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Review

Gut Metabolism of Sugars: Formation of Glycotoxins and Their Intestinal Absorption

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Abstract: Glycotoxins include the group of advanced glycation end-products (AGEs) and their precursors, most of them highly reactive intermediary compounds of sugar metabolism. Glycotoxins and products of the Maillard reaction are present in high concentrations in foods rich in sugars and processed at high temperatures and are often associated with the flavour of the food. Proteins undergoing this type of molecular modification are targets for gut peptidases and may be absorbed into circulation. AGEs are associated with the toxic effects of glucose in diabetic patients, and some studies have shown that they also contribute to metabolically unhealthy obesity and prediabetes development. Restriction of dietary glycotoxins was shown to improve insulin resistance in humans. However, the real contribution of dietary AGEs to such mechanisms is still not understood. This review summarizes the current knowledge about glycotoxin formation from dietary sugars, their digestion throughout the gastrointestinal system, and the mechanisms of their intestinal absorption.

Keywords: glycation; glycotoxins; dietary sugars; AGEs digestion; intestinal absorption; gut microbiota

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1. Introduction

Free sugars are often very reactive and are non-enzymatically degraded under physiological conditions, leading to the formation of intermediary compounds that may react with other molecules and cause harmful effects. This pool of intermediary and advanced products is generally called glycotoxins. This is a heterogeneous group of compounds that includes advanced glycation end-products (AGEs) and their precursors, most of them highly reactive intermediary compounds. Methylglyoxal (MG) is a dicarbonyl and a major precursor that originates as a by-product of glucose and fructose metabolism (reviewed by [1]). It modifies arginine and lysine residues of biomolecules, namely, proteins and DNA, forming AGEs [1–4]. The AGEs Nδ-(5-hydro-5-methyl-4-imidazolon-2-yl)-ornithine (MG-H1) and argpyrimidine are formed after MG-induced arginine modification, whereas lysine modification leads to methylglyoxal lysine dimer (MOLD) and (carboxyethyl)lysine (CEL) formation [5–8]. Alternatively, NE-(carboxymethyl)-lysine (CML), one of the major AGEs, may be formed directly from the Maillard reaction between lysine residues and reducing sugars, fructose being more harmful than glucose [1]. Such reactions may occur intracellularly (cytoplasmic proteins and transcription factors) or with circulating (haemoglobin, albumin, or lipoproteins) extracellular matrix and food proteins [1–4,9]. The endogenous formation of MG-derived AGEs has been associated with diabetes-like vascular and metabolic complications. Their contribution to nephropathy and retinopathy

has been consistently shown, not only due to direct effects on endothelial cells but also on podocytes and pericytes. In the development of the diabetic foot, glycotoxins have been shown to contribute both to vascular dysfunction and neuropathy, leading to hypersensitivity of nerve fibres and neuronal degeneration (reviewed by [1,8]). They have also been shown to cause insulin resistance, mainly in already obese models and beta-cell dysfunction. Although a few reports show that their decrease in diet may reduce insulin resistance in diabetic patients, rodent models of AGEs supplementation fail to show insulin resistance. Otherwise, if AGE supplementation is made to high-fat diet-fed rodent models, they potentiate the diet's effects and trigger insulin resistance (reviewed by [10]). Glycotoxins and AGEs are well-known contributors to a myriad of other metabolic disease-related disorders. Their contribution has been shown in cardiovascular and cerebrovascular diseases due to endothelial dysfunction in macrovessels, alterations in cardiac muscle contractility/relaxation, tendon stiffness, and even rheumatoid arthritis. Glycotoxins have also been linked with the molecular mechanisms of central nervous system disorders, namely, mitochondrial dysfunction and oxidative stress in Alzheimer's disease and glycation of alpha-synuclein in Parkinson's disease (reviewed by [1,8,11]).

Modification of intracellular proteins by dicarbonyls like MG changes the cellular redox state (oxidative and nitrosative stress), proteasomal activity, and gene expression modulators, while modification of extracellular and circulating proteins leads to increased stiffness of the matrix and alteration of biological properties of circulating factors, such as hormone loss of function and modification of albumin and haemoglobin [1]. MG may be detoxified into D-lactate through the glyoxalase system (GLO-1 and GLO-2), while AGEs and their intermediary Amadori products, such as fructoselysine, may be cleared by amadoriases. Of those, the fructosyl amine oxidase (FAOX) amadoriase, it is the most well studied and characterized for its catalytic activity, cleaving the adducts between sugars and amino acids. Other enzymes include amadoriase II and other amadoriases occurring in other organisms (reviewed by [1,12]). The GLO system is GSH-dependent and its downregulation is associated with higher endogenous AGE formation and the development of diabetic complications in humans and animal models [8].

Despite their quantitative contribution to the circulating pool is not completely understood, glycotoxins may also originate in the diet, namely, in foods rich in sugars and cooked at high temperatures. Using human serum albumin as a model, the dicarbonyls glyoxal and methylglyoxal have been shown to modify the lysyl and arginyl groups in 9 and 14 sites, respectively [13]. Although this depends on each specific protein and the sugars involved, sugar-rich foods and cooking also lead to the initiation of similar reactions involving food proteins. Even in healthy individuals, circulating AGE levels are correlated with their intake, contributing to the endogenous pool of AGEs and activation of inflammatory signals [14–16]. Intestinal absorption of glycotoxins and AGEs has been shown, as well as their deposition in tissues [17]. In foods, the initial steps of the Maillard reaction originate from such Amadori products as fructoselysine and lactuloselysine and AGEs, which are estimated to be consumed on a scale of daily 500–1200 mg in the diet. About 25–75 mg are estimated to be AGEs. Pasteurized milk and bakery products are the main dietary sources of Amadori products [18,19]. However, the digestion and absorption processes are very different among distinct AGEs, imposing extra difficulties in their study.

Although AGEs may be absorbed from the diet, mainly through the Maillard reaction, in sugar-rich foods, there are also other components that may prevent such reactions. The presence of antioxidants and scavenging molecules may hamper AGE formation, although this is still mostly unknown ground. Nevertheless, pectin oligosaccharides were recently shown to prevent food browning (Maillard reaction) and inhibit AGE formation. This is a complex group of non-digestible oligosaccharides originating from pectin, present in the plant cell wall. These compounds also reduced intestinal absorption in an in vitro system, suggesting their use as a dietary supplement to prevent food glycation [20]. Another way to promote the detoxification of AGEs is through the ingestion of vegetables, fruits, and

natural foods rich in phenolic compounds, which have anti-glycating [21] and antioxidant activity [22,23].

2. Formation of Glycotoxins in the Gut and Their Digestion

Advanced glycation end-product (AGE) formation during carbohydrate digestion: Carbohydrates can be found in the most varied sources: they can be intrinsic to fruit and milk or they can be added to food (extrinsic sugars) to increase palatability and conservation [24]. In recent times, the new habits of the world population are associated with a greater consumption of sugars and consequently AGEs. In general, AGEs provide greater palatability and help to increase shelf life [25]. Although food is an important exogenous source, they may also be produced during digestion, becoming an endogenous source of AGEs [14] (Figure 1). The energy value offered by sugar is 4 kcal g^{-1}, and the recommended intake of carbohydrates is based on the minimum amount of sugar consumed by the brain, which is 130 g day^{-1} for both adults and children [26]. Despite this, the actual consumption is above the recommended daily average, according to the Centers for Disease Control and Prevention [27]. The increased consumption of sugars is directly related to the development of obesity, type 2 diabetes, and associated pathologies [23].

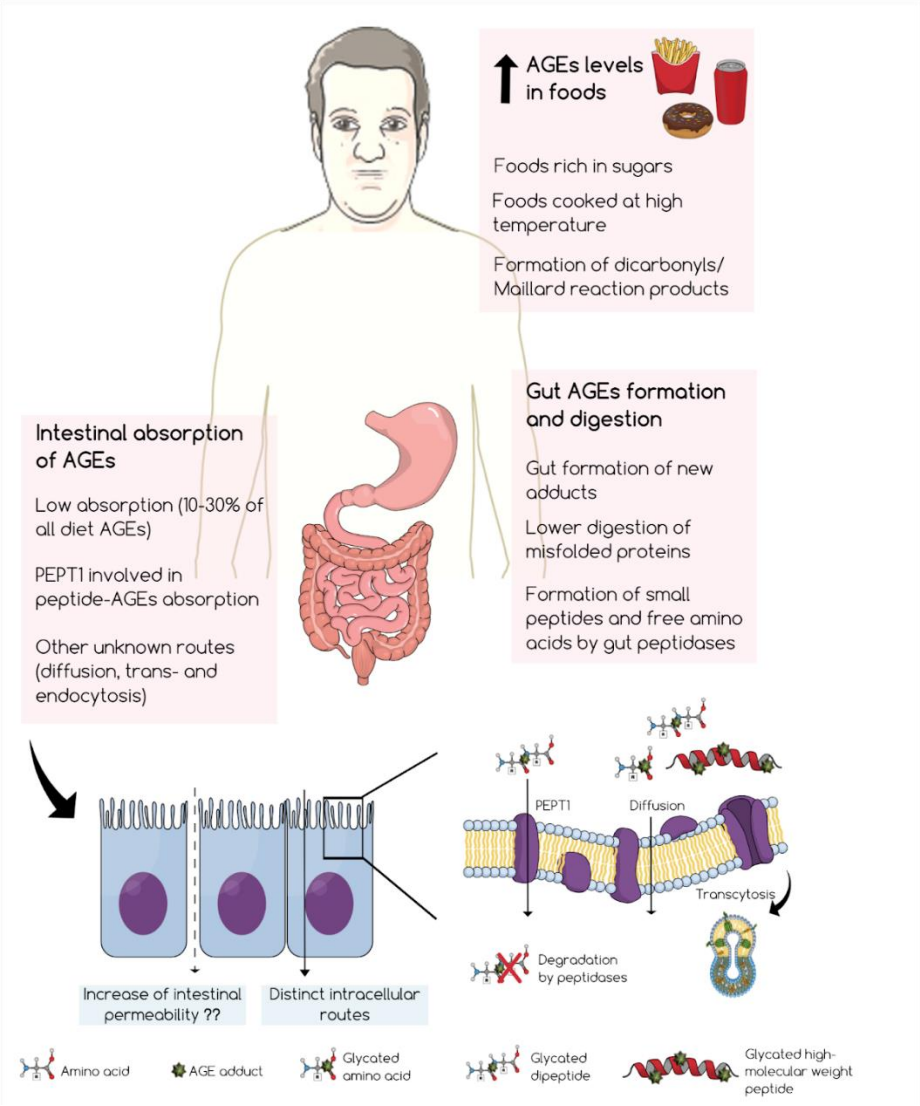

Figure 1. Overview of the events involved in glycotoxin consumption from sugar-rich foods, their digestion in the gastrointestinal tract, and their intestinal absorption. The lower part of the image shows the different mechanisms described to be involved in intestinal AGE absorption.

Carbohydrate digestion begins in the mouth with the entire physical and chemical process that occurs with the concomitant action of α-amylase and the subsequent effect of pancreatic amylase, located in the small intestine, which is responsible for the digestion of 60% of carbohydrates. Then, the monosaccharides are absorbed by enterocytes into the bloodstream through intestinal epithelial cell enzymes [28]. Finally, they are transferred to cells to participate in energy production, which can be aerobic or anaerobic [29], and are eventually oxidized [30]. As consequence of the exaggerated intake of sugars, the reactions that occur from glucose with the body's proteins give rise to dicarbonyls and AGEs, which gradually accumulate in the body. One of the sugar-driven modifications is the case of glycated haemoglobin (HbA1c), a biochemical marker of glycaemic control in diabetic patients, which reflects the mean glycaemia of the last 90 to 120 days [31].

In addition to the ingestion of exogenous AGEs, their formation can occur through chemical processes of food degradation. Diet-derived MG interacts with intestinal proteins and culminates in the formation of the derivative of arginine MG-H1, which is absorbed in the intestine by enterocytes [32]. In simulations of digestive conditions, the concentrations of these AGEs were reduced in the presence of pancreatic enzymes. Regarding MG, its stability is greater in the gastric juice, but its degradation occurs in the intestinal juice, which probably is related to an enzymatic action [33]. It is believed that the digestive characteristics of AGEs in general lead to their susceptibility to the metabolism of reversibly bound adducts during digestion, and may later promote some local or systemic effect if they are reabsorbed [34] (Figure 1).

For the digestion of AGEs, gastric and intestinal functions are critical and depend on the function of such enzymes as elastase, peptidases, trypsin, and chymotrypsin. Glycation of arginine and lysine residues may directly block the trypsin site (which occurs by the attraction of negative charges between the trypsin active centre (negatively charged) and the amino acid groups (positively charged), being responsible for the impairment of the protein digestive process. Additionally, this modification may also hinder the effect of other digestive proteases, such as β-lactoglobulin and β-casein [35]. On the other hand, in another study, it was confirmed that alterations in the conformation of lactoferrin, caused by glycation, can lead to greater exposure of cleavage sites, increasing susceptibility to proteolysis [36]. The anti-digestion profile of AGEs ends up functioning as a natural barrier against the absorption of AGEs that are bound to proteins, because they have a lower bioavailability than free fractions [37].

Other studies with mice revealed the formation of specific AGEs from dietary sugars, namely, the detection of AGEs derived from MG in the liver tissue after glucose intake, and the detection of glyoxal (GO) when ingesta were based on fructose [32]. A study carried out by Martínez-Saez [38], which aimed to define the products derived from the Maillard reaction from meals, determined that physiological concentrations of sugars (43 mM) already caused the formation of these products. Fructose at a concentration of 314 mM was able to promote the formation of fructosamine and other AGEs, and fructose at 43 mM with lysine was able to give rise to CML [38]. In another assay, where different products obtained from gastric and intestinal digestion were analysed, namely, CEL, CML, MG-H1, and hydroimidazolone 1 derived from GO (G-H1), the binding of these structures in the free form associated with proteins was observed, showing that the link between both survives after the gastrointestinal digestion process, in addition to having the ability of entering the human gastrointestinal tract and triggering a pro-inflammatory environment [39] (Figure 1).

Regarding conformational changes, dietary glycated proteins may naturally trigger changes that can play an important role in the digestion of these sets of glycated amino acids. Studies show that the non-cross-linked structures display a reduction in the digestibility of the glycated protein, as occurred with CML-casein. When submitted to a proteolysis procedure, its digestibility was considerably lower than the native casein [40]. This condition is probably associated with a reduction in molecular accessibility that allows the cleavage of the main chain of the protein. In this context, AGEs that have non-crosslinked structures, such as CMA, CML, and pyrraline, originate from the covalent alteration of residues of

arginine and lysine, and because of this change, can cause trypsin blockage in the intestinal digestion process [9].

The role of gut microbiota and sugar/AGE metabolism: Several recent studies have brought evidence that relates the imbalance of the intestinal microbiota caused by the intake of sugars with insulin resistance, diabetes, obesity [41–43], and metabolic syndrome, by interrupting the immune-mediated protection necessary for body homeostasis [43]. Leptin-deficient ob/ob mice, for example, have a completely different microbial composition from normal mice, and the different taxa observed suggest the existence of a microbiota–host cross-talk that relates body composition to the metabolism of animals [42]. Although so far not many details are known about the metabolism of AGEs, there are reports regarding the probable action of the intestinal microbiota in this process, especially regarding Amadori products. This is based on a recent characterization of bacterial enzymes (fructoseamine-6-kinase) that allow the metabolism of these products by different bacteria, such as *Escherichia coli* [44].

In a study carried out by Mastrocola [45], it was reported that a diet enriched with MG-H1 can cause an increase in tissue AGEs, which culminated in an inflammatory imbalance and an alteration in the homeostasis of the intestinal microbiota. It has been proven that the faecal excretion of AGEs does not exceed 50%, and thus it is believed that AGEs are neither absorbed nor excreted and can be metabolized intraluminally by the intestinal microbiota itself. Bacteria such as *Anaerostipes*, *Candidatus Arthromitus*, *Bacteroidales*_S24-7, *Ruminococcus*, and *Prevotella*, among others, in general (not yet fully understood) are related to the maintenance of the immune system, regulation of the intestinal inflammatory process, insulin sensitization, have a direct relationship with metabolic diseases such as obesity and diabetes, and may undergo changes in their colonies due to the presence of AGEs in the gut [45]. Finally, in another study, this one carried out by Wang, in a trial where AGEs were also supplemented in the diet of animals, the authors also identified a negative change in *Bacteroidales*_S24-7, *Ruminococcaceae*, and related this condition with increased insulin resistance and a process of chronic inflammation [46].

3. Intestinal Absorption of Glycotoxins

Dietary AGE bioavailability: Whether dietary glycotoxins are absorbed at the intestinal level and contribute to the endogenous pool is still under debate, and several studies suggest that dicarbonyls and some AGEs may be scavenged and eliminated during digestion [47]. In studies carried out on humans, it was possible to detect mainly MG and GO after glucose intake [48]. However, in another human study carried out with a physiological intake of MG, it was not possible to detect MG or its metabolites in urine [33], suggesting that MG is possibly not absorbed into the bloodstream [32]. However, questions also remain about the methods to measure AGEs and their intermediaries in the circulation. Although several antibodies and kits are available for specific AGEs, they require further validation, because the epitope is an adduct and not an amino acid sequence. Even more complicated is the detection of intermediaries like carbonyls. For instance, MG detection is often made by high-performance liquid chromatography after derivatization. In fact, the most reliable method is mass spectrometry, as stated by Schalkwijk in his work (reviewed by [8]).

About 80% of all Amadori products are degraded by the intestinal flora and do not become AGEs. Moreover, recent evidence suggests that, of all AGEs in the diet, only about 10% are absorbed into the circulation and at least about 30% of these are excreted by urine, being this excretion percentage is higher for free AGEs than peptide-bound AGEs [16]. This was recently observed for the commonly found AGEs CEL, CML, and MG-H1 [49,50]. In animal models, CML accumulation in tissues was observed after consumption of an AGE-enriched diet. Higher concentrations were observed in the kidney, intestine, and lungs (81–320 μg CML g^{-1} dry matter), although it was also found in cardiac tissues, muscle, liver, and tendons [9]. Nevertheless, other studies did not find any correlation between dietary AGEs and free and peptide-bound AGEs in circulation [16]. The percentage of urinary recovery varies according to the type of AGE and the individual/model studied. For instance, faecal excretion of dietary CML was shown to be related to its dietary intake in

adolescents, but its urinary excretion apparently has a progressive saturation [15]. Dietary pyrraline was described to be recovered in 50% in urine samples, while the free form of fluorescent AGE pentosine was found in up to 60% in urine after ingestion. For peptide-bound pentosane, the urinary recovery was much lower [51]. Free AGEs/glycated amino acids and protein-bound AGEs have distinct bioavailability and their renal excretion may vary according to several factors, such as kidney function, which is often compromised in diabetic patients. In healthy subjects, free AGEs are excreted much more, in part because protein-bound AGEs are reabsorbed in the proximal tubule, although it is also expected that their filtration rate could also be different [16]. However, such mechanisms may be completely different in patients with chronic kidney disease. In both healthy subjects and patients, these measures do not really inform about intestinal absorption, since AGEs may suffer conversion in the gut or after absorption or may simply be retained in tissue.

Mechanisms of dietary AGE absorption: Glycated peptides in general have much less affinity to membrane transporters than native amino acids [9]. Free and peptide-bound AGEs are likely to have distinct intestinal absorption mechanisms. AGEs bound to low-molecular-weight peptides like dipeptides were shown to be absorbed by the peptide transporter (PEPT1). These peptide-bound AGEs are later degraded by peptidases inside the enteric cells, appearing as free AGEs on the basolateral side [52] (Figure 1). This was observed, for instance, for pyrraline linked to alanine, but is less observed for other AGEs, suggesting that these mechanisms are AGE-specific [53]. AGEs bound to high-molecular-weight peptides, such as CML, argpyrimidine, or MG-H1, are most likely absorbed by simple diffusion, because they were shown not to inhibit the transport of endogenous ligands of the transporters, namely lysine transporters [54]. This type of AGE needs previous intestinal degradation before absorption, although hydrophobic AGEs like argpyrimidine were shown to pass the intestinal barrier more easily [52]. Transcytosis is also an alternative route of absorption for this type of AGE, although it is not expected to account for the major number of AGEs absorbed. A recent report on *C. elegans* showed that dietary CML may be effectively absorbed by endocytosis in the intestine wall [55]. Interestingly, free AGEs (single modified amino acids) were also shown to be poorly absorbed by peptide transporters and were suggested to be absorbed in low contents by simple diffusion [52]. It may be hypothesized that AGEs have different routes for absorption, considering not only their size but also their hydrophobicity and charge. It is also of note that lumen peptidase may have a role in preventing AGE absorption by cleaving peptides into single amino acids, which have been consistently shown to be poorly absorbed [37]. Furthermore, changes in protein conformation resulting, for instance, from cooking may alter these mechanisms, although further studies are necessary. One main concern about the absorption studies is that some of them are performed in cultured monolayer CACO-2 cells, which may not properly mimic in vivo conditions. Not only the transport system of these cells may be different but also the intracellular machinery responsible for AGE hydrolysis, which has major relevance for their absorption. Another major concern regarding the impact of dietary AGEs is that intestinal permeability has been shown to be increased in metabolic disorders and to be potentiated by poor dietary habits. It is possible that a significant number of dietary AGEs may be absorbed by intercellular transport due to a decrease in barrier integrity, while this is yet to be studied.

Inhibition of AGE intestinal absorption: As mentioned, foods rich in antioxidants and scavenging molecules may prevent intestinal absorption of Maillard reaction products and specific AGEs. However, specific products from the diet can directly inhibit AGE absorption. As also mentioned, pectin oligosaccharides were shown to reduce intestinal AGE formation and absorption at least in in vitro systems [20]. Other compounds, such as catechins and chlorogenic acid, were recently shown to inhibit AGE absorption in vitro [21,56]. Gut microbiota are a major player in degrading many of the diet's nutrients and components, and AGEs are no exception. Recently, it was shown that *Lactococcus lactis* bacteria can degrade dietary CML, mainly through β-galactosidase activity, significantly reducing intestinal absorption in healthy volunteers [57]. Nevertheless, the knowledge about this

topic is still scarce and the discovery of new compounds able not only to prevent gut AGE formation but also their absorption may be a promising research area toward the prevention of harmful effects. In fact, several compounds have been shown in the last few years to scavenge glycotoxins in vitro and some were tested in vivo. Of those molecules, aminoguanidine, pyridoxamine, NAC, resveratrol, and sulforaphane stand out. However, few reports suggest their action in clearing dietary glycotoxins (reviewed by [1,8,58]). Some of them are known activators of NRF2, suggesting that could have beneficial effects on gut anti-glycation defences, although no studies have been reported in this topic. Thus, more research is needed in order to identify molecules able to directly scavenge dietary glycotoxins or to promote their clearance by the gut microbiota.

4. Conclusions and Future Perspectives

Glycotoxins are a heterogeneous group of compounds that were initially observed to contribute to the development of diabetic complications due to their increased endogenous formation from glucose. Later, data revealed their increased formation and accumulation in tissues, since earlier stages of the disease result from the dysregulated activity of detoxification systems and increased dietary consumption, namely, from high-glucose and high-fructose foods processed at high temperatures.

Despite the little information obtained so far, we have brought here what we already have about the deleterious effect of AGEs and the glycation of target molecules on the whole that involves the process of metabolizing AGEs in the GUT and the triggering of metabolic diseases, immunological and inflammation and nutritional homeostasis. Additionally, the microbial fraction also has incredible importance regarding the molecules absorbed, and the presence of certain strains is often mandatory for the development of physiological and pathological processes.

Its intestinal absorption seems to be AGE-dependent and is apparently more facilitated by AGEs linked to small peptides through peptide transporters. Other routes of absorption have also been suggested for free AGEs and AGEs linked to high-molecular-weight peptides, although their true role in the in vivo absorption of dietary AGEs is still to be proven. Nevertheless, the presence of dietary AGEs in circulation and urine is constant in several studies and the mechanisms of passage through the intestinal barrier should be addressed in the future. Additionally, the identification of molecules able to prevent their absorption may be of significance to reduce their biological impact.

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Abbreviations

AGEs	advanced glycation end-products
CEL	(carboxyethyl)lysine
CMA	pg 8 só
CML	NE-(carboxymethyl)-lysine
G-H1	hydroimidazolone 1 derived from glyoxal

GLO	glyoxalase system
GO	glyoxal
MG	methylglyoxal
MG-H1	Nδ-(5-hydro-5-methyl-4-imidazolon-2-yl)-ornithine
MOLD	methylglyoxal lysine dimer
PEPT1	peptide transporter

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