, and is thus topically and temporally variable. Although AGEs are normally formed already under anaerobic conditions (imidazolones, pyrraline, argpyrimidine, carboxymethyllysine (CML)), their production is substantially enhanced in the presence of ROS. Some AGEs (pentosidine, crosslines), advanced lipoxidation end-products (ALEs) of reaction between proteins and carbonyl compounds produced by lipid peroxidation (malondialdehyde, 4-hydrohynonenal, and acrolein) and oxidative markers (3-nitrotyrosine) are formed exclusively under oxidative conditions [3].

Turnover of AGEs/ALEs (without going into details regarding factors influencing concentration of each specific known group) depends generally on the balance among (i) the rate of endogenous formation, (ii) intake of exogenous AGEs, and (iii) excretion rate (see Fig. 1). Each parameter alone (or in combination) could contribute to the overall quantitative changes and partially explain results of human studies repeatedly reporting increase of AGEs/ALEs concentration during aging [7 – 13], in chronic diabetes [14 – 16], renal insufficiency [9, 17 – 20], in the atherosclerotic vessel wall [21, 22], and other situations [23].

2.1 AGE production *in vivo*

Endogenous AGEs are formed in both extracellular (plasma and tissue extracellular matrix) and intracellular compartments (proteins, DNA); the latter seems to have a much higher concentration than plasma [24]. Substrates for intracellular protein and DNA glycation include glucose, fructose, glycolytic intermediates, and α-oxoaldehydes (especially methylglyoxal). Most commonly in hyperglycemia (see below), increased concentration gradient-dependent facilitated glucose diffusion into cells significantly contributes to the formation of AGEs. Effect of substrate overload on increasing the oxidative and carbonyl stress could be partly limited by natural defence mechanisms – antioxidant and deglycation enzymes – suppressing the formation or detoxifying AGE precursors. Enzymatic defence against glycation includes glyoxalase system [25], aldehyde reductases and dehydrogenases, amadoriases [26], fructosamine-3-kinase [27, 28], and DNA nucleotide excision repair mechanism. Antioxidant enzymes (superoxide dismutases, glutathione peroxidases, synthase, reductase and transfer-

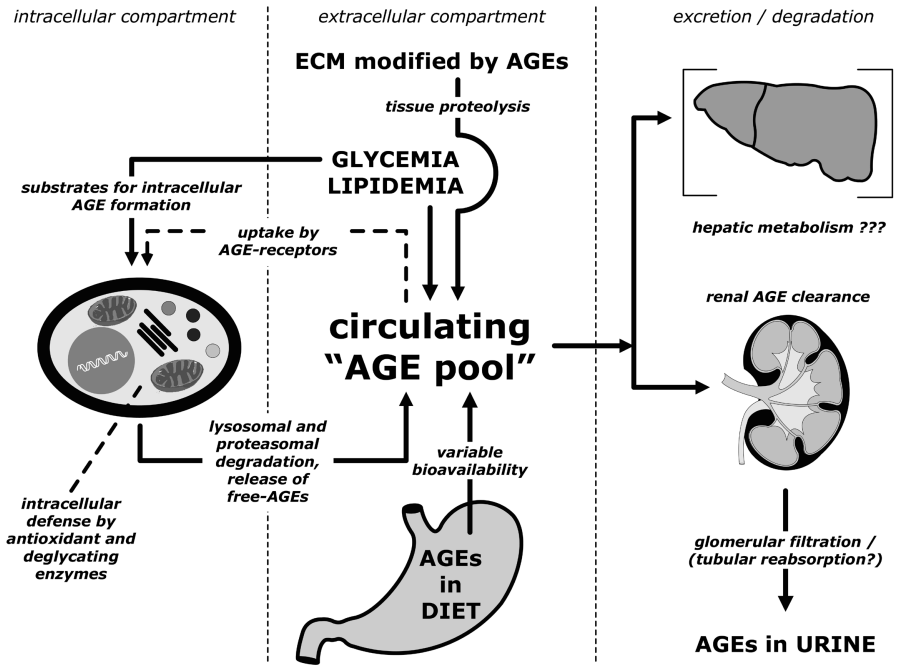

Figure 1. Overview of AGE metabolism and factors influencing the AGE turnover and concentration of AGEs in particular body compartments (self-explanatory). ECM, extracellular matrix.

ase, catalase, *etc.*) metabolize ROS, produce reduced cofactors for other reactions, and modulate intracellular and extracellular environment where reactions proceed. Proteins modified by AGEs are subjects of rapid intracellular proteolytic degradation releasing free AGEs into the circulation (*i. e.*, AGE-adducts) [29]. The long time overlooked significance of glycation damage to DNA is now associated with an accelerated aging, increased mutagenesis and carcinogenesis accompanying disease states associated with accumulation of AGEs, especially diabetes and uremia [30, 31].

Diabetes mellitus was one of the first clinical settings where pathophysiologic role of increased glycoxidation became apparent. Hyperglycemia starts a number of alternative metabolic pathways arising from intermediate products of glycolysis: polyol and hexosamine pathways, nonenzymatic glycation, α-oxoaldehydes production, and *de novo* synthesis of diacylglycerol. The common denominator and driving force is a sustained hyperglycemia-induced overproduction of superoxide in mitochondrial respiratory chain and decreased availability of NAD^+ [32]. Proximal hyperglycemia-induced effects cause changes in cell signalling by activation of multiple systems and reactions including formation of AGEs (see Fig. 2). AGEs binding to signalling receptors – receptor of advanced glycation end-products (RAGE) especially – potently contribute to the downstream events. Induction of pro-inflammatory cellular phenotype by $NF_\kappa B$-mediated gene expression is probably the most significant pathologic consequence of hyperglycemia [33]. Details of mechanisms implicated in molecular pathogenesis of diabetic complications were recently extensively reviewed [32, 34, 35].

2.2 Tissue and circulating AGEs *in vivo*

In circulation, the total pool of AGEs consists of those bound to polypeptides, peptides, and amino acids (in the form of free AGE-adducts). Circulating AGEs are a sum of AGEs formed primarily on plasma proteins, AGEs bound to peptides released by extracellular proteolysis from tissue-immobilized AGEs, free adducts formed by proteolytic degradation of intracellular proteins and exogenously–derived AGEs, primarily those contained in food and absorbed from the intestine. Circulating AGE-modified molecules interact with specific cell surface receptors on the range of cell types (in circulation predominantly on monocyte/macrophages and endothelium) and are subjects of endocytosis and degradation or, alternatively, activate respective intracellular pathways and influence cellular phenotype. Several types of receptors for AGE-modified molecules have been identified up to now – RAGE [36, 37], galectin-3 [38], OST-48, 80K-H [39], scavenger receptors class A (I and II) [40] and B (CD36 and BI), LOX-1, FEEL-1/-2- and probably others remain yet unidentified [41].

2.3 AGE excretion *in vivo*

Renal clearance is the predominant means of excretion of AGEs, particularly the low-molecular-weight fraction. Plasma AGE levels inversely correlate with renal function. AGE adducts and peptides are filtered into glomeruli, a small part might be reabsorbed and degraded by proximal tubular cells [42]. AGEs accumulate in uremic patients to a much greater extent than in subjects with normal renal function

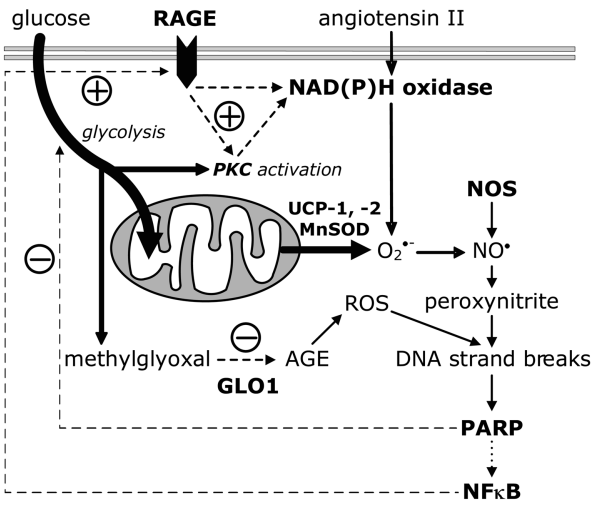

Figure 2. Proximal hyperglycemia-induced changes cause multiple direct effects and also changes in cell signalling by activation of protein kinase C (PKC), NAD(P)H oxidase, poly-ADP-ribose polymerase (PARP-1), and other more upstream events finally activating transcription factors AP-1 and $NF_\kappa B$. Hyperglycemia-induced metabolic alterations lead to activation of PARP-mediated energetic depletion and $NF_\kappa B$-mediated inflammation. Hyperglycemia causes overproductions of superoxide and other ROS by (i) mitochondrial respiratory chain, (ii) NAD(P)H-oxidase, and (iii) formation of AGEs. Moreover, hyperglycemia induced expression of endothelial and inducible forms of nitric oxide synthetase (NOS) enhances production of nitric oxide (NO). Reaction of superoxide with NO produces peroxynitrite. Reactive dicarbonyls (mainly methylglyoxal), if not sufficiently metabolized by glyoxalase system (GLO1 and 2), are precursors of AGEs. ROS and AGEs activate transcription factors AP-1 and $NF_\kappa B$ and cause DNA damage. Mainly single strand breaks of DNA cause activation of PARP-1, which apart from depletion of intracellular NAD^+ further activates AP-1 and $NF_\kappa B$. Hypothetically, variably functional variants of RAGE, GLO1, NOS, NAD(P)H, and PARP could, in itself or along, influence the cumulative degree of damage.

[17, 43–45]; however, they do not significantly differ between uremic patients due to diabetes and nondiabetic cases [46, 47]. The origin of increased AGEs in uremia is complex and not solely dependent on decreased renal function (it is more likely a consequence of enhanced oxidative and carbonyl stress), since the majority of plasma AGEs comes from protein-bound fraction and conventional dialysis techniques do not significantly decrease AGE plasma concentration [48, 49]. Besides the kidney, the liver also seems to be involved in the removal of AGEs; however, quantitative significance of hepatic clearance is currently under debate. Some preliminary experimental data indicated hepatic uptake and metabolism of AGEs [50]; likewise, elevation of AGEs in subjects with liver cirrhosis and subsequent normalization after liver transplantation was demonstrated [51]. Nevertheless, whether these observations reflect primarily liver malfunction or they are purely surrogate indicators of changes in plasma protein life span, for instance, needs to be yet elucidated. Moreover, extraction of *in vivo* formed AGEs from the blood entering and leaving the liver, both in healthy subjects and patients with liver cirrhosis, was not confirmed [52]. Thus, the proposed role of *in vivo* AGE liver clearance still lacks solid evidence.

3 Role of genetic factors in determination of the extent of glycoxidation in health and disease

On top of the list of already mentioned factors influencing the individual's AGE levels, an interesting study on nondiabetic twins recently demonstrated that interindividual variation in AGE levels is significantly determined by genetic factors [53]. Using serum specimens of 84 healthy female twin pairs authors ascertained a 74% heritability (95% (CI) 58–84) of AGE levels (assessed by serum CML). Heritability of AGE levels (*e.g.*, proportion of phenotype variability ascribed to genetic factors) was independent on heritability of fasting glucose or HbA_{1c}. Predominantly endogenous origin of AGEs and substantial heritability of AGE levels could thus indicate that genetic factors play an important role in determining this intermediate phenotype already in the healthy state and, consequently, could all the more modulate the effect of a disease or nutrition on the individual's AGE levels.

Genetic variability resulting in functional variability in loci collectively denominated as "glycoxidation-related genes" could contribute to observed heritability and determination of the extent of glycoxidation. Orchestration of ROS and AGEs production in common metabolic disorders, and thus individual's susceptibility to develop clinically manifest disease, might be influenced by genetic variability in glycoxidation-related genes. Those genes thus belong to paramount candidates for studies of predisposition to certain common diseases including diabetes and its complications [54]. Summarization of all hitherto available results of association studies of different phenotypes with glycoxidation-related genes would far exceed the scope of this review; it will confine itself just to one such example – relationship between genetic variability in the RAGE gene and susceptibility to diabetic complications.

There are many indices that development of diabetic complications (especially diabetic nephropathy) is influenced by genetic factors. RAGE gene was one of the first candidate gene studied in this context soon after its isolation and characterization in 1992 [36, 55]. RAGE is an immunoglobulin-type receptor recognizing particular tertiary structure of multiple ligands – AGEs, amyloid β-peptide

[56], S100 proteins [57], and high-mobility group protein B1 (HMGB1, amphoterin) [58]. Binding of AGEs to RAGE activate intracellular signal transduction pathways including the ERK1/2 kinases, the $p38^{MAPK}$, the SAPK/JNK kinases, JAK/STAT, and the $NF_{\kappa}B$ pathway. All these effects make RAGE an important factor in the propagation of inflammation in many pathologic conditions. Several groups analyzed genetic polymorphism in the RAGE gene and identified over 25 different substitutions in coding and noncoding regions, whereas at least five of them (–429T/C, –374T/A, 1704G/T, 2184A/G, and 2245G/A) were common variants (minor allele frequency >10%). Hudson *et al.* [59] analyzed the functional impact of two of those polymorphisms in the 5′-flanking region of the RAGE (–429T/C and –374T/A) by reporter gene assay and found a significant increase of transcriptional activity in the presence of minor alleles compared to the wild type. Moreover, in the same study, they also detected marginal association of the –429C allele with diabetic retinopathy in type 2 diabetic subjects. Results from a Finnish study of type 1 diabetic subjects with diabetic nephropathy indicated a possible protective role of the –374AA genotype for the development of proteinuria and coronary heart disease in poorly controlled type 1 diabetics [60]. This finding was independently corroborated in Italian population of nondiabetic subjects with coronary artery disease (CAD) where allele –374A conferred a moderate protective effect [61] and was associated with lower number of diseased vessels [62]. Japanese authors found an association of the 1704T allele in combination with the 242C variant in the gene encoding p22phox subunit of the NAD(P)H oxidase with diabetic nephropathy in T2DM [63]. Our group originally described association of the 1704T and 2184G alleles with diabetic dermatoses [64], but not with diabetic retinopathy [65]. Recently, we performed extensive haplotype analysis of the RAGE gene including all six most common SNPs followed by haplotype-based association study and survival analysis in a sample of approximately 600 diabetic (with and without diabetic nephropathy) and nondiabetic subjects [66]. A total of ten haplotypes were inferred with five of them having population frequency >5%. The frequency of a haplotype containing minor alleles in positions –429 and 2184 (denoted $RAGE_2$ by frequency-dependent order number) was roughly twofold in the group of patients with diabetic nephropathy than in control groups. Survival analysis, carried out to ascertain whether $RAGE_2$ haplotype influences the onset of nephropathy, revealed significant differences among particular diplotype groups; the median nephropathy-free interval was significantly shorter (9.6 years) in $RAGE_2$ homozygotes than in heterozygotes (15.2 years) and non-$RAGE_2$ carriers (17.0 years). Pursuant to these results we concluded that this haplotype could be regarded a disease marker for diabetic nephropathy.

4 Pathogenic significance of dietary AGEs

Of all the glycated products present in food as a result of the Maillard reaction, only a small proportion – approximately 10% of total dietary content – is intestinally absorbed and subsequently found in plasma [67]. AGE content is highest in cooked foods, particularly those rich in fat and proteins; besides, it depends also on the preparation conditions, presence of metals and water content [68]. Kinetic studies in humans revealed that only one-third of ingested AGEs from diet are excreted by the kidney; thus, a large proportion remains retained [67].

Contribution of diet AGEs to an individual's total AGE levels is currently a subject of intensive research since thermally processed foods represent a prevailing part of human diet. Thermal processing is essential for producing microbiologically safe products with desired nutritional quality, sensory properties, and shelf life; however, such treatment leads to formation of heat-induced components, some of them with presumably health-promoting properties (such as antioxidants or melanoidins), but others, AGEs in particularly, possessing pathologic characteristics. An increasing body of literature supports pathogenic significance of dietary AGEs. Results of *in vitro* studies showed that AGEs derived from common thermally processed foods (animal products, vegetables, starches) possess significant pro-oxidative (depletion of reduced glutathione, cross-link formation), pro-inflammatory (induction of tumor necrosis factor α (TNF-α)) and signalling properties prior to their ingestion [69]. Comparison of the effect of low and high intake of dietary AGEs on modification of plasma low-density lipoprotein (LDL) in diabetic patients with equal glycemic control and lipidemia have shown that high AGEs can transform circulating macromolecules to a much greater extent and render them more pro-atherogenic than those from subjects with low AGEs [70]. *In vivo* animal studies in nonobese diabetic mice (NOD) with type 1 diabetes and db/db mice with type 2 diabetes showed a progressive development of diabetic nephropathy (both models) and shorter survival (NOD mice) in animals exposed to a long-term high-AGE diet [71]. Further, genetically hypercholesterolemic apolipoprotein E-deficient diabetic mice fed by a low-AGE diet for 4 weeks following the experimental injury of the femoral artery developed significantly lesser extent of neointimal formation than animals on high-AGE diet [72]. Moreover, in the same animal model with streptozotocin-induced diabetes, 2-month dietary AGE restriction was associated with significantly lower serum AGEs, reduced formation of atheromatous lesions, lower tissue expression of AGE receptors and infiltration with inflammatory cells without concomitant differences in plasma glucose, triglycerides, or cholesterol [73]. In humans, a 6-week nutritional intervention study demonstrated that circulating AGEs can be modulated by altering dietary AGE intake in diabetics,

consequently, decrease of circulating AGEs was followed by a parallel decrease in levels of inflammatory molecules (C-reactive protein (CRP) TNF-α) and markers of endothelial dysfunction (vascular cell adhesion molecule 1 (VCAM-1)) [74].

It was shown and generally accepted that 10 – 30% of the ingested AGEs, particularly the low-molecular-weight fraction, are absorbed into the circulation [75]. Their *in vivo* fate remains rather unclear. In adults, about 3% is excreted *via* urine and up to 16% in feces [67, 75]. A parallel rise of the circulating AGEs and their urinary excretion after AGE dietary load was shown in several animal and human studies [67, 76 – 79], while others were able to report only increased urinary excretion [80, 81]. Urinary output of glycated compounds is considered to be strictly dependent on their daily dietary intake [82]. Experimental data suggests that high (110 – 310 mg CML/kg/d) but not moderate (11 mg CML/kg/d) oral intake of AGEs results in their accumulation in various organs, mainly kidney, and liver [76, 81]. The former findings were confirmed by the study of biodistribution and elimination of AGEs (namely N_ε-carboxymethyllysine and N_ε-carboxyethyllysine) in rats after intravenous injection using positron emission tomography. Results clearly showed a first-pass effect in the liver followed by a 84% elimination in the kidney within 2 h after single i.v. injection [83].

In spite of the fact that the metabolic transit data for the majority of ingested AGEs remain unknown, several lines of evidence suggest that an AGE-rich diet can lead, at least in susceptible individuals (such as infants, elderly and diseased people), to potentially pathologic consequences – body and organ weight gain, obesity with metabolic syndrome [79, 84 – 86], renal damage (*via* induction of proteinuria and/or enhanced formation of pro-fibrotic transforming growth factor β_1 (TGF-β_1)) [79, 84, 85, 87], accelerated atherosclerosis (*via* lipid peroxidation) [73, 84], and low-degree inflammation [74, 88].

To our knowledge, only one experimental study has so far shown a lack of any toxic effect from a diet with high AGE content [89]. Interesting findings came also from the study of plasma AGE levels of vegetarians and omnivores. Surprisingly higher plasma AGE levels in vegetarians, compared to subjects eating heat-processed meat, were not associated with typical AGE-toxicity, such as induction of insulin resistance, nephrotoxicity, inflammation, or accelerated atherosclerosis [90]. It might be anticipated that high levels of antioxidants, for instance, as often observed in vegetarians, may be effective in antagonizing the effect of higher intake of dietary AGEs, at least in healthy subjects. The discrepancy between reported data concerning the effect of alimentary AGEs can be due to many experimental and methodological factors (different composition and preparation of high-AGE diet, duration of administration, analytical approaches employed, medical condition of studied subjects and, finally, type of the species studied, since only humans are accustomed to consume heat-treated food). This might also explain the relatively poor efficiency of certain anti-AGE drugs in humans compared to animal models.

5 Gene-diet interactions, implication of polymorphism in the RAGE gene for nutrigenetics and nutrigenomics

Beyond a primary role of diet as an energetic resource, there has been a growing recognition that micronutrients (vitamins A, D, E, calcium, iron, zinc, *etc.*) and macronutrients (fatty acids, cholesterol, glucose, amino acids) are potent environmental signals that influence cellular metabolic programming, homeostasis, and gene expression. Nutrigenomics seeks to provide a molecular understanding of these processes, particularly of the effects of nutrients on gene expression [91]. The concept of gene-diet interaction implies the modulation of the effect of dietary components on a specific phenotype by genetic polymorphism in a certain locus. This equals the working definition of nutrigenetics. So far the best examples of the importance of the nutrigenetic approach came from studies of an interaction between genetic variability in loci encoding proteins involved in lipoprotein metabolism and dietary intake of lipids (and smoking) on the determination of plasma lipid levels, response to lipid-lowering diet interventions and, eventually, development of CAD [92-94]. Another frequently cited example is the variable penetrance of folate deficiency (*i. e.*, hyperhomocystinemia) in carriers of polymorphism 677C/T in the gene encoding methylenetetrahydrofolate reductase (MTHFR).

Considering gene-environment interactions in study designs becomes of paramount importance since the rise in the population frequency of obesity, diabetes, CAD, and some types of cancer is evidently sequel to changes in lifestyle rather than genome. Many association studies assume (and without studying gene-environment interactions at the same time there cannot be any other conclusion) that a particular single nucleotide polymorphism (SNP) or haplotype is associated with the same phenotype in all affected individuals. However, considering gene–environment interactions, such association (or the real genotype-related risk) might be different under different environmental exposures, *i.e.*, mimicked in the best case or nonlinearly aggravated in the worst.

We propose that glycoxidation-related genes, and particularly RAGE, might be another factor with nutrigenetic and nutrigenomic significance, especially in diseases showing broad phenotypic plasticity – such as T2DM or athero-

sclerosis – where gene-environment interactions, and specifically those initiated by diet, play undeniably an important role. Recently, an effect of food compounds formed by heat treatment during processing of food on the expression of the RAGE and the p44/42 MAP kinase activation was experimentally studied [95]. The authors documented dose-dependent activation of RAGE signal transduction pathways in response to food-derived AGEs and other thermally produced compounds and inhibition of such activation by pre-incubation with anti-RAGE antibody or in cells expressing *C*-terminally truncated RAGE. Hence, these findings support the nutrigenomic significance of the AGE/RAGE system. Besides, in a study investigating relationship between four common RAGE variants and circulating levels of selected nonenzymatic antioxidants, Amadori products, and AGEs in diabetics and nondiabetics without external supplementation of antioxidants, significant differences in serum levels of nonenzymatic antioxidants (but not glycation parameters) between subjects bearing wild-type and mutated genotypes of the 1704G/T and 2184A/G were ascertained [96]. Whether RAGE gene variants could modulate hypothetical nutrition-dependent risk has to be rigorously tested in future studies. One can think of several hypotheses, *e.g.*, changes in AGE levels, inflammatory or oxidative markers in response to AGE-enriched/depleted diet could be studied in subjects with known RAGE genotypes/haplotype.

6 Summary and perspectives

Recently many studies of a different scale and design investigate genetic susceptibility to complex diseases. All of them, though, follow more or less the same goals – targeted disease screening, individualized patient follow up, tailored pharmacotherapy and individualized life style precautions (an approach corresponding to the concept of "personalized medicine"). Findings from studies of genetic and functional variability in "glycoxidation-related genes/proteins" and identification of particular disease- and diet-related risk variants might help to further minimize the long-term consequences of diabetes in the situation when preventing the disease itself is not possible yet, and also adopt individualized nutrition which does not further aggravate or superimpose on factors already present and inevitable. To achieve this, however, more data about AGE content, bioavailability and intestinal degradation are needed before any eventual diet AGE-specific interventions will be adopted.

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