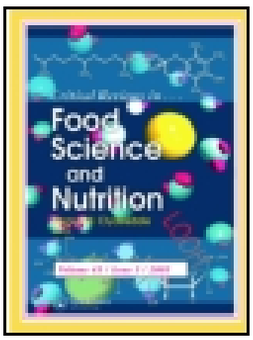

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REVIEW

The fate of dietary advanced glycation end products in the body: from oral intake to excretion

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ABSTRACT

Advanced glycation end products (AGEs), which are closely associated with various chronic diseases, are formed through the Maillard reaction when aldehydes react with amines in heated foods or in living organisms. The fate of dietary AGEs after oral intake plays a crucial role in regulating the association between dietary AGEs and their biological effects. However, the complexity and diversity of dietary AGEs make their fate ambiguous. Glycated modifications can impair the digestion, transport and uptake of dietary AGEs. High and low molecular weight AGEs may exhibit individual differences in their distribution, metabolism and excretion. Approximately 50–60% of free AGEs are excreted after dietary intake, whereas protein-bound AGEs exhibit a limited excretion rate. In this article, we summarize several AGE classification criteria and their abundance in foods, and in the body. A standardized static *in vitro* digestion method is strongly recommended to obtain comparable results of AGE digestibility. Sophisticated hypotheses regarding the intestinal transportation and absorption of drugs, as well as calculated physicochemical parameters, are expected to alleviate the difficulties determining the digestion, transport and uptake of dietary AGEs. Orally supplied AGEs with low or high molecular weights must be supported by well-defined amounts in investigations of excretion. Furthermore, unequivocal evidence should be obtained regarding the degradation and metabolism products of dietary AGEs.

KEYWORDS

Absorption; classification criteria; digestion; distribution; excretion; Maillard reaction; metabolism

Introduction

Advanced glycation end products (AGEs) are compounds derived from reducing saccharides that are nonenzymatically attached to proteins and nucleic acids (Vlassara, Brownlee, and Cerami 1984). On the basis of differences in their origins, AGEs primarily include two classes: biologically-derived AGEs (biological-AGEs) and food-derived AGEs (food-AGEs or dietary AGEs, d-AGEs). Biological-AGEs have been reported to be toxicants closely associated with various chronic diseases, in particular, diabetes (Yan, Ramasamy, and Schmidt 2008; Milne and Brownstein 2013) and kidney disorders (Busch et al. 2010; Mallipattu and Uribarri 2014; Rabbani and Thornalley 2018). Numerous studies have aimed to alleviate the health risk associated with AGEs. Restricting d-AGE intake or consuming a low-calorie diet can alleviate the burden of health risks associated with AGEs (Gugliucci et al. 2009; Snelson, Clarke, and Coughlan 2017). Cathepsins D and L are essential for decreasing AGE-induced cytotoxicity (Grimm et al. 2012). Pioglitazone treatment inhibits AGE-induced classical macrophage activation (Jin et al. 2016).

For the d-AGEs, preliminary food restriction experiments have indicated that food intake is a causative factor in glycation levels *in vivo* (Aoki et al. 1992a, 1992b; Sell 1997; Koschinsky et al. 1997; Teillet et al. 2000). Subsequent investigations of oral ingestion in animals have suggested a significant association between dietary AGE content and circulating or tissue AGE levels. Decreased dietary AGE is correlated with a ~40% decrease in circulating AGE levels (Lin et al. 2002). A low-AGE diet can markedly alleviate the burden of serum AGEs in both diabetic and nondiabetic mice (Lin et al. 2003). Regular consumption of d-AGEs in healthy individuals promotes carboxymethyllysine (CML) accumulation in some organs, such as the kidneys, heart, liver, tendons and lungs (Roncero-Ramos et al. 2014; Li et al. 2015a, 2015b). Similar results have frequently been reported in clinical investigations of human populations (Koschinsky et al. 1997; Vlassara et al. 2002; Uribarri et al. 2003a, 2003b).

Therefore, the absorption and elimination of d-AGEs strongly affect the associated health risk. Förster, Kühne, and Henle (2005) have reported the recovery of approximately 50% of pyrraline and 60% of pentosidine in urine samples after the ingestion of food containing defined

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amounts of AGEs. Uribarri et al.'s (2005) comprehensive review has concluded that d-AGEs are directly absorbed into the circulation and contribute to the body's AGE pool. However, the health risks of d-AGEs are not convincingly demonstrated by the relationship between d-AGEs and biological-AGEs. More convincing evidence could be obtained by determining how the modulation of AGE load by d-AGEs influences health risk behaviors in clinical, laboratory and observational studies. There is an interdisciplinary debate regarding the health risk of d-AGEs. Ames (2007) has supported the notion that d-AGEs are not a risk to human health; however, Sebekova and Somoza (2007) have provided some evidences contradicting this notion. Thus, it is probably prudent to state that a high AGE diet may contribute to risk factors associated with chronic diseases (Luevano-Contreras and Chapman-Novakofski 2010; Clarke et al. 2016). Additionally, d-AGEs modulate the AGE load, at least in patients with chronic diseases, such as diabetes, renal failure, overweight or obesity (Uribarri et al. 2015; Yamagishi and Matsui 2016; Luevano-Contreras et al. 2017).

Consequently, d-AGEs are an emerging concern for the processed food industries (Sharma et al. 2015). Numerous studies have focused on d-AGE formation in model systems (Morales and van Boekel 1997; Pellegrino, De Noni, and Cattaneo 2000; Smales, Pepper, and James 2000) and the identification and quantification of AGEs in commercial food products (Utzmann and Lederer 2000; Pellegrino and Cattaneo 2001; Goldberg et al. 2004). Furthermore, extensive studies have shown that some natural products, such as quercetin (Li et al. 2014; Navarro and Morales 2017), resveratrol (Buttari et al. 2013; Sheng et al. 2016; Shen, Xu, and Sheng 2017) and polyphenols (Zhang et al. 2014; Yoon and Shim 2015; Grzegorczyk-Karolak et al. 2016) can decrease AGE formation in food or *in vivo*.

Because AGEs can exist in food and living organisms, their complexity and diversity may result in obscure differences between d-AGEs and biological-AGEs. Although the biological effects, formation, quantification and inhibition of d-AGEs have been extensively investigated and well-reviewed, limited attempts have been made to ascertain and summarize the fate of d-AGEs from dietary intake to excretion. In addition, no review has attempted to use a cross-disciplinary approach incorporating pharmaceutical sciences and structural chemistry to critically assess this issue.

This review was undertaken to rethink the fate of d-AGEs including digestion, absorption, distribution, metabolism and excretion. The flow diagram of the review is shown in Figure 1. The diagram of d-AGE fate after oral intake is presented in Figure 2. To gain insights into the complexity and diversity of AGEs, we systematically classified AGEs according to different criteria, such as their structure and active carbonyl precursors. Our objective was to identify gaps in the current understanding of d-AGEs and generate insight into the most important roadblocks to understanding the fate of d-AGEs in the body.

The structure, properties, and existence matrices of AGEs

Because of the complexity and diversity of AGEs, understanding their structure is crucial and necessary before exploring the fate of d-AGEs.

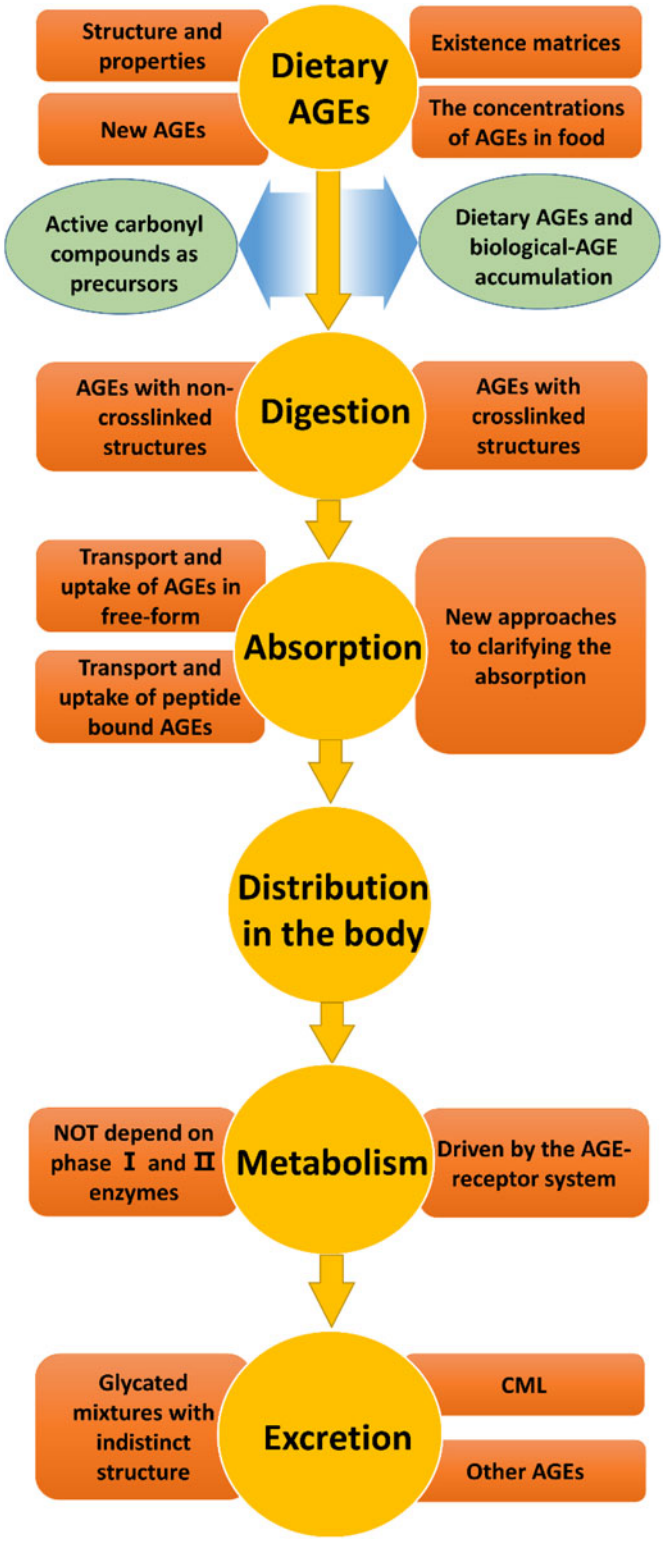

Figure 1. Flow diagram of the systematic review.

The structure and photophysical properties of AGEs

AGEs are a heterogeneous group derived from reducing saccharides that attach nonenzymatically to amino acids, peptides, proteins and nucleic acids. To date, at least four criteria are used for AGE classification: photophysical properties, existence matrices, amino acid residues and structural prototypes.

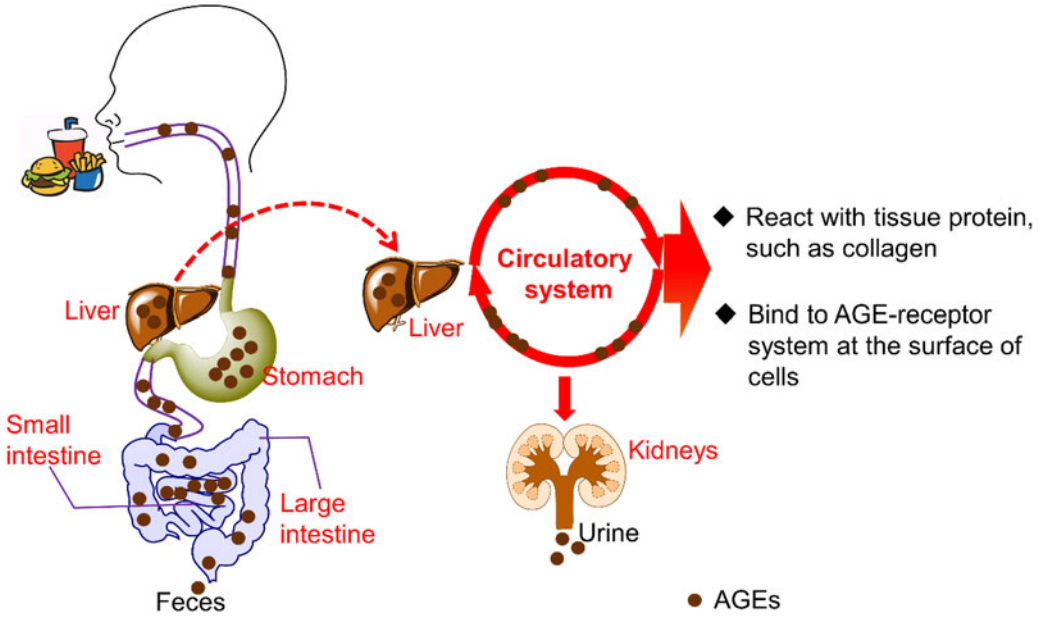

Figure 2. The fate of dietary AGEs after oral intake.

To better understand AGEs, Professor Harry Nursten (Nursten 2005) has classified AGEs into six distinct groups based on structural prototypes. This classification depends on the amino acid involved and whether the glycation affects that residue alone or results in crosslinking to another amino acid. In his book, approximately forty AGEs associated with lysine and arginine residues are included and classified. In fact, more than forty AGEs have been found, because different saccharides and amino acids can participate in the Maillard reaction. However, a considerable amount of published literature has focused on AGEs with a lysine residue, arginine residue or both. The ε-amino group of lysine and the guanidinium group of arginine have higher reactivity than the α-amino group when they react with saccharide; therefore, AGEs with lysine, arginine or both are more easily detected and investigated than other AGEs.

AGEs with lysine, arginine or both, and their physicochemical properties, are presented in Table 1. The presence of AGE species can be preliminarily confirmed from structural prototypes of AGEs. For example, CML and pyrraline are produced mainly from food or biological matrices with lysine involved; argpyrimidine and THP are mainly derived from food or biological matrices with arginine involved. Therefore, a preliminary result regarding the probability of the presence of AGEs species can be obtained when amino acid composition and content are determined.

On the basis of photophysical properties, AGEs can be categorized according to ultraviolet-visible (UV-Vis) absorption, fluorescence, both and neither. The photophysical properties can be used to monitor AGEs through instrumental analysis. AGEs with distinct photophysical properties can be easily separated and purified from complex mixtures through liquid chromatography with a UV detector or fluorescence detector. However, some AGEs have neither UV absorption nor fluorescence, such as CML, CEL, and carboxymethylarginine (CMA). These AGEs can be determined by mass spectrometry. In fact, the photophysical properties of AGEs are derived from their structure. Conjugated systems usually have UV or visible absorption because overlap of the π orbitals allows the electrons to be delocalized over the whole system. For example, UV absorption of pyrraline and pronyl-lysine is driven by their cyclic or linear conjugated systems. Most fluorescent compounds have an aromatic structure. A few highly unsaturated aliphatic compounds are also fluorescent. Generally, AGEs with coumarin, quinoxalinone and benzoxazinone structures are fluorescent (Azuma et al. 2003), such as pentosidine, argpyrimidine and vesperlysine A. As shown in Table 1, one interesting finding is that most fluorescent AGEs have UV-Vis absorption properties; conversely, AGEs with UV-Vis absorption may not be fluorescent. This finding is consistent with the π-electron system in fluorescent AGE also leading to UV-Vis absorption. The UV-Vis absorption and fluorescence peak region in Table 1 are empirical data from previous studies. The fluorescence and UV-Vis absorption characteristics of these compounds are solvent-dependent and pH-dependent. Therefore, some shifts in UV-Vis absorption and fluorescence peak region can occur when these AGEs exist in different solvents or pH solutions. For instance, the UV absorbance maximum of pentosidine dissolved in 0.1 M HCl has been observed at 325 nm (Słowik-Żłka et al. 2004), but it shifts to 320 nm in solution with pH values from 2 to 12 (Sell and Monnier 1989). When an AGE molecule is surrounded by solvent molecules, the stability of its ground and excited states is influenced by solute-solvent interactions (Hu et al. 2018), depending on the chemical nature of both AGE and the solvent molecules. The acid-base properties of AGEs in the ground and excited states depend on the pH of the solution, which influences proton ejection in the excited state and proton back-recombination in the π-electron system (Erez et al. 2014).

Existence matrices of AGEs

Biological-AGEs are formed in the body's circulation or tissues at physiological conditions, and d-AGEs are produced

Table 1. AGEs with lysine residues, arginine residues or both, and their photophysical properties.

		Photophysical properties		Existence matrices		
Classification criteria	AGE monomer	UV absorption	Fluorescence	In food[a]	In body[b]	References
Structure with lysine residue	CML	N	N	Y	Y	(Hull et al. 2012; Li et al. 2015a)
	CEL	N	N	Y	Y	(Ahmed et al. 1997; He et al. 2014)
	GALA	N	N	N.R.	Y	(Glomb and Pfahler 2001; Sell and Monnier 2012)
	Pyrraline	298 nm	N	Y	Y	(Miyata and Monnier 1992; Rufián-Henares, Guerra-Hernández, and García-Villanova 2004)
	AFGP	300 nm	N	N.R.	Y	(Farmar, Ulrich, and Cerami 1988; Makita et al. 1992)
	Pronyllysine	363 nm	N	Y	N.R.	(Lindenmeier, Faist, and Hofmann 2002; Selvam et al. 2009)
	Trihydroxy-triosidine	276 nm	N	N.R.	N.R.	(Tessier, Monnier, and Kornfield 2002; Tessier et al. 2003)
	Triosidine-carbaldehyde	297 nm	N	N.R.	N.R.	(Tessier, Monnier, and Kornfield 2002; Tessier et al. 2003)
Structure with arginine residue	Carboxymethylarginine	N	N	N.R.	Y	(Iijima et al. 2000; Odani et al. 2001)
	Carboxyethylarginine	N	N	N.R.	Y	(Alt and Schieberle 2005; Smuda et al. 2015)
	S12	235 nm	λ_{ex} 370 nm; λ_{em} 450 nm	N.R.	N.R.	(Hayase, Konishi, and Kato 1995; Hayase et al. 2005)
	S11	235 nm	λ_{ex} 370 nm; λ_{em} 450 nm	N.R.	N.R.	(Hayase, Konishi, and Kato 1995; Hayase et al. 2005)
	S17	235 nm	λ_{ex} 370 nm; λ_{em} 450 nm	N.R.	N.R.	(Hayase, Konishi, and Kato 1995; Hayase et al. 2005)
	Imidazolonylornithine	235 nm	λ_{ex} 370 nm; λ_{em} 445 nm	Y	Y	(Henle et al. 1994; Niwa et al. 1997)
	Argpyrimidine	335 nm	λ_{ex} 335 nm; λ_{em} 382 nm	Y	Y	(Wilker et al. 2001; Takeuchi et al. 2015)
	THP	220 nm	N	N.R.	Y	(Oya-Ito et al. 2002; Nemet, Varga-Defterdarović, and Turk 2006)
	G-H	225 nm	N	N.R.	Y	(Thornalley et al. 2003)
	MG-H	225 nm	N	Y	Y	(Ahmed et al. 2003; Ahmed et al. 2005)
Structure with arginine residue	3DG-H	225 nm	N	N.R.	Y	(Thornalley et al. 2003)
	GLARG	N	N	N.R.	N.R.	(Schwarzenbolz et al. 1997)
Structure with crosslinking between two lysine residues	GOLA	N	N	N.R.	Y	(Glomb and Pfahler 2001)
	GOLD	228 nm	N.R.	Y	Y	(Wells-Knecht, Brinkmann, and Baynes 1995; Frye et al. 1998)
	MOLD	228 nm	N.R.	Y	Y	(Frye et al. 1998; Ahmed et al. 2005)
	DOLD	228 nm	N.R.	Y	Y	(Skovsted et al. 1998; Ahmed and Thornalley 2002)
	FFI	278 nm, 330–335 nm	λ_{ex} 290-370 nm; λ_{em} 440 nm	N.R.	Y	(Pongor et al. 1984; Huber et al. 1988)
	Lysylhydroxytriosidine	232, 269, 349 nm	λ_{ex} 354 nm; λ_{em} 440 nm	N.R.	Y	(Tessier, Monnier, and Kornfield 2002)
	CROSSPY	256 nm	N.R.	Y	Y	(Hofmann, Bors, and Stettmaier 1999)
	Vesperlysine A	302, 363 nm	λ_{ex} 366 nm; λ_{em} 442 nm	N.R.	Y	(Nakamura, Nakazawa, and Ienaga 1997; Tessier, Obrenovich, and Monnier 1999)
	Pentodilysine	385 nm	λ_{ex} 320, 326 nm; λ_{em} 440 nm	Y	Y	(Graham et al. 1998; Bosch et al. 2007)
	Crossline	256 nm	λ_{ex} 379 nm; λ_{em} 463 nm	N.R.	Y	(Nakamura et al. 1992; Obayashi et al. 1996)
	Lysylpyrropyridine	256 nm	λ_{ex} 376 nm; λ_{em} 450 nm	Y	Y	(Hayase et al. 2002, 2005)
	Pyranopyrazine	399 nm	N	N.R.	N.R.	(Knerr et al. 2001)
Structure with crosslinking between two arginine residues	N.R.					
Structure with crosslinking between a lysine residue and an arginine residue	Pentosidine	320 nm	λ_{ex} 335 nm; λ_{em} 385 nm	Y	Y	(Słowik-Żłka et al. 2004; Sharma et al. 2015)
	C-Pentosidine	320 nm	λ_{ex} 335 nm; λ_{em} 385 nm	N.R.	Y	(Miyazaki, Nagai, and Horiuchi 2002a, 2002b)
	Pentosinane	248 nm	N	N.R.	N.R.	(Biemel et al. 2001b)
	GODIC	242 nm	N.R.	Y	Y	(Biemel et al. 2001a; Biemel, Friedl, and Lederer 2002)
	MODIC	242 nm	N.R.	Y	Y	(Biemel et al. 2001a; Biemel, Friedl, and Lederer 2002)
	DOGDIC	243 nm	N.R.	N.R.	Y	(Biemel et al. 2001b; Biemel, Friedl, and Lederer 2002)
	DOPDIC	243 nm	N.R.	N.R.	N.R.	(Biemel et al. 2001b)
	Glucosepan/Glucosepane	251 nm	N	Y	Y	(Biemel et al. 2001a; Sell et al. 2005)
	ALI	254 nm	N	N.R.	N.R.	(Al-Abed and Bucala 2005)
	2-ornithyldihydroimidazolium-4-imide	253 nm	N.R.	N.R.	N.R.	(Gerum, Severin, and Lederer 1998)
	Isomeric ornithyldihydroimidazolium -4-imide	253 nm	N.R.	N.R.	N.R.	(Gerum, Severin, and Lederer 1998)
	Arg-hydroxy-triosidine	330 nm	λ_{ex} 331 nm; λ_{em} 380 nm	N.R.	N.R.	(Tessier, Monnier, and Kornfield 2002)
Others	N.R.					

[a]AGEs can be detected in foodstuffs rather than in model food systems.
[b]AGEs can be found in human or animal circulation and tissues (AGEs *in vitro* and *in vivo* with model experiments were not included).
N.R., not reported.

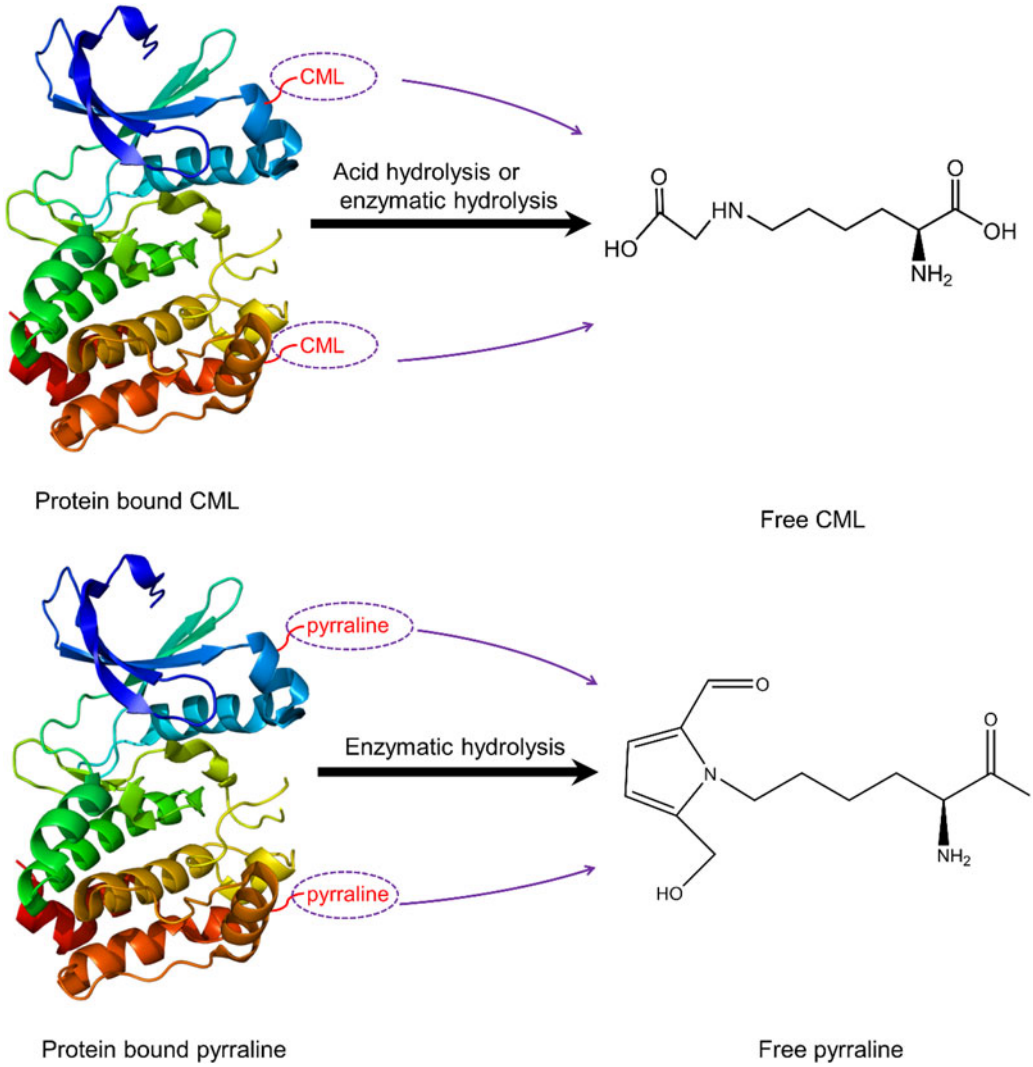

Figure 3. Protein bound AGEs and free AGEs.

in food under food processing conditions. This classification is critical to research in the field of food and medical sciences. As shown in Table 1, some AGEs, such as CML, pyrraline and pentosidine, can exist both in food and in the body. However, a substantial fraction of AGEs can be measured in the body rather than in food, such as vesperlysine A, GOLA and crossline. Other AGEs have been reported neither in food nor in the body. They have been found or synthetized solely *in vitro* and *in vivo* in model experiments. Such examples include trihydroxy-triosidine, S11, S12, S17, and ALI. Therefore, determining the effects and accumulation of AGEs present both in food and in circulatory fluid will be crucial to controlling AGEs in the future. d-AGEs are likely to be factors contributing to AGE accumulation in the body in terms of AGEs found both in food and in the body. However, as presented in Table 1, for AGEs which limited data are available in food, such as GALA and AFGP, further research is required to better understand the possible link between food intake and AGE accumulation.

As presented in Figure 3, on the basis of the amino acid residue, AGEs mainly comprise protein bound AGEs, peptide bound AGEs (not shown in Figure 3) and free AGEs. The particular structure of protein-bound AGEs is a novel modification to the native protein. This classification system is strongly associated with the digestion and absorption of AGEs. This issue will be discussed in more detail later.

The evidences for new AGEs

In recent years, many studies have investigated novel AGEs. Baldensperger et al. (2018) have found two novel AGEs in rat liver, N^6-glyoxylyl lysine and N^6-pyruvoyl lysine, through incubation of N^2-*t*-Boc-lysine with GO and MGO, respectively. In addition, 2,15-diamino-8-methyl-9-oxo-7,10-diaza-1,16-hexadecanedioic acid, named MOLA, an MGO-derived AGE, has been identified in rat senescent tendon collagen (Jost, Zipprich, and Glomb 2018). As presented in Table 1, AGEs with cross-linking between two arginine residues have not been reported. These AGEs must be clarified and updated in further studies.

The concentrations of AGEs in food

A considerable amount of literature has been published on AGE determination and quantification, especially AGE content in food produced from different raw materials with different processing conditions. Generally, AGE formation is

not a single reaction but a series of reactions whose pathways and outcomes depend critically on temperature, moisture and food ingredients.

AGEs are virtually ubiquitously present in foodstuffs, and particularly form during processing at elevated temperatures. Broiling (225 °C) and frying (177 °C) give rise to the highest content of CML, followed by roasting (177 °C) and boiling (100 °C) (Goldberg et al. 2004). Dry heat treatment is a significant factor resulting in elevated concentrations of d-AGEs by >10- to 100-fold above the concentrations in various uncooked foods across the United States (Uribarri et al. 2010). In addition, clear increases in CML and CEL in heat-treated (100 °C) fish muscle, as compared with raw fish muscle, have been reported (Niu et al. 2017). These findings are also in good accordance with commercially sterilized (121 °C) pork compared with raw pork (Niu et al. 2018). These results indicate that elevated temperatures promote d-AGE accumulation in foodstuffs.

Dry heat treatment produces a higher d-AGE content than moist heat treatment when the same food item is treated with the same temperature. Frying (177 °C) produces a higher content of CML than roasting (177 °C) (Goldberg et al. 2004). Moreover, when the same food item is treated with high temperature and low moisture procedures, the d-AGE content is significantly higher than that formed under low temperature and high moisture procedures. Generally, frying, broiling, grilling, baking and roasting produce more CML than boiling, poaching, stewing and steaming (Uribarri et al. 2010; Hull et al. 2012). The production of water is a result of the Maillard reaction and AGE formation. From the perspective of chemical equilibrium, low moisture procedures promote AGE formation.

AGE concentrations differ among the components in food. Fat-enriched foods contain the highest AGE content, followed by meat and meat-substitute foods from animal sources. Milk and carbohydrate-rich foods such as vegetables, fruits and whole grains have relatively low concentrations of AGEs, even after cooking (Goldberg et al. 2004; Uribarri et al. 2010). However, some evidences contradict these results. A dietary AGE database including CML, CEL and MG-H1 in 190 food items indicates that high-heat processed nut or grain products, and canned meats contain the highest AGE levels. Fruits, vegetables, butter and coffee have the lowest AGE content (Scheijen et al. 2016). Cereals have the highest mean concentrations of CML (281.29 mg/kg protein), in contrast to meat and fish (44.53 mg/kg protein) and meat dishes (167.60 mg/kg protein) (Hull et al. 2012). In addition, the protein and fat content in beef or pork has very little or no effect on the formation of protein-bound AGEs (CML and CEL) during the sterilization process (Sun et al. 2016). Some paradoxical results among these reports may have resulted from the processing procedures and determination methods. The same food category may include different processing procedures. The ELISA method usually has limited antibody specificity, and the data may be expressed in units that are not comparable with those in any other reported work. Therefore, a validated method is recommended in the assessment of d-AGEs. Moreover, the data on a wide range of AGEs beyond CML should be collected in further studies to comprehensively support these preliminary conclusions.

More significantly, the content of glucose derived AGEs (presented as U/bottle) in some lactic acid bacteria-containing beverages, carbonated drinks, sugar-sweetened fruit drinks, sports drinks, mixed fruit juices, confectionery (snacks), dried fruits, cakes, cereals and prepared foods are prominently higher than those in other classes of beverages and foods (Takeuchi et al. 2015). According to industrial practice, these special beverages and foods are usually sweetened by fructose, glucose and high fructose corn syrup. During processing, these sweeteners easily produce dicarbonyl compounds, which are the precursors of AGEs.

Active carbonyl compounds as precursors of AGEs

Active carbonyl compounds are produced primarily from carbohydrate degradation during food processing and storage. These compounds can broadly be defined as precursors of AGEs or intermediate products during AGE formation. Table 2 presents an overview of precursors and their derivative AGEs. As shown in Table 2, all precursors can be detected both in food and in the body. Therefore, active carbonyl compounds, particularly their occurrence in food samples, may play a pivotal role in AGE formation both in food and in the body.

The occurrence of active carbonyl compounds in foodstuffs, particularly 3-DG, is strongly dependent on food ingredients and processing procedures. First, the content of carbonyl compounds in food samples is most prominently influenced by the type of sugar, such as monosaccharides, disaccharides, and reducing and nonreducing sugars. Extensive studies have suggested that 3-DG can be estimated as the predominant dicarbonyl compound in most food items, such as fruit juices, carbonated soft drinks, balsamic vinegars, candies and cookies (Degen, Hellwig, and Henle 2012; Gensberger et al. 2012; Gensberger, Glomb, and Pischetsrieder 2013). Significantly higher amounts of 3-DG have been measured in in fruit juices than in soft drinks on the German market. The concentration of 3-DG is independent of fruit content, regardless of whether there is a direct juice source or juice concentrate source (Degen, Hellwig, and Henle 2012). In addition, dicarbonyl compounds can accumulate in samples in which no reactants such as amino acid side chains of proteins are present. High fructose corn syrup may be an important source of dicarbonyl compounds, owing to sugar degradation; the total concentrations of dicarbonyl compounds have been reported to range from 293 to 1130 μg/mL (Gensberger et al. 2012). The levels are significantly higher in carbonated soft drinks sweetened with only high-fructose corn syrup compared with those sweetened with high-fructose corn syrup and sucrose or with sucrose alone (Gensberger, Glomb, and Pischetsrieder 2013). Glucose, fructose and high fructose corn syrup are widely used as sweeteners in juice and drink production. Because they are susceptible to degradation in processing procedures, these reducing monosaccharides and mixtures are more prone to producing carbonyl compounds than disaccharides

Table 2. Active carbonyl compounds as precursors of AGEs.

Active carbonyl compounds	Existence matrices		Active carbonyl compounds derived AGEs
	In food[a]	In body[b]	
GO	Y	Y	CML, GOLA, GOLD, GALA, GODIC, vesperlysine A, G-H, 2-ornithyldihydroimidazolium-4-imide, GLARG, FFI
MGO	Y	Y	CEL, MG-H, argpyrimidine, MODIC, MOLD, imidazolonylornithine, isomeric ornithyldihydroimidazolium-4-imide, THP
DG	Y	Y	Pyrraline, DOLD, AFGP, 3DG-H, lysylpyrropyridine, pentosidine, DOGDIC, DOPDIC, S11, S12, S17
DP	Y	Y	DOPDIC
Glycolaldehyde	Y	Y	CROSSPY
GLA	Y	Y	Glucosepan, lysylhydroxytriosidine, arg-hydroxy-triosidine, trihydroxy-triosidine, triosidine-carbaldehyde
Not reported	—	—	Carboxymethylarginine, carboxyethylarginine, C-pentosidine, crossline, pentodilysine, pentosinane, pronyllysine, pyranopyrazine, ALI

[a]Active carbonyl compounds can be detected in foodstuffs rather than in model food systems.
[b]Active carbonyl compounds can be found in human or animal circulation and tissues. AGEs *in vitro* and *in vivo* with model experiments were not included.

and nonreducing sugars. High fructose corn syrup is a widely used liquid sweetener derived from corn starch by hydrolysis and partial isomerization of glucose to fructose. In commercial production of high fructose corn syrup, carbonyl compounds are easily produced because the temperature of starch liquefaction and saccharification processes can range from 60 to 150 °C (Antrim, Colilla, and Schnyder 1979).

Second, the extent of heat effects during manufacturing accompanied by a decrease in the water content contributes to the occurrence of carbonyl compounds. Because of the more intensive heat treatment during the baking process in the outermost layer of bread, the amount of 3-DG is significantly higher in the crust than in the crumb (22 mg/kg versus 3.3 mg/kg) (Degen, Hellwig, and Henle 2012). The GO and MGO content in commercial cookies ranges from 4.8 to 26.0 mg/kg and from 3.7 to 81.4 mg/kg, respectively, and increases linearly with prolonged baking time (Arribas-Lorenzo and Morales 2010). From the perspective of chemical equilibrium, intensive heat effects and decreased water content can accelerate the formation of carbonyl compounds from sugar.

Third, some food processing procedures, such as ripening, fermentation and storage, promote the formation of dicarbonyl compounds. A considerable amount of 3-DG is present in balsamic vinegars, and soy sauces, owing to the manufacturing process, such as the cooking of must, ripening, and fermentation (Degen, Hellwig, and Henle 2012). In honey samples, 3-DG concentrations are 79 to 1266 mg/kg and show a linear increase during storage at 35 °C and 45 °C. However, the content of GO and MGO has been estimated to range from 0.2 to 2.7 mg/kg and 0.4 to 5.4 mg/kg, respectively, and is not affected by storage time and temperature (Weigel, Opitz, and Henle 2004). In fact, the considerable amounts of dicarbonyl compounds in these food items may be attributed to the presence of ingredients with reducing sugars or intensely heated carbohydrate sources. These ingredients can sustainably produce dicarbonyl compounds during manufacturing processes.

Consequently, the presence of active carbonyl compounds in food can promote the formation of d-AGEs and biological-AGEs. Dietary dicarbonyl compounds are the precursors of not only d-AGEs but also biological-AGEs after digestion and absorption. However, the active and reactive properties are the major obstacles to determining their digestion and absorption. Therefore, dicarbonyl compounds in food cannot easily be concluded to play a critical role in biological-AGE accumulation.

Dietary AGEs are partially responsible for biological-AGE accumulation

Evidence from most studies suggests that elevated levels of d-AGEs are associated with elevated levels of biological-AGEs. Initially, bioavailability is used to indirectly evaluate the association between them. Approximately 50% of pyrraline has been recovered in urine samples after ingestion of pretzel sticks. For pentosidine, approximately 60% of the free-form and 2% of the peptide-bound form have been recovered in urine samples after ingestion of coffee brew and bakery products, respectively (Förster, Kühne, and Henle 2005). These data suggest that d-AGEs may have considerable bioavailability and contribute to biological-AGE accumulation. However, solely on the basis of bioavailability data, no clear conclusion can be reached. d-AGEs may be metabolized to other products that are nontoxic or currently have unknown toxic effects. Monitoring the association between metabolites of d-AGEs and biological-AGEs is very difficult.

Subsequently, clear evidences indicate that oral intake of d-AGEs promotes biological-AGE accumulation. In animal experiments, an AGE-enriched diet significantly increases the concentration of CML in all tissues tested except fat, such as the cardiac tissue, tendons (Roncero-Ramos et al. 2014), kidneys, heart, liver, lungs, spleen and pancreas (Li et al. 2015b). In addition, higher deposition of CML (81–320 μg CML/g dry matter) has been found in the kidneys, intestine and lungs, whereas low deposition (<5 μg CML/g) has been found in the heart, muscle and liver (Tessier et al. 2016). In clinical trials, high consumption of dietary CML, CEL and MG-H1 has been positively associated with elevated levels of the free forms in plasma and urine (Scheijen et al. 2018). From this evidence, a preliminary hypothesis can be formulated that more intensive participation in d-AGE metabolism is expected to account for

the increased burden of AGEs in tissues, such as kidney and intestine, and in plasma and urine.

However, evidence not supporting an association between d-AGE and biological-AGE accumulation cannot be ignored. As much as 80% of dietary Amadori rearrangement products (pre-AGEs) cannot be absorbed but are degraded by the intestinal flora. Most d-AGEs absorbed into the circulation are rapidly excreted by the kidneys (Ames 2007). In healthy subjects, intake of d-AGEs neither correlates with nor contributes to sustained levels of AGEs in the blood or pentosidine-related free and protein-bound AGEs (de la Maza et al. 2008, Piroddi et al. 2011).

Consequently, there is a paradox in the association between d-AGEs and biological-AGEs. In fact, this paradox may be attributed to the sample selection in these studies, particularly the samples involving unhealthy animals or individuals. In most cases, samples from individuals with chronic diseases (*e.g.* diabetes and chronic kidney disease) are used, and it is difficult to distinguish the effects of dietary intake, uremic comorbidity and dialysis on circulating AGEs.

Digestion of dietary AGEs

The levels of free amino acids in commonly consumed foods are always much lower than those of peptides and proteins. Thus, protein bound AGEs and peptide bound AGEs are the prevailing AGEs in the diet. However, the presence of a glycated structure is an expected novel modification of the native protein. Therefore, structural features of AGEs may play a significant role in the digestion of glycated proteins and peptides.

Evidence in several studies indicate that AGEs with non-crosslinked structures may result in a considerable decrease in glycated protein digestibility. After a two-step proteolysis procedure for simulating gastrointestinal digestion, the digestibility of CML-casein (60% modification of target lysine) is significantly lower than that of native casein; however, tryptophan liberation and digestion are not significantly lower than those of native casein (Hellwig et al. 2014). After glycation with furosine and pyrraline, a release of β-casomorphins (opioid peptides generated by the proteolysis of bovine β-casein) during gastrointestinal digestion is not observed in the model system of liquid infant formula, as compared with that before the glycation (Cattaneo et al. 2017). Therefore, the decrease in glycated protein digestibility should reflect decreased accessibility and cleavability of the protein backbone. AGEs with non-crosslinked structures, such as CML, pyrraline and CMA, mainly result from covalent modification of Lys and Arg residues, and thus, can block the action of trypsin during intestinal digestion (Wada and Lönnerdal 2014; Zhao et al. 2017b).

Subsequently, the decreased glycated protein digestibility can be observed clearly in the presence of AGEs with crosslinked structures. A decline in the digestibility of glycated β-casein and β-lactoglobulin can be attributed primarily to the formation of AGEs with crosslinked structures, such as GOLD and MOLD (Zhao et al. 2017a). The decrease in the fibrillation capacity of glycated β-lactoglobulin is driven by lower content of β-sheet secondary structures after glycation (Zhao et al. 2018). These AGEs with crosslinked structures have been expected to consolidate peptide chains and thus may limit the flexibility of the protein, thereby further hindering the action of digestive proteases.

In addition, various digestion models often prevent the comparison of results across research teams. In simulated gastrointestinal digestion, the noncomparable results may be attributed to many factors. For example, enzymes from different sources can differ in their activity and characterization. Simulated gastric fluid and intestinal fluid with differences in pH, mineral type, ionic strength, which alter enzymatic activity and other phenomena, may also considerably affect results. Therefore, a standardized static *in vitro* digestion method (an international consensus) (Minekus et al. 2014; Brodkorb et al. 2019) is strongly recommended to obtain comparable results for d-AGEs digestion. This consensus article has provided a detailed protocol with a frameset of parameters including oral, gastric and small intestinal digestion. The protocols would allow simulated digestion systems to be adapted and validated for specific applications and endpoints by setting the physiological relevant parameters.

Absorption of dietary AGEs

The major products of intraluminal digestion of protein are amino acids and small peptides. Amino acids, small peptides (especially di- and tripeptides) and even small amounts of intact protein may enter the portal circulation directly (Fuller and Tomé 2005). Therefore, d-AGEs might be absorbed in circulation mostly in the forms of free AGEs and peptide bound AGEs after gastrointestinal digestion.

Transport and uptake of AGEs in free-form

The intestinal epithelial cell lines (*e.g.* Caco-2 and HT29) have been used extensively in studies of the transepithelial transport of digesta and drugs. Most studies of d-AGE transport in cell monolayers have been performed in Caco-2 cells and are mechanistic in nature. Initially, whether free AGEs (glycated amino acids) and peptide bound AGEs (glycated peptides) are substrates for amino acid and peptide transporters expressed at the apical membrane of Caco-2 cells should be clarified. Intestinal transport of the CML, N^{α}-hippuryl-N^{ε}-(1-deoxy-D-fructosyl)-L-lysine, N^{α}-hippuryl-CML, and N^{ε}-(1-deoxy-D-fructosyl)-L-lysine is low and is not mediated by amino acid carriers or peptide carriers (PEPT1). In addition, these MRPs in free-form do not affect the integrity of the Caco-2 monolayer and cell membrane fluidity (Grunwald et al. 2006). These findings suggest that these MPRs may permeate Caco-2 cell monolayers weakly through simple diffusion rather than through PEPT1 and carriers for neutral amino acids. Furthermore, free pyrraline is not a substrate for the intestinal lysine transporter. The absorption of free pyrraline probably occurs in the form of

glycated dipeptides rather than the glycated amino acid (Hellwig et al. 2009).

Transport and uptake of peptide bound AGEs

Peptide bound AGEs, as glycated peptides, are expected not to be transported across intestinal cell monolayers in intact form. Ala-Pyrraline (Ala located at the N-terminus of glycated peptide) and Pyrraline-Ala (glycated peptide with Ala located at the C-terminus) are taken up into intestinal cells across the apical membrane by the peptide transporter PEPT1. Once inside the intestinal cells, Ala-Pyrraline and Pyrraline-Ala are hydrolyzed to free pyrraline and alanine (Hellwig et al. 2009). In addition, in the presence of a hydrogen ion gradient, PEPT1 can accumulate peptides intracellularly against a concentration gradient (Brandsch, Knütter, and Bosse-Doenecke 2008). Consequently, a pyrraline gradient may form across the basolateral membrane, and the basolateral efflux of free pyrraline can occur via simple diffusion.

Similar results have been obtained for other AGEs, such as CML, CEL, N^6-(1-fructosyl)-lysine, formyline, argpyrimidine and MG-H1. Clear evidence indicates that glycated amino acids have lower affinities than their corresponding unglycated structures towards the L-[^{3}H]lysine transporter(s). Glycated dipeptides are medium- to high-affinity inhibitors of [^{14}C]glycylsarcosine uptake except Ala-N^6-(1-fructosyl)-lysine. After addition of glycated dipeptides to the apical membrane, free AGEs rather than peptide bound AGEs can be detected in the basolateral compartment. However, in contrast to pyrraline transport, only small amounts of glycated amino acids and glycated dipeptides derived from CML and CEL pass through Caco-2 cell monolayers (Hellwig et al. 2011).

Therefore, peptide bound AGEs are likely to be taken up into intestinal cells across the apical membrane by the peptide transporter PEPT1, a process followed by intracellular enzymatic hydrolysis, then basolateral efflux of free AGEs. However, several hypotheses must be tested in future studies:

I. Can AGE-induced modification of peptide change the transport progress of PEPT1?
II. Can the structural features of AGEs influence intracellular enzymatic hydrolysis of glycated peptides?
III. Do similar glycated peptides with different amino acid sequences, such as Ala-Pyrraline and Pyrraline-Ala, have the same transport process with PEPT1? Do they have same intracellular enzymatic hydrolysis efficiency?

New approaches to clarifying the absorption of dietary AGEs

As previously mentioned, d-AGEs may be absorbed into circulation in the form of glycated amino acids and glycated peptides after digestion; therefore, the effect of glycation on the native structure of amino acids and peptides after digestion is crucial.

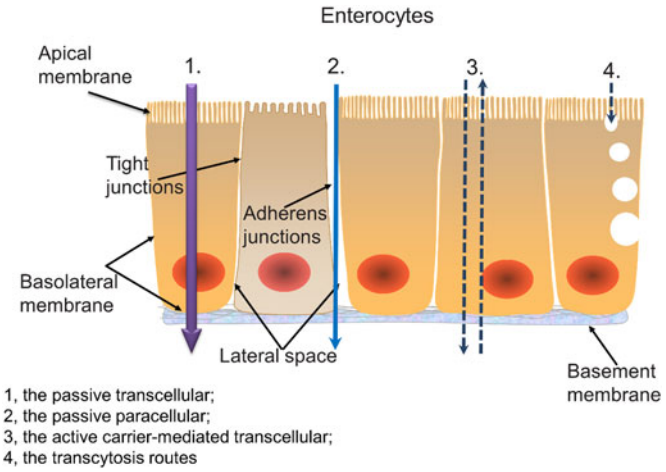

Figure 4. Schematic drawing of the intestinal epithelium.

The transport systems of native amino acids and peptides and their differences have been reviewed in detail by Freeman et al. (Freeman and Kim 1978). Amino acids are absorbed mainly via four transport systems for neutral (monoaminomonocarboxylic) amino acids, dibasic (diamino) amino acids, dicarboxylic (acidic) amino acids, in glycine and imino acids. Mucosal uptake of amino acids is independent of that of peptides. Dipeptides and tripeptides share a common transport mechanism and are actively transported against a concentration gradient. Amino acids are absorbed more rapidly in the proximal intestine, whereas peptides appear to be absorbed well in both the proximal and distal small intestine. Therefore, various glycated amino acids and peptides may have different transport systems. Furthermore, the transport systems of amino acids and peptides may be influenced by glycation. Unfortunately, the current mechanistic understanding suffers from the lack of a strong theoretical framework.

Recently, extensive investigations of intestinal drug transportation and absorption have provided inspiring findings regarding d-AGEs transportation and absorption (Artursson, Palm, and Luthman 2012; Estudante et al. 2013). As shown in Figure 4, the transport of drugs across the intestinal epithelium may occur through one or more of four different routes: the passive transcellular and paracellular routes, the carrier mediated route and transcytosis. The transport efficiency of these four routes is influenced by drug structural features. Several physicochemical parameters have been used to estimate intestinal permeability in both *in vitro* and *in vivo* models (Balimane, Chong, and Morrison 2000); these important physicochemical parameters are size, charge, lipophilicity (*e.g.,* octanol/water partitioning coefficients, presented as P_{oct}) and hydrogen-bonding potential (*e.g.,* hydrogen bonding capacity, presented as $\Delta \log P$) as well as other molecular descriptors (Dressman, Thelen, and Jantratid 2008; Tian et al. 2011). In the field of drug transport, the Biopharmaceutical Drug Disposition and Classification System (BDDCS) divides drug compounds into four classes according to their permeability and solubility (Figure 5). Changing the permeability component to a route of elimination component in BDDCS may be useful in

Figure 5. The Biopharmaceutics Drug Disposition Classification System (BDDCS), after Wu and Benet (Wu and Benet 2005).

predicting overall drug disposition for new molecular entities, including routes of drug elimination, the potential for drug-drug interactions and the effects of efflux and absorptive transporters on oral drug-absorption. The change components in BDDCS can also be referenced as an approach to studying d-AGE transport. Further details on intestinal drug transport could be referenced from reviews by Estudante et al. (2013) and Artursson, Palm, and Luthman (2012).

The physicochemical parameters of d-AGEs can be calculated by several computational software programs, such as Gaussian 09, Discovery Studio and Amsterdam Density Functional software. The collected physicochemical parameters of peptide bound pyrraline by using Gaussian 09 indicate that several physicochemical parameters are partially responsible for peptide bound pyrraline formation, such as residue volume, polarizability, molecular volume, localized electrical effect, hydrophobicity and pK_b (Liang et al. 2016). Therefore, a similar approach can be used in predicting d-AGE transportation and absorption.

Distribution of dietary AGEs in the body

After crossing digestive tract epithelial cells, the d-AGEs proceed into circulation and merge with biological-AGEs. Therefore, it is necessary to knock out biological-AGEs when d-AGE distribution in the body is seated. Normally, oral AGE intake experiments are used to explore the distribution of d-AGEs.

Evidence of oral disturbance indicates that d-AGE intake can lead to AGE accumulation throughout the body, including tissues (gastrointestinal tract, liver, kidneys, lungs, heart and spleen), serum, urine and feces. After long-term consumption of AGEs from bread crust, a significantly higher CML level has been observed in the gastrointestinal tract tissue of rats fed an AGE-enriched diet as compared with rats fed a control diet, especially in the ileum tissue (bread crust group: 35.79 ng CML/mg protein; control group: 26.63 ng CML/mg protein) (Yuan et al. 2018). After normal Sprague-Dawley rats are fed isotope-labeled AGEs, the low molecular weight AGEs (LMW-AGEs) are readily distributed throughout the body including tissues (liver, kidneys lungs, heart and spleen), serum, and 72-h urine, and with more than 60% of radiolabeled AGEs is bound to the liver and kidneys (He et al. 1999). Regular consumption of d-AGEs in healthy rats promotes CML accumulation in some tissues, such as heart and tendons (Roncero-Ramos et al. 2014). In addition, substantial accumulation of protein-bound CML has been observed in the kidney, heart, lung, pancreas and muscle after long-term oral exposure to free CML (Li et al. 2015a, 2015b). Mice exposed to protein ^{13}C-labeled dietary CML also has shown CML accumulation in all tissues (i.e. kidney, gut, lung, heart and brain) except fat (Tessier et al. 2016).

The distribution of d-AGEs in the urine and feces will be discussed in the section on d-AGE excretion. Overall, d-AGEs are distributed in most tissues after they are absorbed into circulation. The distribution of d-AGEs in the body is driven by their higher affinity for some tissues on the basis of covalent or noncovalent binding interactions. However, whether the d-AGE accumulation in tissues occurs through intracellular deposition, extracellular deposition or both still remains unclear.

Metabolism of dietary AGEs

After d-AGEs proceed into the circulation and merge with biological-AGEs, they may be subjected to the same metabolic mechanism.

AGE metabolism does not depend on phase I and II enzymes

AGEs have not been expected to be substrates for enzyme systems involved in detoxification by phase I and II enzymes (Ott et al. 2014). According to the hydrophile-lipophile balance, hydrophilic AGEs may not be substrates of the phase I enzymes in the fatty membranes of the endoplasmic reticulum. Owing to the glycation of side groups, most AGEs have insufficient typical side groups for phase II coupling reactions, except acidic groups for esterification (Sharma et al. 2015). Another finding reported by Wenzel et al. (2002) indicates that dietary intake of heat-treated proteins leads to changes in the activity of phase II enzymes, particularly ingestion of protein-bound CML. This result may partially explain why glycated proteins are not expected to be substrates for phase II enzyme. Unfortunately, this study showed varied control measurements.

AGE metabolism is driven by the AGE-receptor system

Biological-AGEs can be metabolized by innate defense and/or intracellular degradation after receptor-dependent uptake. As shown in Figure 6, the AGE-receptor system can be broadly divided into two sides: one is associated with increased oxidant stress, growth and inflammatory effects, typically represented by the receptor for AGE (RAGE) (Bierhaus et al. 2005); the other, involved in AGE detoxification, comprises scavenger receptors class A, type II (SR-AII), and class B, type I (SR-BI, CD36) (Suzuki et al. 1997; Miyazaki, Nakayama, and Horiuchi 2002), as well as AGE

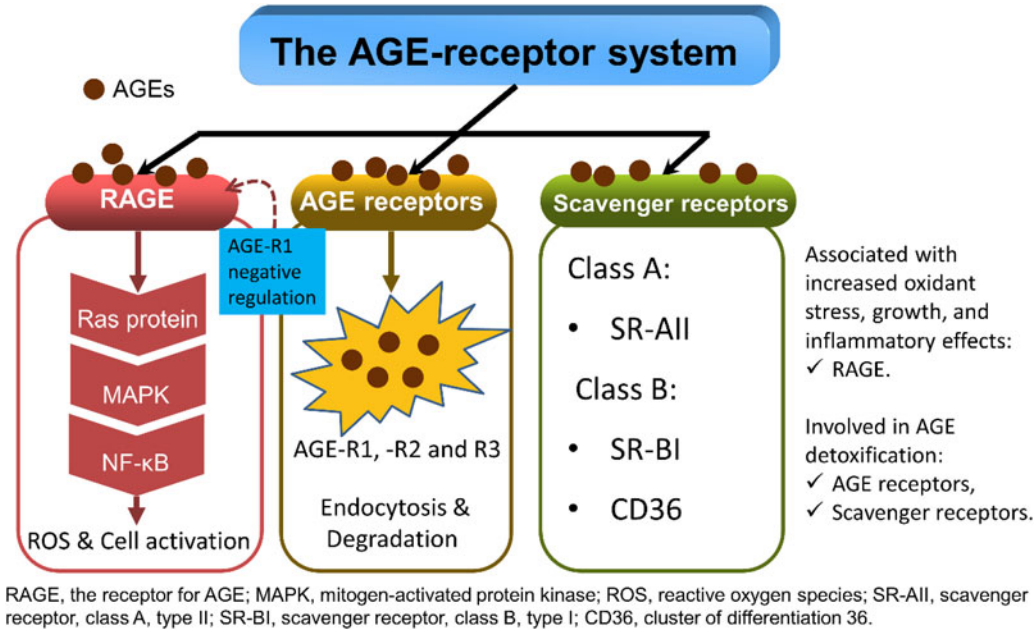

Figure 6. The AGE-receptor system.

receptors 1, 2 and 3 (AGE-R1, -R2, and -R3) (Thornalley 1998). AGE-R1 not only enhances AGE removal but also suppresses AGE-mediated mesangial cell inflammatory injury through negative regulation of RAGE. Binding of AGEs to AGE-R1 stimulates receptor endocytosis, and this mechanism contributes to the detoxification and clearance of LMW-AGEs (Tang and Chen 2014). Unfortunately, whether these receptors contribute to the detoxification of AGEs with high molecular weight (HMW-AGEs), such as protein bound AGEs and peptide bound AGEs, remains unknown. In addition, the metabolic products of AGEs are unclear and must be further elucidated.

Excretion of dietary AGEs

The excretion of d-AGEs is crucial in their health hazard assessment. There is controversy regarding the health risk of d-AGEs (Šebeková and Somoza 2007; Ames 2007). However, it seems clear that more excretion of d-AGEs would alleviate the health risk.

AGE excretion after intake of glycated mixtures with indistinct structure

In earlier studies, AGE mixtures have been used by incubating reducing saccharide with proteins or amino acids. The renal excretion of d-AGEs has been estimated to be approximately 30% of the absorbed amount in healthy adults, but less than 5% in renal disease patients (Koschinsky et al. 1997). In agreement with findings in humans, administering a reaction product of ^{14}C-glucose with ^{125}I-labeled ovalbumin by gavage to healthy Sprague-Dawley rats has been found to result in excretion of approximately 26% of labeled AGEs into the urine (He et al. 1999). However, these reports used glycated mixtures with indistinct structure and therefore provide little evidence regarding the excretion of AGE monomers. Therefore, there has been growing interest in the excretion of AGE monomers in subsequent studies.

Excretion of CML

Dietary intake of free CML facilitates a higher urinary excretion rate than that of protein bound CML. The renal clearance of free CML and CEL after an intravenous injection in rats is rapid, and 86.5% and 93.2% is detected in the urine after 2 h, respectively (Bergmann et al. 2001). However, a maximum of 29% of CML in the urine and 22% in the feces has been recovered with casein linked CML administered to rats for 10 days (Somoza et al. 2006). These findings can be explained by the limited absorption of free CML from its protein-bound form or the slow excretion of peptide-associated CML. Fecal excretion rates after intake of a low and a high CML diet have been reported to be 31.7% and 22.5% of dietary intake, respectively. In addition, 24% and 15% urinary excretion rates have been obtained, respectively (Delgado-Andrade et al. 2012). In summary, urinary and fecal excretion contributes to a maximum 56% clearance of CML after dietary intake. A high CML diet, as compared with a low CML diet, may lead to a lower urinary excretion rate and fecal excretion rate. Thus, the maximum excretion rates of CML in urine and feces may differ, and the threshold must be further investigated.

Excretion of other AGEs

Other typical AGEs, such as pyrraline and pentosidine, show different excretion rates from those of CML. After intravenous administration of radio-labeled pentosidine to rats, 83% and 3.4% were recovered intact in the urine and feces after 72 hours, respectively (Miyata et al. 1998). When well-defined amounts of pyrraline and pentosidine, which are present in selected food items, were specifically investigated

in healthy humans, approximately 50% of free pyrraline and 60% of free pentosidine were recovered in the urine, respectively. However, when the dose was orally supplied with protein bound pentosidine, only 2% of the ingested amount was recovered in urine samples (Förster, Kühne, and Henle 2005). Therefore, the excretion rate of free pyrraline is expected to be higher than that of free CML (∼50% in urine versus maximum 56% in urine and feces together) after dietary intake, as well as free pentosidine (∼ 60% in urine). However, as previously mentioned, free CML and pentosidine exhibit high excretion rates (86.5% versus 83%) after intravenous injection. These findings indicate that the complex structures of free pyrraline and pentosidine, including the pyrrole ring and imidazopyridine, may contribute to the lower absorption rates than those of CML with carboxymethyl. However, protein bound AGE exhibits a lower excretion rate than free AGE after oral administration. This result suggests that there are different resorption and metabolic pathways for these compounds, particularly impaired proteolytic breakdown and/or metabolic degradation pathways.

Two issues need further consideration

The first additional consideration is whether the excretion rates of d-AGEs are dependent on dietary intake amounts, particularly well-defined LMW-AGEs (free AGEs and short peptide bound AGEs) and HMW-AGEs (protein bound AGEs and long-chain peptide bound AGEs). Notably, urinary excretion of d-AGEs is derived from AGEs that are digested and absorbed, whereas indigestible or unabsorbable AGEs mainly contribute to fecal excretion.

The second issue is that evidence of the degradation products of HMW-AGEs formed in the gut is particularly scarce. HMW-AGEs may impede proteolytic breakdown and/or change metabolic transformation pathways.

Conclusions and perspectives

AGE formation is derived from manifold processes either in food matrices or in the body; however, the fate of d-AGEs in the body still remains ambiguous. The complexity and diversity of the Maillard reaction pathways result in many possible compounds being defined as AGEs. The fate of d-AGEs in the body is closely related to their particular structures. Glycated modifications can impair the digestion, transport and uptake of d-AGEs. A standardized static *in vitro* digestion method is strongly recommended to obtain comparable results of AGEs digestibility. LMW-AGEs and HMW-AGEs may exhibit individual differences in their distribution, metabolism and excretion.

However, research must be supported by synthesis of better chemical standards for quantification of LMW- and HMW-AGEs. The BDDCS and calculated physicochemical parameters may be novel approaches to clarifying the absorption of d-AGEs. The amounts of orally-supplied LMW- and HMW-AGEs must be known to determine their excretion. In addition, stronger evidence of the degradation and metabolism products of d-AGEs should be obtained.

Abbreviations

AGEs	advanced glycation end products
d-AGEs	dietary AGEs
MRPs	Maillard reaction products
GO	glyoxal
MGO	methylglyoxal
DG	deoxyglucosone
1-DG	1-deoxyglucosone
3-DG	3-deoxyglucosone
DP	deoxypentosone
GLA	glyceraldehyde
RAGEs	receptor of advanced glycation end products
AGE-R	advanced glycation end product receptor
LMW	low molecular weight
HMW	high molecular weight
CML	carboxymethyllysine
CEL	carboxyethyllysine
CMA	carboxymethylarginine
CEA	carboxyethylarginine
GALA	glycolic acid lysine amide, N^6-glycoloyllysine
AFGP	1-alkyl-2-formyl-3,4-diglycosylpyrrole
S11	2-(N^{ε}-benzoyl-N^{δ}-ornithylamide)-5,6a-di(2,3,4,-trihydroxybutyl)-5,6-dihydroxydehydrofuro[2,3-*d*]imidazole
S12	2-(N^{ε}-benzoyl-N^{δ}-ornithylamide)-5-(2,3,4-trihydroxybutyl)-2-imidazoline-4-one
S17	2-(N^{ε}-benzoyl-N^{δ}-ornithylamide)-5-(2,3,4-trihydroxybutyl)-4-imidazolone
THP	tetrahydropyrimidine
GLARG	5-(2-imino-5-oxo-1-imidazolidinyl)norvaline
GOLA	glyoxal lysine amide
GOLD	glyoxal lysine dimer
MOLD	methylglyoxal lysine dimer
DOLD	3-deoxyglucosone lysine dimer
FFI	4-furanyl-2-furoyl-1H-imidazole
CROSSPY	1,4-bis(5-amino-5-carboxy-1-pentyl)pyrazinium radical cation
GODIC	glyoxal-derived imidazolium cross-link
MODIC	methylglyoxal-derived imidazolium cross-link
DOGDIC	deoxyglucosone derived imidazolium cross-link
DOPDIC	deoxypentosone derived imidazolium cross-link
ALI	Arg-Lys-Imidazole
G-H	glyoxal-derived hydroimidazolone, N^{δ}-(5-hydro-4-imidazolon-2-yl)ornithine (G-H1), 2-amino-5-(2-amino-5-hydro-4-imidazolon-1-yl)pentanoic acid (G-H2)
MG-H	methylglyoxal-derived hydroimidazolone, N^{δ}-(5-hydro-5-methyl-4-imidazolon-2-yl)-ornithine (MG-H1), 2-amino-5-(2-amino-5-hydro-5-methyl-4-imidazolon-1-yl)pentanoic acid (MG-H2), 2-amino-5-(2-amino-4-hydro-4-methyl-5-imidazolon-1-yl)pentanoic acid (MG-H3)
3DG-H	3-deoxyglucosone derived hydroimidazolone, N^{δ}-[5-(2,3,4-trihydroxybutyl)-5-hydro-4-imidazolon-2-yl]ornithine (3DG-H1), 5-[2-amino-5-hydro-5-(2,3,4-trihydroxybutyl)-4-imidazolon-1-yl]norvaline (3DG-H2), 5-[2-amino-4-hydro-4-(2,3,4-trihydroxybutyl)-5-imidazolon-1-yl]norvaline (3DG-H3).

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