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The Role of Dietary Advanced Glycation End Products in Metabolic Dysfunction

*Domenico Sergi, Hakim Boulestin, Fiona M. Campbell, and Lynda M. Williams**

Advanced glycation end products (AGEs) are a heterogeneous group of molecules produced, non-enzymatically, from the interaction between reducing sugars and the free amino groups of proteins, nucleic acids, and lipids. AGEs are formed as a normal consequence of metabolism but can also be absorbed from the diet. They have been widely implicated in the complications of diabetes affecting cardiovascular health, the nervous system, eyes, and kidneys. Increased levels of AGEs are also detrimental to metabolic health and may contribute to the metabolic abnormalities induced by the Western diet, which is high in processed foods and represents a significant source of AGEs. While increased AGE levels are a consequence of diabetic hyperglycaemia, AGEs themselves activate signaling pathways, which compromise insulin signaling and pancreatic β-cell function, thus, contributing to the development of type 2 diabetes mellitus (T2DM). Furthermore, AGEs may also contribute to the obesogenic effects of the Western diet by promoting hypothalamic inflammation and disrupting the central control of energy balance. Here, the role of dietary AGEs in metabolic dysfunction is reviewed with a focus on the mechanisms underpinning their detrimental role in insulin resistance, pancreatic β-cell dysfunction, hypothalamic control of energy balance, and the pathogenesis of T2DM and obesity.

1. Introduction

Advanced glycation end products (AGEs) are a complex and heterogeneous group of protein, lipid, and DNA adducts implicated in the development of numerous chronic diseases including diabetes related complications, cardiovascular, renal, and neurodegenerative disease, and have recently also been implicated in hypothalamic inflammation and obesity.[1] AGEs are produced both naturally in the body, as part of normal metabolism, and during the cooking and processing of food with a significant proportion being absorbed in the gastrointestinal tract. The rate of AGE formation in the body is greatly enhanced in diabetes.[2,3] Furthermore, the Western diet not only contains large amounts of AGEs, due to high levels of food processing, but is also high in fat and sugar, particularly fructose, which increases AGE production in the body, in part, by increasing circulating glucose levels via enhanced hepatic glucose production and insulin resistance.[4] Additionally, fructose can increase AGE formation independently of glucose by increasing α-oxoaldehydes levels.[5]

AGEs were first described in 1912 being initially identified in food and drink as a result of the browning effect termed the Maillard reaction.[6] The identification of AGEs in vivo did not occur for the next 60 years when their formation was recognized as part of the normal ageing process with irreversible AGEs accumulation in tissues containing long-lived proteins, such as collagen in the extracellular matrix, crystalins in the eye lens, and the basement membrane in the kidney.[7–9] Excessive AGE formation is particularly associated with cross-linking of matrix proteins such as collagen, vitronectin, and laminin.[2,10,11] The level of AGEs in the body increases with time due to their accumulation in proteins and this process is thought to contribute to aging,[12] particularly as their formation alters the structure and function of proteins producing the hallmark features of ageing.[13] Also, the increased presence of AGEs in collagen across eight mammalian species has been shown to be associated with reduced lifespan, indicating that AGE levels determine lifespan and rate of ageing.[14] More recently, AGEs have been identified as one of the molecular mediators in the onset and progression of metabolic dysfunction via the activation of intracellular pathways, which promote inflammation and increased levels of reactive oxygen

Dr. D. Sergi
Nutrition and Health Substantiation Group
Nutrition and Health Program
Health and Biosecurity
Commonwealth Scientific and Industrial Research Organisation (CSIRO)
Adelaide, SA 5000, Australia
Dr. D. Sergi
Adelaide Medical School
The University of Adelaide
Adelaide, SA 5000, Australia
H. Boulestin, Dr. F. M. Campbell, Prof. L. M. Williams
Rowett Institute
University of Aberdeen
Aberdeen AB25 2ZD UK
E-mail: l.williams@abdn.ac.uk

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species (ROS). This review will summarize the molecular process of AGEs formation as well as their role in metabolic dysfunction.

Lynda Williams is a professor emeritus at the Rowett Institute, University of Aberdeen. Her research has centered on the effect of a Western diet on the hypothalamus and hippocampus using transcriptomic and proteomic approaches to identify novel dietary targets and processes in mice.

2. AGE Formation

AGEs are synthesized endogenously as well as during food cooking and processing via the Maillard reaction. This is a complex, multistage, non-enzymatic reaction initially involving a glycation/condensation process between reducing sugars, such as glucose and fructose and the free amino group of proteins, lipids, and nucleic acids resulting in formation of a Schiff base. This reaction is relatively fast and highly reversible. The subsequent rearrangement of the Schiff base leads to the formation of the more stable Amadori products which progress to covalent adducts and accumulate on proteins.[15] One outcome of this process, in the body, is an Amadori product; glycated haemoglobin (HbA1c) which is used as an accurate marker of long-term exposure to high circulating glucose. The formation of intermediate Amadori products is reversible (see section on AGE detoxification).

Despite its ability to react with free amino groups, glucose is a poor glycating agent compared to dicarbonyls such as methylglyoxal.[16] The Maillard reaction generates these highly reactive dicarbonyls, also referred to as α-oxoaldehydes, which in addition to methylglyoxal include glyoxal and 3-deoxyglucosone.[17] These molecules can also be generated from glucose autoxidation, lipid peroxidation, and the polyol pathway.[18] Dicarbonyls, initiate the process of advanced glycation leading to the synthesis of the well characterized AGEs, Nϵ-(carboxymethyl) lysine (CML) and Nϵ-(carboxyethyl) lysine (CEL)[18] (**Figure 1**).

Besides the Maillard reaction and the oxidation of glucose, the polyol pathway represents a further mechanism leading to the formation of AGEs. An increase in intracellular glucose levels as a result of hyperglycaemia, is toxic and glucose is subsequently funneled toward the polyol pathway. The first step of this pathway is the conversion of glucose to sorbitol mediated by the enzyme aldose reductase, sorbitol is then converted to fructose by sorbitol dehydrogenase. Over-activation of the polyol pathway results in the depletion of NAD^+, the cofactor of sorbitol

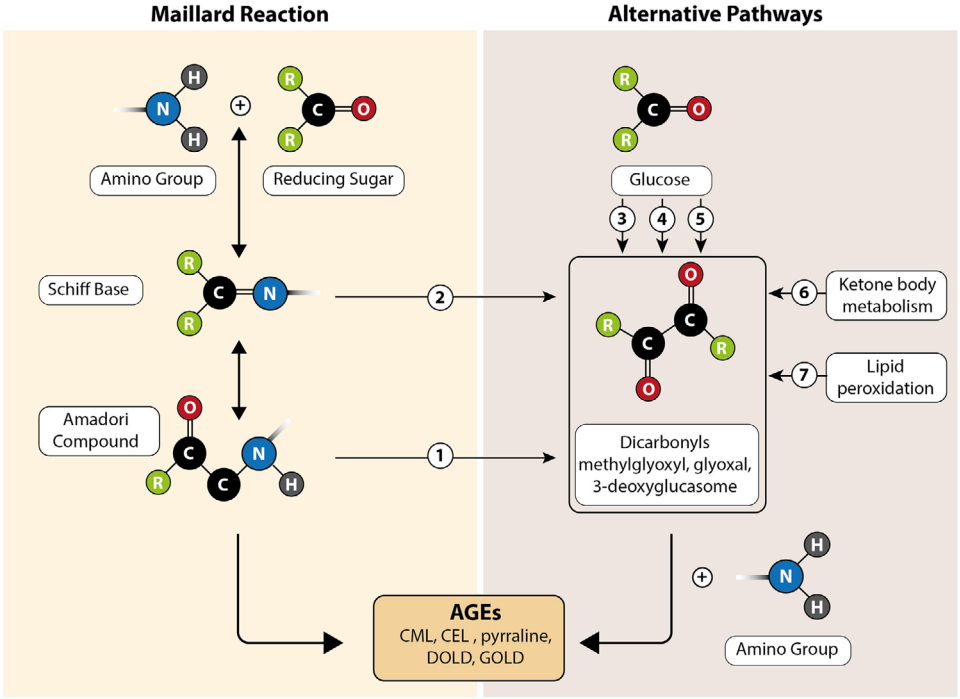

Figure 1. Formation of advanced glycation end products (AGEs). Left panel: Maillard reaction. Right panel: Alternative pathways, Hodge pathway: fructosamine, non-oxidative Amadori product cleavage (1); Namiki pathway: cleavage of dicarbonyl compounds from aldimines (2); Wolff pathway: metal catalyzed glucose autoxidation (3); glycolytic pathway intermediates, for example, glyceraldehyde 3 phosphate (4); polyol (sorbitol aldose reductase) pathway (5); amino acid derived ketone body metabolism (6); lipid peroxidation (7). These pathways lead to formation of reactive dicarbonyls, which if not detoxified form AGEs, (e.g., carboxyethyl lysine [CEL], carboxymethyl lysine [CML], glyoxal lysine dimer [GOLD], 3-deoxyglucosone lysine dimer [DOLD], and pyrroline).

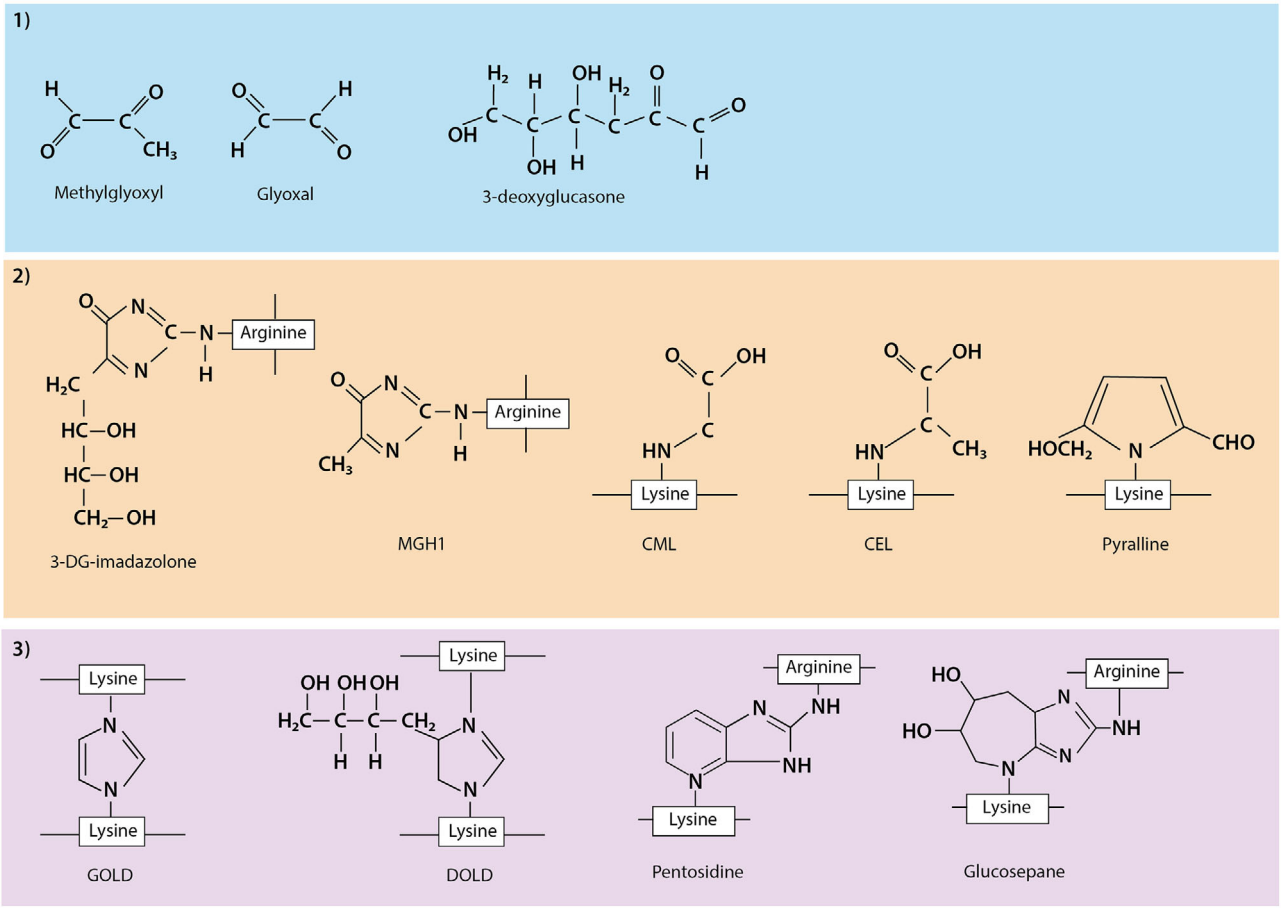

Figure 2. Chemical structures of selected physiologically important dicarbonyl intermediates and advanced glycation end products (AGEs). Reactive dicarbonyl AGE precursors: methylglyoxyl, glyoxyl, and 3-deoxyglucasone (1). Arginine derived AGEs: methylglyoxal-derived hydroimidazolone [MGH1], pentosidine, and 3-3-deoxyglucosone derived imidazolone [3-DG-imadazolone]. Lysine derived AGEs: carboxyethyl lysine [CEL], carboxymethyl lysine [CML], and pyrroline (2). AGE crosslinks: GOLD (glyoxal lysine dimer), DOLD (3-deoxyglucosone lysine dimer), pentosidine, and glucosepane (3).

dehydrogenase, which inhibits the activity of the glycolytic enzyme glyceraldehyde triphosphate dehydrogenase and consequently promoting the accumulation of upstream metabolites, including fructose and triose phosphates. The build-up of these metabolites gives rise to highly reactive molecules including fructose 3 phosphate and dicarbonyl derivatives, glyoxal, methylglyoxal, and 3-deoxyglucosone, which interact with intracellular and extracellular proteins to form AGEs.[8,19] The chemical structures of these compounds are detailed in **Figure 2**.

Lipid peroxidation products also form reactive carbonyls such as malondialdehyde and methylglyoxal, derived from the oxidation of polyunsaturated fatty acids. Additionally, reactive carbonyls are formed from ketones generated by breakdown of amino acids, including the formation of methylglyoxal from threonine catabolism. Thus, reactive carbonyl groups are constantly being produced via normal metabolism and when production overrides detoxification, AGEs accumulate. AGE formation may take several days or weeks to complete in the body[20,21] with final AGE concentration depending on the half-life of the glycated proteins.

The amino residues arginine, lysine and, to a lesser extent, cysteine and the nucleotides guanosine and deoxyguanosine are particularly vulnerable to dicarbonyl modification[22] forming AGEs and DNA-AGEs such as N2(1-carboxyethyl)-2′-deoxyguanosine (CEdG). Some of the most commonly formed AGEs include the hydroimidazolones, the most prevalent of these in human tissues is formed from the interaction of methylglyoxal with arginine residues.[23] Other prevalent AGEs are CML and CEL. However, less common AGEs such as, pentosidine (very elevated in uraemia and a good marker of "carbonyl stress"), pyrraline, and glucosepane are found at much lower levels, but also play a role in human disease risk[24,25] (Figures 1 and 2).

3. Source and Absorption of Dietary AGEs

Dietary AGEs are formed during the cooking, processing, and storage of foods as a result of the non-enzymatic browning, Maillard reaction, between a carbonyl group of a reducing sugar and a primary amine group as shown in Figure 1 and described in detail earlier. Factors affecting the AGE content of food depends on the content of protein, fat, and sugar and the types of processing and cooking methods employed, predominantly on the temperature and duration of preparation.[26,27] Prolonged

high temperatures such as those used in the processing of some dairy products and cooking techniques like roasting and frying increase the production of dietary AGEs.[26,27] When CML, CEL, and MG-H1 are measured by ultra-performance liquid chromatography tandem mass spectrometry, food items such as peanuts, biscuits, cereals, toast, and heat-processed meats have the highest levels, ranging from 2–5 mg for CML, from 2–7 mg for CEL, and from 15–60 mg for MG-H1 per 100 g, in contrast coffee, fruits, vegetables, butter, olive oil, and red wine contain negligible amounts of these AGEs.[27]

Dietary AGEs are absorbed by the gastrointestinal tract to exert their effects on health with dietary and circulating free-AGEs concentrations highly correlated,[28–30] making free-AGEs a good marker for dietary AGE intake while plasma protein-bound AGEs better represent endogenously produced AGEs.[31] The heterogeneity of dietary AGEs makes it challenging to predict their rate of absorption or pinpoint potential transporters. Nonetheless, the rate and the mechanisms of absorption of CLM, CEL, pentosidine, and pyrraline have been reported with around 10–30% being absorbed depending on their chemical characteristics.[28–30] AGEs can reach the gastrointestinal tract as free AGEs, which include amino acids and small peptides with a molecular weight lower than 5 kDa or bound to proteins as high-molecular weight complexes.[30,32] Free CML is absorbed by simple diffusion,[33] with dipeptides requiring the peptide transporter 1,[34] which also transports pyrraline dipeptides.[35] Thus, the absorption of AGEs as single amino acids or dipeptides occurs more efficiently than protein-bound AGEs, evidenced by higher levels of CML in the faeces when protein-bound CML is ingested.[36] The same is true for the AGE pentosidine the absorption of which is greater when derived from brewed coffee (free-form) compared to bakery products where pentosidine occurs as a protein-bound AGE.[37]

AGE modification inhibits proteolytic digestion[32,38] thus, low molecular weight AGEs are absorbed more efficiently than protein-bound AGEs.[39] Nonetheless, albeit at a lower rate, protein-bound AGE absorption still does take place. This was demonstrated in rodents where organ accumulation of dietary ^{13}C-labeled CML occurs following feeding ^{13}C-labeled-CML-BSA.[40] The presence of ^{13}C-labeled CML in the faeces indicates that AGEs have the potential to interact with the gut microbiota which has been extensively reviewed elsewhere.[29]

4. Receptors for AGEs

4.1. RAGE

AGEs are ligands for several receptors, the main one being the receptor for advanced glycation end products (RAGE). Full-length, membrane bound RAGE (mRAGE) is present on numerous cell types throughout the body while soluble RAGE (esRAGE), produced via alternative splicing and lacking a transmembrane domain, is found in the circulation. A separate soluble receptor is ectodomain-shed RAGE (ecRAGE), which is derived via the action of metalloproteases on mRAGE.[41] All three isoforms of the receptor are equally effective in binding ligands, however the two secreted forms of RAGE lack the capacity to elicit the activation of the intracellular signal transduction pathways activated by AGEs. Furthermore, the soluble forms of the RAGE competitively bind AGEs preventing their interaction with mRAGE and the activation of downstream pathways, including pro-inflammatory responses.[42,43]

RAGE belongs to the immunoglobulin superfamily of pattern recognition receptors and is not exclusively stimulated by AGEs but can also be activated by other intracellular and extracellular ligands. mRAGE is a surface receptor and expressed on a variety of cells, including peripheral immune cells, but also in the microglia, endothelial cells, smooth muscle cells, and neurons.[1,44]

As AGEs comprise such a diverse and heterogeneous group of compounds, information relating to specific interactions between different AGEs and RAGE are limited. mRAGE consists of extracellular hydrophobic transmembrane and cytoplasmic domains with the extracellular structure of mRAGE further subdivided into three immunoglobulin-like domains: a variable (V) domain and two constant C1 and C2 domains. mRAGE interacts with AGEs, such as CML, CEL, which bind to the V domain of mRAGE to trigger an immunoinflammatory response. CML and CEL can only bind to mRAGE if they are incorporated into larger peptide structures.[45,46] Chemically synthesized peptides containing hydroimidazolones bind specifically to the V domain of mRAGE resulting in signal transduction. In contrast to CML or CEL, the hydroimidazolone MG-H1 does not require attachment to a peptide carrier to exert its effect[47] and as the MG-H1 content of foods is much higher than either CML or CEL, free MG-H1 absorbed from the diet is likely to be a significant activator of mRAGE.[27,48]

Upon binding to their cognate receptor, AGEs trigger the activation of different downstream effectors, including extracellular-signal-regulated kinase 1/2 and p38 mitogen-activated protein kinase, rho-GTPases, Janus kinase, c-Jun N-terminal kinase (JNK), and the transcription factor nuclear-factor-kappa B (NF-κB).[49–53] Besides activating inflammatory pathways, the activation of RAGE is also implicated in promoting oxidative stress by activating NAPDH oxidase which enhances ROS production with ROS promoting AGE formation.[18,54] Moreover, ROS potentiate the inflammatory response by activating NF-κB, which, once activated, migrates to the nucleus and induces not only the expression of inflammatory mediators, but also upregulates RAGE, thus establishing a positive feedback loop.[55,56] mRAGE has also been shown to transport β-amyloid into neurons[57] and to facilitate the gut uptake of oxytocin from milk and the transport of circulating oxytocin into the brain, indicating that it mediates physiological as well as pathological effects[58,59] (**Figure 3**).

4.2. Other Receptors

AGEs can also bind to other cell surface receptors in addition to RAGE. These receptors mediate endocytosis and the degradation of AGEs to maintain AGE homeostasis and include the cluster of differentiation 36, macrophage scavenger receptors I and II, and the advanced glycation end products receptors (AGER1, AGER2, and AGER3).[60] AGER1 is present in almost all cells and tissues, is upregulated by AGEs and increases their uptake and removal.[18] AGER1 can counteract AGE-induced oxidative stress[61,62] as well as inhibit the activation of NF-κB by promoting a sirtuin1-dependent deacetylation and suppression

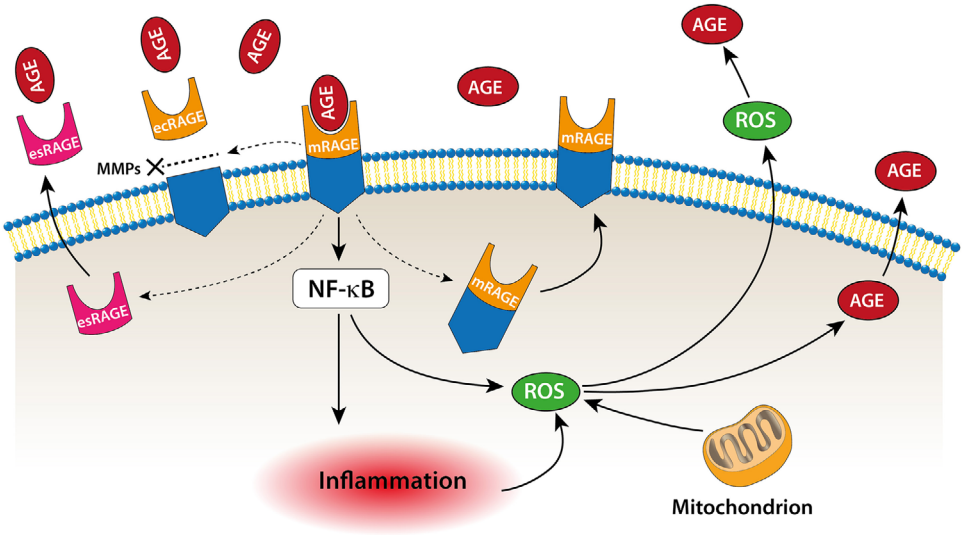

Figure 3. Receptor for advanced glycation end products (RAGE): RAGE signals via the transcription factor nuclear-factor-kappa B (NF-κB) increasing gene expression of inflammatory mediators and the production of ROS. Full-length, membrane bound RAGE (mRAGE), soluble RAGE (esRAGE) is found in the circulation. Ectodomain-shed RAGE (ecRAGE) is derived via the action of metalloproteases (MMP) on mRAGE. All three isoforms of the receptor are equally effective in binding ligands however, the two secreted forms of RAGE lack the capacity to elicit any signaling mechanisms.

of NF-κB.[63,64] Nonetheless, this protective mechanism begins to fail as the concentration of AGEs increases, with high levels of AGEs leading to a downregulation of both AGER1 and sirtuin1.[64]

The close structural and functional RAGE homologue, CD116/activated leukocyte cell adhesion molecule (ALCAM), elicits the inflammatory effects of AGEs when RAGE is absent[65] and ALCAM expression is upregulated by CML challenge when RAGE activation is blocked.[66] In mice, where AGEs were identified as being the mechanism by which a high-fat diet causes hypothalamic inflammation, knockdown of both RAGE and ALCAM was required to block the proinflammatory effects of CML.[1]

5. Detoxification of AGEs

The toxicity of the dicarbonyl precursors of AGEs is underlined by the numerous mechanisms that the body employs to remove them. It has been estimated that around 99% of all methylglyoxal is broken down via the glyoxalase pathway[67] detailed below.

5.1. Glyoxalases (GLO1 and 2)

The glyoxolase system is well characterized and comprises two enzymes; glyoxalases 1 and 2 (GLO1 and 2), which require the thiohemiacetal produced by the non-enzymatic reaction between glutathione and a 2-oxoaldehyde, particularly methylglyoxal, as a substrate.[68] This system acts to convert the dicarbonyls; glyoxal and methylglyoxal to lactic and glycolic acid, respectively. Activity of the glyoxolase is upregulated in diabetes to prevent the build-up of reactive dicarbonyls thereby suppressing AGE formation.[69] However, the scavenging capacity of this system can be overridden by an increase in dicarbonyl formation, leading to dicarbonyl stress which results in enhanced AGE production.[70,71]

Underlining the deleterious effect of dicarbonyl stress at the cellular levels, over expression of GLO1 in cultured cells and model organisms prevents hyperglycemia induced oxidative stress and AGE accumulation while a reduction in GLO1 expression using siRNA is associated with elevated levels of methylglyoxal-derived hydroimidazolone 1 protein adducts and increases in pathological changes associated with diabetic nephropathy.[72] Furthermore, silencing GLO1 in endothelial cells has been reported to upregulate genes linked with coronary heart disease[73] as well as resulting in glucose intolerance, oxidative stress, and decreased lifespan in *Caenorhabditis elegans*.[74,75] Thus, the glyoxalase detoxifying system is pivotal in maintaining dicarbonyl homeostasis and preventing the formation of AGEs.

5.2. DJ-1 Deglycase (GLO3)

The role of DJ-1/PARK7 is more contentious. The protein has been shown to have numerous roles and is referred to as a multifunctional stress response protein[76] acting as a covalent chaperone for the thiol proteome[77] a chaperone for synuclein,[78] a protease and as a cofactor-independent glyoxalase.[79] However, it has been argued these functions are much weaker than major proteins, which normally fulfill these roles.[76,79,80] More recently DJ-1 has been shown to be important in the carbonyl stress response acting as a protein deglycase repairing methylglyoxal- and glyoxal-glycated proteins and amino acids, releasing deglycated products plus lactate or glycolate.[81] DJ-1 is also reported to be important in reversing DNA glycation and has subsequently been renamed as the DJ-1 family of Maillard deglycases.[82,83]

5.3. Other Enzymes

Other enzymes have been identified for their capability to break down dicarbonyls and rid the organism of damaged proteins, with minor metabolism by aldo–keto reductases and aldehyde dehydrogenases.[84] While knockdown of any of these enzymes can cause upregulation of the dicarbonyls in the short-term, their absence does not appear to have any pathological consequences and their activity seems to be important only when AGE levels are low.[85–88]

The enzymes and detoxifying systems described so far are responsible for neutralizing AGE precursors, thus preventing or retarding AGE formation. However, AGEs, once formed can also be degraded. Dietary AGEs which are the result of digestion and absorption are likely to be "free" either as glycated peptides or amino acids while endogenously formed AGES can also be adducts of cellular proteins and may be broken down via proteasomal degradation as indicated by an increased release of proteolytic products of glycated proteins in response to increased levels of glycated proteins in type 1 diabetes.[88] AGEs can also be taken up by the cells, via receptor-mediated endocytosis, and degraded by the endosomal–lysosomal system and particularly by the enzymes cathepsin L and D.[89] Initially, the AGE–RAGE complex is internalized via clathrin-dependent mechanism, clathrin-coated vesicles are then transported to endosome where, the drop in pH leads to the release of the AGE–RAGE binding with the receptor being recycled back to the cell membrane. Endosomes containing AGEs fuse with lysosomes where AGEs are degraded by the lysosomal proteases cathepsin L and D.[52]

A further mechanism implicated in preventing AGE-induced toxicity, independent of AGE degradation and dicarbonyl detoxification, is the upregulation of AGER1 as stated earlier (see Section 4).

6. AGEs and the Western Diet

The Western diet is associated with the increased incidence of obesity and obesity-related diseases. The relationship between diet and metabolic dysfunction is poorly understood, but it appears that the combination of refined carbohydrates and long-chain saturated fat is key. The quantity of highly processed food consumed globally has greatly increased spanning most of the food categories including snacks, reconstituted meat, and soft drinks.[90] There is an association between elevated intake of highly processed food and cardiovascular disease[91] and mortality,[92] both linked to excessive calorie intake and weight gain[93] but also involving unidentified mechanisms. Highly processed foods are relatively inexpensive, have long shelf lives, and are microbiologically safe and highly convenient.[94] However, food processing involves the exposure of food to high temperatures for prolonged periods of time increasing the formation of AGEs.[95]

There is some debate as to the relative importance of dietary AGEs with limited digestion and absorption by the gastrointestinal tract, particularly of high molecular weight AGEs while low molecular dietary AGEs appear to be efficiently disposed of by the kidneys. Nonetheless the restriction of dietary AGEs has been associated with reductions in inflammation and an increase in vascular function in humans,[96,97] while high loads of dietary AGEs have been associated with premature cognitive decline in humans[98] and in animal models fed a high MG diet equivalent to 19 μmol per day.[99] Also feeding NF-κB-luciferase transgenic mice with AGE modified albumin leads to a systemic activation of inflammation.[100] Taken together, these studies strongly implicate dietary AGEs in metabolic dysfunction. However, in contrast two feeding studies showed no effect of dietary AGEs on inflammatory and cardiovascular profiles in humans.[101,102]

A suggested strategy to limit dietary AGE ingestion is the use of DJ-1 deglycases, especially those from thermophilic organisms, to prevent the formation of dietary AGEs during food processing, sterilization, and storage. This class of enzymes would also prevent acrylamide formation in food, likely by degrading the asparagine/glyoxal Maillard adducts responsible for its formation.[103]

Components of the Western diet itself may increase endogenous formation of AGEs. Increased consumption of sucrose, a disaccharide composed of fructose and glucose, is associated with the development of obesity and related diseases. Glucose is the most abundant sugar in the circulation, giving rise to AGEs with its high concentration in diabetes overcoming its relative inactivity. However, the much more reactive dicarbonyls (2–3 times more reactive than glucose) which are only present in much lower amounts are considered the major drivers of AGE formation leading to the concept of dicarbonyl stress when formation exceeds the bodies capacity to detoxify them (see Section5).

The more recent widespread use of fructose as part of the Western diet[104] is highly associated with metabolic syndrome.[105,106] When relatively low levels of fructose are present in the diet, it is metabolized by the small intestine to form glucose and lactate, but higher dietary levels travel to the liver where it is metabolized, first to lactate and glucose, and the excess glucose was converted to lipid. When physical activity is high fructose derived glucose and lactate are efficiently metabolized in muscle.[107] While circulating levels of fructose are much lower than those of glucose, their intracellular levels are similar. However, in diabetes, where the polyol pathway is active, concentrations of fructose are elevated and are thought to be responsible for many of the complications of raised blood glucose.[108] It should be noted that glucose has the slowest rate in the glycation reaction of any sugar in cells while the rate for fructose-dependent intracellular formation of AGEs is 7.5-fold faster than that of glucose.[109]

It is important to note that there are intrinsic problems in comparing AGE concentrations across studies particularly those that measure the AGEs content of foods.[110] These discrepancies are due to the use of different measurement techniques as well as the influence of food matrixes on AGE values obtained. Many of the initial studies on AGE content have used immunobased techniques, including ELISA which do not give absolute values[95] with some assays for measuring AGEs employing antibodies raised against glycated proteins such as AGE-RNase[111] or glyceraldehyde-derived AGE-BSA[112] rather than to specific AGE structures, for example, CML. However, the mass spectrometry techniques used now give absolute concentrations for AGEs such as CML meaning that values can be compared between studies carried out using this methodology.[27,48,110] The same is true for measuring AGEs concentrations in plasma, although to a lesser extent. Thus, care should be taken when comparing AGE

concentrations from different studies. Comparative values for AGEs using these different methodologies have been extensively reviewed elsewhere.[113]

7. AGEs in Metabolic Health: From Type 2 Diabetes to Obesity

7.1. Insulin Resistance and Type 2 Diabetes Mellitus

There is growing evidence of the impact of AGEs on metabolic health. Indeed, apart from playing a pivotal role in diabetic complications, including cardiovascular, kidney and neurodegenerative diseases such as Alzheimer's and Parkinson's disease, AGEs have also been implicated in the pathogenesis of insulin resistance and type 2 diabetes mellitus (T2DM) as well as obesity.[1,18,114–118]

T2DM is a metabolic disorder, which accounts for 90% of the over 400 million individuals affected by diabetes worldwide (https://www.who.int/news-room/fact-sheets/detail/diabetes). It is characterized by chronically elevated circulating glucose levels which arise from a state of insulin resistance in concert with pancreatic β-cell dysfunction. Insulin resistance, the hallmark of T2DM, is described as a blunted response of target tissue to insulin. This results in impaired glucose uptake and glycogen synthesis in the skeletal muscle, increased hepatic glucose production and a decrease in glycogen synthesis in the liver, inhibition of glucose uptake and increased lipolysis in the adipose tissue and impaired control of peripheral glucose homeostasis by the brain. Although, insulin resistance is initially counteracted by a compensatory insulin hypersecretion, when this compensatory response becomes impaired, due to pancreatic β-cells dysfunction, overt T2DM manifests. AGEs can contribute to both pathogenetic features of T2DM by promoting inflammation and oxidative stress in humans.[18]

The low-grade chronic inflammation associated with obesity may be one of the mechanistic links between AGEs and insulin resistance.[118,119] Inflammation promotes insulin resistance by activating intracellular pathways, which in turn, interfere with the insulin signal transduction pathway. Particularly, the activation of JNK has been shown to impair insulin signaling by promoting threonine/serine phosphorylation of insulin receptor substrate (IRS),[120] similarly the activation of the IκB kinase (IKK)/NF-κB signaling pathway has also been shown to inhibit insulin signaling.[121] Importantly, AGEs activate both JNK as well as the IKK/NF-κB signaling pathway supporting the relationship between AGEs and insulin resistance.

In addition to inflammation, the AGE-RAGE axis also triggers oxidative stress, which is associated with the development of insulin resistance.[122,123] The link between AGEs and insulin resistance has been corroborated in studies using animal models. In these studies mice fed a high-AGE diet containing synthetic MG-BSA at 1 mg per g of diet showed a decrease in insulin receptor and IRS phosphorylation, and defective downstream activation of AKT in skeletal muscle, adipose tissue, and liver.[64]

In skeletal muscle, a tissue pivotal for the control of glucose homeostasis, AGEs downregulate GLUT4 and promote the activation of inflammatory pathways as well as endoplasmic reticulum stress as indicated by the upregulation of nuclear factor NF-kappa-B p50 subunit and 78 kDa glucose-regulated protein.[124] Additionally, in both animal models and human studies exposure to high levels of dietary AGEs during fetal development has been shown to trigger metabolic reprogramming which leads to the development of T2DM independently of any genetic predisposition.[125,126]

The detrimental effect of dietary AGEs on insulin signaling in humans has also been demonstrated,[125] with an AGE-restricted diet improving insulin sensitivity in T2DM with a normalization of the expression of AGER1 and sirtuin1 as well as a decrease in NF-κB acetylation circulating TNFα, serum AGEs, and leptin.[63] AGE also directly impact on mitochondrial oxidative metabolism via the downregulation of sirtuin1 which, in turn, deacetylates and activates peroxisome proliferator-activated receptor γ co-activator 1α (PGC 1α), the master regulator of mitochondrial oxidative metabolism.[127] PGC 1α regulates mitochondrial energy metabolism and biogenesis, thus playing a pivotal role in modulating mitochondria bioenergetics, which has been reported to be impaired in individuals affected by T2DM.[128,129] This results in defective oxidative metabolism and impaired ability to completely oxidize fatty acid thus favoring the intramyocellular accumulation of lipotoxic lipid species and metabolites derived from the incomplete oxidation of fatty acids which hamper insulin signaling.[130–132] Importantly, PGC 1α appears to be instrumental in this process as genes under its control are downregulated in individuals suffering from T2DM and its upregulation has also been shown to have insulin sensitizing effects in vitro as well as in animal models.[129,132,133,134]

Thus, given the role of AGEs in disrupting SIRT1 expression and the importance of this NAD-dependent deacetylase in regulating PGC 1α function, defective mitochondria bioenergetics may represent another plausible mechanism linking AGE overload and insulin resistance. The impact of AGEs on insulin resistance in humans has also been confirmed using hyperinsulinemic-euglycemic clamps, the gold standard for the assessment of insulin sensitivity[48] with a low AGE diet inducing an improvement in insulin sensitivity compared to a diet high in AGEs, which decreases insulin sensitivity.[48] Additionally high circulating AGE levels are associated with insulin resistance[111] and correlate with HOMA-IR in nondiabetic subjects.[112] Taken together, the evidence so far supports the role of AGEs as drivers of the detrimental effects of a Western diet on metabolic health.

AGEs also contribute to pancreatic β-cell dysfunction, another key component in the pathogenesis of T2DM. AGEs exert cytotoxic effect on β-cells and induce apoptosis, which may be dependent on ROS production. Studies using primary β-cells and cell lines demonstrate that inhibition of RAGE or antioxidant treatment prevents AGE-induced cell toxicity.[135] Cell culture studies also showed that the molecular mechanism responsible for AGE-induced oxidative stress relies on increased mitochondrial ROS production as well as the activation of JNK which, in turn, activates NADPH oxidase further fueling oxidative stress.[136] Additionally, in a mouse model in which different doses of AGE-BSA were administered by intraperitoneal injection, AGEs not only exerted a cytotoxic effect on pancreatic β-cells, but also impaired glucose-induced insulin secretion. ATP-mediated K^+ channels closure and β-cell depolarization is pivotal in mediating insulin secretion from pancreatic β-cells.

AGEs, by inhibiting mitochondrial cytochrome oxidase,[137] compromise β-cell ATP synthesis capacity causing an impairment in ATP-induced shutdown of K^+ channels, β-cell depolarization and consequently the influx of Ca^{2+} thereby preventing the exocytosis of insulin-containing granules.[138]

Another mechanism which, albeit in part, underlies the ability of AGEs to inhibit insulin secretion is the activation of P38/mitogen-activated protein kinase (MAPK) and the downstream disturbance of microtubule dynamics marked by an increase in microtubule depolymerization in pancreatic β-cells in culture.[139] Finally, AGEs have been reported to interfere with β-cell insulin secretion by directly targeting insulin transcription with a mechanism, which appears to be depended on FOXO-1-induced inhibition of pancreatic-duodenal homeobox factor-1.[140]

7.2. AGEs in the Pathogenesis of Obesity

AGEs, beside their well-documented role in promoting insulin resistance and T2DM, also play a putative role in the pathogenesis of obesity indicated by their ability to induce an increase in body weight in adults in a 5 year follow-up study.[117] Importantly, the ability of AGEs to increase body weight was retained after adjusting for total energy intake and other cofounders, suggesting AGEs directly affect energy balance. This is also supported by the profound impact that diets rich in highly processed food have on body weight by increasing energy intake.[93]

Energy balance is controlled by an intricate, finely-tuned neuroendocrine system.[141,142] The hypothalamus receives and integrates central and peripheral information related to the nutritional status of the individual and responds to these neural, nutritional, and hormonal cues by triggering orexigenic and anorexigenic responses in order to preserve energy homeostasis and maintain body weight within a tight range.[142] Insulin and leptin are the main anorexigenic hormones and inform the hypothalamus, particularly the arcuate nucleus of the hypothalamus (ARC), the master regulator of energy balance, about long- and short-term energy status.[143,144] The ARC encompasses two main neuronal population, the anorexigenic neurons expressing proopiomelanocortin (POMC) and cocaine and amphetamine-regulated transcript (CART), and the orexigenic neurons which express neuropeptide Y (NPY) and agouti-related peptide (AgRP). Leptin and insulin exert their anorexigenic effects by activating POMC/CART while inhibiting NPY/AgRP expressing neurons thus resulting in a decrease in food intake and an increase in energy expenditure.

In light of the central role of insulin in regulating energy balance, insulin resistance may be a mechanism underpinning the ability of AGEs to disrupt hypothalamic control of energy balance.[63,131,133] AGEs can also activate pro-inflammatory pathways; JNK and IKK/NF-κB both of which have been implicated in mediating high-fat diet induced hypothalamic insulin and leptin resistance leading to hypothalamic dysfunction.[145–149] Thus, inflammation represents a further potential mechanism, by which AGEs disrupt energy balance leading to body weight gain. In support of this, a diet high in both lipids and carbohydrates is required to induce a significant increase in hypothalamic inflammation in rodents associated with an increase in body weight.[1,150] The high-fat and high-carbohydrate diet also caused an increase in CML immunoreactivity in both POMC and NPY neurons. It is postulated that AGEs released by hypothalamic neurons promote inflammatory responses by targeting microglia and increasing hypothalamic microgliosis,[1] a central process in high-fat diet-induced hypothalamic dysfunction.[148] The role of AGEs in promoting hypothalamic inflammation was confirmed in animals lacking RAGE and ALCAM which have an improved metabolic phenotype and decreased microglial reactivity on a high-fat diet.[1]

8. Conclusions

AGEs are adducts formed during cooking and food processing or produced endogenously as a consequence of metabolism. The Western diet contains elevated levels of highly processed foods and as such represents a source of AGEs, which contributes to promoting obesity, insulin resistance, and deterioration in metabolic health. The deleterious effects of AGEs are underpinned by their ability to trigger mechanisms well known to elicit metabolic dysfunction, including the activation of inflammatory pathways, oxidative stress, and impaired mitochondrial oxidative metabolism. Although, most of the evidence related to the role of AGEs in metabolic health highlights their role in promoting insulin resistance and β-cell dysfunction, emerging evidence supports the possibility that AGEs may directly impact upon the hypothalamic control of energy balance leading to body weight gain and metabolic dysfunction. Thus, strategies aimed at preventing or reducing AGE production during food processing and cooking or preventing the endogenous accumulation of AGE precursors, for example, the dicarbonyls, may represent a further strategy to implement in order to mitigate the impact of the Western diet on metabolic health.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

advanced glycation end products, inflammation, metabolic dysfunction, processed foods, Western diet

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