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Tissue distribution of endogenously formed and orally administered low molecular mass advanced glycation end-products in rats.

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ABSTRACT

This study quantified the tissue distribution in rats of four exogenously administered and endogenously formed low molecular mass (LMM) AGEs, including glycolic acid-lysine-amide (GALA), N-ε-(carboxyethyl)lysine (CEL), N-ε-(carboxymethyl)lysine (CML) and pyrraline. Two hours after gavage administration of a mixture of the AGEs at 10 mg/kg body weight each, the free exogenously administered AGEs were detectable in the tissues, with the highest concentration in the kidneys, where levels of the exogenous AGEs were substantially higher than those of the endogenously formed counterparts. Endogenous and exogenous AGEs showed tissue specific patterns pointing at tissue specific differences in their formation, absorption and/or clearance and variable contributions of exogenous AGEs to the overall exposome. The results confirmed the bioavailability of free AGEs in the body and revealed distinct tissue biodistribution and elimination patterns among the four AGEs, showing that especially in the kidney oral exposure at estimated daily intakes may add to the exposome.

1. Introduction

Advanced glycation end products (AGEs) are a group of compounds which are formed exogenously during food processing via non-enzymatic reactions – known as the Maillard reaction - between reducing sugars and the free amino groups in proteins, lipids, or nucleic acids. AGEs are also formed endogenously during normal cellular metabolism. When the levels of AGEs in tissues or the systemic circulation are too high, it may trigger adverse health effects (Guilbaud et al., 2016; Monteiro-Alfredo & Matafome, 2022), including various pathological conditions associated with aging, and chronic inflammations (Zawada et al., 2022). In addition to being formed within the body, AGEs are commonly generated during food processing, such as grilling, baking, searing, and frying (Zhang et al., 2020). These exogenous AGEs, which are structurally and functionally similar to those produced internally (Cai et al., 2002), can enter the body through food intake, presenting potential health risks (Uribarri et al., 2010). While some consider the potential impact of exogenous AGEs on health to be low compared to that of endogenously formed AGEs, mainly due to their limited absorption and quick elimination (Ames, 2007; Henle, 2007; van Dongen et al., 2022), animal experiments and human trials have conclusively shown that the food-borne AGEs are absorbed and contribute to the body's pool (Koschinsky et al., 1997; Rietjens et al., 2022; Tessier et al., 2016; Yuan et al., 2023).

Considering their potential adverse health impacts, AGEs are commonly referred to as "glycotoxins" (Monteiro-Alfredo & Matafome, 2022). It is a misconception to classify all AGEs as glycotoxins, given their structural and functional diversity (Delgado-Andrade & Fogliano, 2018). Till now, more than 40 varieties of AGEs have been found (Tian et al., 2023). Among them are various low molecular mass (LMM) AGEs which may show higher bioavailability upon oral exposure than high molecular mass (HMM) AGEs (van Dongen et al., 2022). LMM AGEs include compounds like N-ε-(carboxymethyl)lysine (CML) which is the most extensively studied AGE and is commonly employed as a biomarker to evaluate potential exposure and related health risks (Yu et al., 2022). N-ε-(carboxyethyl)lysine (CEL) is another LMM AGE that is extensively studied, particularly regarding its formation during food production and its modes of action in biological models (Zhang et al., 2023). The LMM AGEs included in the present study were, in addition to CML and CEL, also glycolic acid-lysine-amide (GALA) and pyrraline.

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GALA is formed via glyoxal-imine precursors generated from Amadori compounds through retro-Amadori rearrangement, retro-aldol fragmentation and subsequent oxidation (Glomb & Pfahler, 2001). Pyrraline is commonly found in food with low water activity (Feng et al., 2023). Its significance lies in its ability to facilitate protein cross-linking, thereby altering their structure and function. In our previous study we applied an in vitro Caco-2 transwell cell model to study the intestinal uptake and transport of a series of 10 LMM AGEs (Li et al., 2025), including CML, CEL, GALA and pyrraline. The results showed that different AGEs displayed significant variation in their rate of transport across the Caco-2 cell layer and in their accumulation in the intestinal cells. Of the LMM AGEs studied GALA was transported at the highest rate and CML accumulated to the highest extent. Different dietary AGEs enter the systemic circulation through the intestines in different ways. The intestinal transport in the Caco-2 model system was shown to proceed mainly by passive diffusion and to be dependent on the physico-chemical characteristics of the LMM AGEs like their molecular weight, polarizability, and projection area/radius (Li et al., 2025). For some AGEs, specific intestinal transporters may play a role, like the potential role of the proton-coupled peptide transporter PepT1 for translocation of glycated di-tripeptides (Grunwald et al., 2006). Even though the LMM AGEs showed differences in their transport characteristics in the Caco-2 cell model, they were all transported to an only limited extent, an observation also reported in in vivo studies. Human experimental results indicate that approximately 10 % of dietary AGEs are absorbed into the circulation, corroborating their limited bioavailability (Koschinsky et al., 1997). This fuels the debate about the contribution of exogenous AGEs to the total endogenous exposome, given that AGEs will also result from endogenous pathways. While the absorption of AGEs through the intestines and their excretion via urine have been reported, the extent to which oral intake contributes to the total body burden is still highly uncertain, complicating efforts to pinpoint whether their main sources are endogenous or exogenous. Xu et al. (2013) synthesized ^{18}F-CML and further investigated the distribution and elimination of this labeled model LMM AGE in mice. Moreover, Tessier et al. (2016) examined the biodistribution of labeled CML-enhanced proteins following long-term dietary intake, offering a novel perspective on the origin of AGEs within the body. These biodistribution studies used labeled AGEs enabling differentiation of exogenous glycation products from endogenously formed ones, ultimately highlighting the accumulation potential of dietary AGEs within the body, particularly in the kidneys, intestines, and lungs. These studies, however, focused on individual AGEs, hampering comparison between different AGEs because the compounds were studied in different studies, at different dose levels, in different species and in isolation. As a result, the dynamics and interactions of multiple AGEs, when externally dosed at similar dose levels, were not taken into account. Our study innovatively uses a mixture of labeled LMM AGEs, administered in a single oral dose, enabling direct comparison of the plasma and tissue distribution and of different AGEs at similar doses within the same in vivo system, thereby providing new insights into the comparative tissue distribution of multiple AGEs.

The aim of this study was to obtain insight into the differences in bioavailability and biodistribution of a series of selected LMM AGEs and to quantify to what extent exogenous exposure contributes to the total exposome of the AGEs by comparison to their endogenous levels. To this end the levels of a series of isotope labeled LMM AGEs administered exogenously by oral gavage as a mixture in a single oral dose to rats, in blood and various target tissues were quantified and compared to levels of their endogenously formed unlabeled analogues. This provided clues of the biodistribution of dietary free AGEs compared to the endogenous AGEs, of importance to elucidate their biological significance and contribution to the overall internal exposome.

2. Materials and methods

2.1. Chemicals

Commercial analytical standards pyrraline, GALA, CEL, CML pyrraline-d4, CEL-d4, CML-d4, were obtained from Iris biotech GmbH (Marktredwitz, Germany). Solvents employed in Liquid Chromatography-Mass Spectrometry (LC-MS) were all high-performance liquid chromatography grade. All other reagents utilized in this study were either analytical grade or high-purity chemicals.

2.2. Animal study

Sprague Dawley (SD) male rats provided by Beijing Sibeifu Biotechnology Co., Ltd. (Beijing, China) (Certificate No: SCXK (Jing) 2019–0010) were randomly divided into two groups (Exposure group and Control group), with 6 rats per group, 12 rats in total. At the start of the experiment, the average body weight was 198.8 ± 6.5 g. The rats were housed at Hebei Chenguang Detection Technology Services Co. Ltd. All experimental protocols for the animal study were approved by the Laboratory Animal Welfare Ethics Committee of Hebei Chenguang Detection Technology Services Co. Ltd. (No. JC-LL-W24001). All experiments were carried out following guidance on the operation of the Animals (Scientific Procedures) Act 1986 and associated guidelines, EU Directive 2010/63 for the protection of animals used for scientific purposes. The experiment was preceded by a five-day acclimatization period during which the rats were housed in an animal testing facility under a controlled environment with temperatures between 21–23 °C, humidity of 50–60 %, and a 12-h light-dark cycle. Throughout this period, the rats had free access to standard feed which was obtained from Beijing Sibeifu Biotechnology Co., Ltd. (Beijing, China). The concentrations of free CML and free CEL in the rodent chow are approximately 2.78 μg/g and 0.45 μg/g, respectively (van Dongen et al., 2021).

Prior to the start of the experiment, the rats underwent a 12-h fasting period with unrestricted access to water. On the day the experiment started, the weight of the rats was recorded. The rats in the Exposure group were administered an oral gavage administration of an exogenous LMM AGE mixture containing CML-d4, CEL-d4, pyrraline-d4, and GALA, at levels resulting in a dose level of 10 mg per AGE/kg body weight (BW), dosed in around 0.5 mL per rat in saline. The control group was administered an equal volume of saline. Following administration, the rats were housed individually in metabolic cages. All fecal and urinary samples were collected over a period of 2 h. Then the rats were anesthetized with an intraperitoneal injection of sodium pentobarbital (40 mg/kg BW), followed by blood collection from the abdominal aorta in a procoagulant inert separation tube (Kangweishi Medical Apparatus and Instruments Co., Shijiazhuang, China), and then euthanized by transection of the aorta. The time point of 2 h post administration was chosen for quantification based on the fact that the Cmax for CML was observed at 1–2 h post administration in previous studies (Alamir et al., 2013; Helou et al., 2022; Yuan et al., 2023), thus providing the way to detect the highest possible contribution of the exogenously administered AGEs to the total exposome. Each blood sample was centrifuged at 3000 $\times g$ for 10 min at 4 °C to obtain serum, which was then stored at −80 °C until sample processing and analysis. The collected organs and tissues including the kidneys, lungs, brain, heart, duodenum (with luminal content), jejunum (with luminal content), ileum (with luminal content), colon and colon luminal content (collected separately), liver, thigh skeletal muscle, abdominal white adipose tissue, and testes were rinsed with cold 0.9 % saline solution to remove any blood and external contaminants. For the duodenum, jejunum and ileum, the luminal contents were left intact during the rinse. For the colon, the shaped colon luminal content was collected separately by gently massaging the exterior of the colon while maintaining the integrity of the tissue before rinsing. All samples were then stored at −80 °C until prepared for analysis.

2.3. Quantification of free and protein-bound AGEs by high-performance liquid chromatography-tandem mass spectrometry

2.3.1. Sample preparation

Before conducting MS analysis on the levels of all tested AGEs (labeled and unlabeled), each organ or tissue or fecal samples was first lyophilized to determine the dry matter (DM) weight of each organ or tissue, and then the samples were transferred to a fully automatic sample freeze-grinding instrument (JXFSTPRP-CLN, Jingxin, Shanghai, China) for further homogenization into powder before proceeding with the next step of extraction. Urine samples were aliquoted into 100 μL portions in Eppendorf tubes, followed by lyophilization for redissolution and measurement. The extraction process for both free and protein-bound AGEs in the samples was carried out in line with previous protocols (Tessier et al., 2016; Yuan et al., 2021). For tissues, organs, feces, and serum, both free and protein-bound AGEs were measured. For urinary samples, only the levels of free LMM AGEs were quantified.

Briefly, the procedure involved adding 15 μL trichloroacetic acid (TCA) to 30 μL serum or adding 200 μL 10 % (*v*/v) TCA to 10 mg of either lyophilized tissue or fecal samples. These mixtures were then kept on ice for 30 min followed by centrifugation at 4 °C at 21000 ×*g* for 10 min. The supernatant (containing free AGEs) was separated from the protein precipitate (containing bound AGEs), and subsequently dried under a nitrogen flow. After nitrogen evaporation, the serum samples were redissolved with 100 μL ultrapure water, while the tissue and fecal samples were redissolved with 200 μL ultrapure water for further filtration and LC-MS analysis. For urine, lyophilized urine samples were directly redissolved by 200 μL ultrapure water without TCA precipitation step. For analyzing the protein-bound AGEs, the protein pellets from feces, serum, or tissue samples were transferred into acid hydrolysis tubes using 100 μL ultrapure water combined with 500 μL 0.1 mol/L sodium borohydride dissolved in 0.2 mol/L borate buffer pH 9.18 and incubated at room temperature (20 °C) for 2.5 h to reduce the reactive precursors in the sample to inhibit the formation of AGEs under acid environment in further steps. Then, 600 μL 12 mol/L hydrochloric acid was added to each sample to reach a final concentration of reaction solution of 6 mol/L, followed by acid hydrolysis at 110 °C for 21 h. Following nitrogen drying, the protein hydrolysates were redissolved in 200 μL ultrapure water. Before LC-MS/MS analysis, all samples were filtered through a 0.22 μm filter (ANPEL Laboratory Technologies Inc., Shanghai, China). The final results are expressed in μg/mL (serum) and μg/g dry matter (DM), and for feces and urine, they are expressed as μg/2 h.

2.3.2. Analysis of AGEs by LC-MS/MS

The quantification of AGEs on LC-MS/MS was conducted using a Shimadzu Nexera XR LC-20 CE UPLC system (Kyoto, Japan), coupled with a Shimadzu LCMS-8040 triple quadruple mass spectrometer (Kyoto, Japan). The setup included an ACQUITY UPLC BEH Amide Column (1.7 μm, 2.1 mm × 100 mm) along with a matching ACQUITY UPLC BEH Amide VanGuard Pre-column (1.7 μm, 2.1 mm × 5 mm). The column temperature was maintained at 40 °C. The mobile phase consisted of water containing 0.1 % (*v*/v) formic acid (solvent A) and acetonitrile containing 0.1 % (v/v) formic acid (solvent B). The gradient program was set as follows: 0–10 min, 75–12.5 % solvent B; 10–11 min, 12.5 % solvent B; 11–12 min, 12.5–95 % solvent B; 12–14 min, 95 % solvent B; 14–14.5 min, 95–75 % solvent B; 14.5–19 min, 75 % solvent B. The flow rate program was set as follows: 0–0.3 min, 0.30–0.25 mL/min; 0.3–10 min, 0.25 mL/min; 10–11 min, 0.25–0.15 mL/min; 11–12 min, 0.15 mL/min; 12–14 min, 0.15–0.30 mL/min; 14–19 min, 0.30 mL/min. The MS/MS analysis was performed in positive ion mode. During the gradient running period from 1 to 11 min, the line was set to MS, and during other time periods, the line was set to waste. For accurate identification of target analytes, two transitions were selected: one for quantitative analysis and the other for qualitative confirmation as follows: pyrraline *m/z* 255.05 → 175.30 for quantitative and 255.05 → 237.15 for qualitative analysis; pyrraline-d4, *m/z* 259.05 → 179.30 for quantitative and 259.05 → 241.15 for qualitative analysis; GALA, *m/z* 205.00 → 84.10 for quantitative and 205.00 → 142.30 for qualitative analysis; CEL *m/z* 219.05 → 84.25 for quantitative and 219.05 → 130.10 for qualitative analysis; CEL-d4, *m/z* 223.05 → 88.25 for quantitative and 223.05 → 134.10 for qualitative analysis; CML *m/z* 204.95 → 84.10 for quantitative and 204.95 → 130.15 for qualitative analysis; CML-d4, *m/z* 208.95 → 88.10 for quantitative and 208.95 → 134.15 for qualitative analysis.

2.4. Data and statistical analysis

The Shimadzu LabSolutions software facilitated system operation and data acquisition. Linear calibration curves were developed by plotting concentrations against peak areas, which were prepared by adding different concentrations of a mixture of labeled AGEs to blank (control) dried tissues/organ/feces powder or blood or urine samples, which were subjected to the same extraction procedure as applied to the samples to be analysed. The peak areas of analytes from the samples were interpolated onto the calibration curves. Based on existing studies (Yuan et al., 2023), serum levels of the free LMM AGE - CML, stabilize back to baseline levels at 12 h following administration of a dose of 10 mg CML per kg BW. Therefore, in the present study the rats underwent a 12-h fasting period before dose administration, so that it could be assumed that endogenous unlabeled levels of the LMM AGEs detected are unlikely to result from exogenously unlabeled AGEs present in the diet, thus negating the need for correction for dietary exposure when quantifying endogenously formed levels of the AGEs. As a result, the labeled AGEs detected can be considered of exogenous origin, whereas the unlabeled AGEs can be considered as endogenous. In the case of GALA, for which there was not commercially available labeled compound, levels detected in exposed rats were compared to levels detected in controls to obtain insight in the exogenous versus exogenous origin of this LMM AGE. In addition, since the calibration curves for unlabeled GALA were made in tissue samples, these calibration curves also provide information on the endogenous concentration of GALA in each organ, reflected by the y-axis intercept above zero. Using this information, the level of GALA in the control group can be derived from the x-axis intercept.

Data analysis was conducted using Microsoft Excel and GraphPad Prism version 5.0. The results are expressed as the mean ± standard error of the mean (SEM). Statistical analysis was performed using SPSS 20.0 (IBM Corporation, Armonk, NY, USA) for *t*-tests and one-way ANOVA. Statistical significance was established at a $p \leq 0.05$.

3. Results

3.1. Levels of free AGEs

Fig. 1 presents the levels of free exogenous and endogenous AGEs in the serum of rats at 2 h following gavage administration of a mixture of LMM AGEs. The average serum concentration of endogenous pyrraline, GALA, CEL and CML, were 0, 144.6, 50.7, 43.8 ng/mL, respectively. Serum free concentrations of the labeled AGEs, reflecting AGEs originating from the oral exogenous dose, amounted for pyrraline, GALA, CEL and CML, to 129.2, 5832.5, 2381.1, 1928.9 ng/mL, respectively. These results imply that in serum the levels detected 2 h upon oral dosing of 10 mg/kg BW were 40.3, 47.0 and 44.0-fold higher than the endogenous unlabeled serum levels for GALA and CEL and CML, respectively. For pyrraline, the endogenous unlabeled amount was below the detection limit (0.005 mg/L sample solution). Following 2 h of oral administration, the exogenous AGEs dosed as a mixture, were present in the bloodstream at different levels, with the serum concentrations ranking in the order GALA>CEL>CML> > pyrraline while the order for the endogenously formed counterparts was comparable being GALA > CEL = CML > > pyrraline.

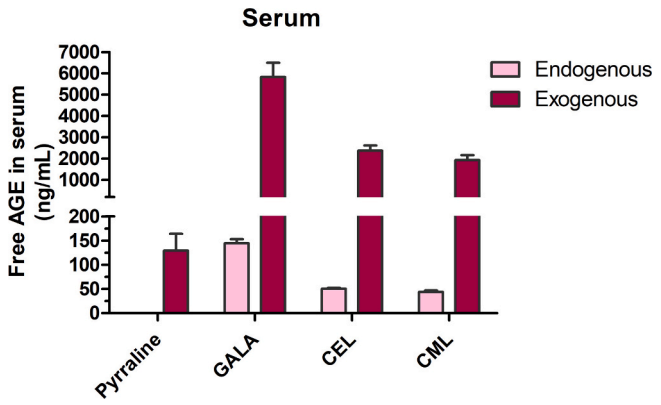

Fig. 1. Serum concentration of free- exogenous and endogenous AGEs in rats at 2 h after oral gavage administration of an exogenous LMM AGE mixture of 10 mg/kg BW each.

Fig. 2 presents the levels of free endogenous and exogenous AGEs in different segments of the gastrointestinal tract including the duodenum, jejunum, ileum, and colon 2 h after gavage administration of the LMM AGE mixture.

The results indicate that after oral gavage administration of a LMM AGE mixture, the free exogenously added AGEs display varying occurrence patterns throughout the intestine, pointing at differences in their absorption and/or transit time. With the exception of CML in the ileum, endogenous LMM AGEs were hardly detected so that exogenous AGEs represent the predominant AGEs in the intestine. For the duodenum (with luminal content), the concentrations of exogenous CEL and CML are relatively high, reaching 890.2 μg/g DM and 900.7 μg/g DM, followed by those of pyrraline and GALA amounting to 38.8 μg/g DM and 29.0 μg/g DM. For the jejunum (with luminal content), the concentration of CEL is at a level similar to that in the duodenum, whereas the levels of the other AGEs are lower compared to those in the duodenum. In the ileum (with luminal content), the concentration of pyrraline is higher than in the jejunum, whereas CML remains similar to that in the jejunum. Both CEL and GALA are lower than that in the jejunum. The incompletely absorbed AGEs in the small intestine will be further transported into the colon. The results show that exogenous GALA is somewhat more noticeable in the colon, compared to other AGEs, but overall, the amounts in colon, presented as the sum of what was detected in the separately collected colon tissue and content, are low compared to the other intestinal compartments. This is likely due to the fact that time after dosing was shorter than full gastrointestinal transit time in rats, know to amount to about 8–12 h (Dalziel et al., 2016), even for liquids, at the test meal volume (0.5 mL) involved in this study. The transit time through the stomach and small intestine has been reported to be longer than 2 h (Purdon & Bass, 1973).

Fig. 3 presents the free exogenous and endogenous AGEs detected in various organs, including the kidneys, lungs, heart, liver, spleen, brain, muscles, testes, and epididymal fat. Compared to all the other organs/tissue, the kidney showed the highest levels of free exogenous AGEs. However, the levels of accumulation differed between the LMM AGEs, ranking from highest to lowest as CEL (878.7 μg/g DM), CML (537.0 μg/g DM), GALA (64.3 μg/g DM), and pyrraline (5.4 μg/g DM). Notably, two hours after oral gavage administration of the AGE mixture, in the kidney exogenous AGEs were predominant over the background concentrations of endogenous analogues. In particular, at 2 h post dosing, in the kidneys exogenous labeled CML reached concentrations 12.5 times the level of endogenous unlabeled CML, and exogenous labeled CEL was 29.9-fold higher than endogenous unlabeled CEL, while endogenously

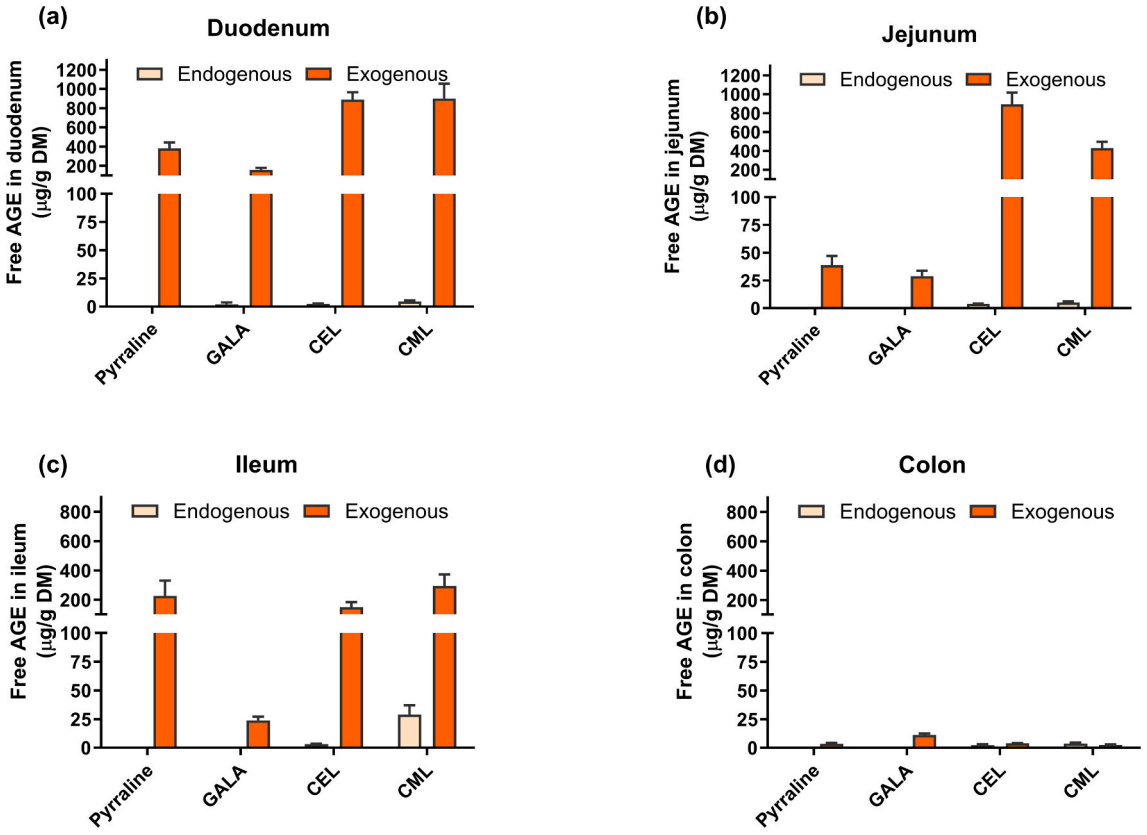

Fig. 2. Concentration of free endogenous and exogenous LMM AGEs in different segments of the gastrointestinal tract in rats 2 h after oral gavage administration of an exogenous LMM AGE mixture of 10 mg/kg BW each for (a) duodenum, (b) jejunum, (c) ileum, and (d) colon. Data presented reflect the levels in tissue plus luminal content.

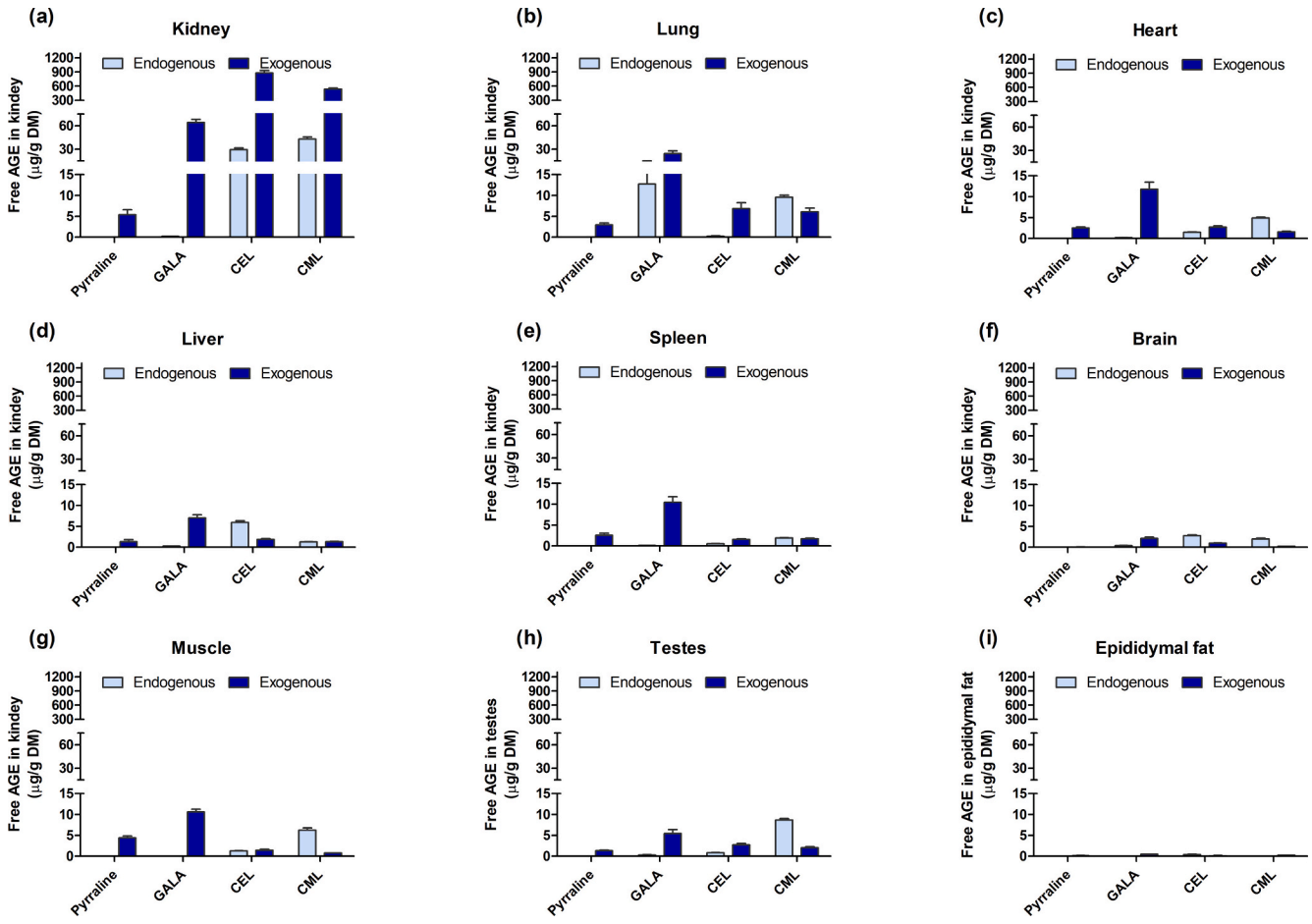

Fig. 3. Concentrations of free- endogenous and exogenous AGEs in rats in different organs and tissues after oral gavage administration of an exogenous LMM AGE mixture; (a) kidney, (b) lung, (c) heart, (d) liver, (e) spleen, (f) brain, (g) muscle, (h) testes, (i) epididymal fat.

formed levels of GALA and praline were even not detectable and insignificant compared to the levels of the exogenously administered counterparts.

The levels of exogenous AGEs in the lungs were also relatively high, with the concentration of GALA, CEL, CML, and pyrraline decreasing in that order. The accumulation of AGEs in the heart, liver, and spleen was noteworthy, though substantially lower than that in the kidneys. Moreover, different levels of exogenous AGEs were detected in muscles, testes, and even fat, indicating the contribution of dietary AGEs to the AGE pools of the whole body. The baseline levels of endogenous AGEs varied across different organs and tissues. For instance, the levels of endogenous GALA and CML were relatively high in the lungs, whereas the endogenous level of CML was high in the heart, muscles, and testes where the exogenous CML only accounted for a small fraction (32.0 %, 11.7 %, 23.5 %, respectively) of the endogenous levels. The concentration of endogenous CEL in liver and brain were higher, being 3.19 and 2.83 times the level of exogenous CEL.

Fig. S1 shows the concentration of free AGEs in the urine of rats collected over the 2 h following dosing. In the urine collected from 0 to 2 h post dosing exogenous AGEs were found at varying but relatively low levels, and at different mutual ratios than what was observed in serum or kidney. The excretion of labeled, orally administered CML and CEL was lower than that of their unlabeled endogenous counterparts, while dietary and not endogenously formed GALA and pyrraline were the main sources of these AGEs in urine. Due to the limited time period compared to the intestinal transit time, no exogenous and only limited amounts of endogenously formed AGEs were detected in the feces.

3.2. *Levels of bound AGEs*

In addition to the levels of free LMM AGEs, for CEL and CML also the levels of bound forms of these LMM AGEs in serum and relevant tissues were quantified. Since acid hydrolysis was applied prior to extraction, the detection of acid-labile AGEs like pyrraline and GALA was compromised (Akıllıoğlu & Lund, 2022). Thus, only data on the bound forms of CEL and CML are provided. Fig. 4 presents the results obtained and shows that in serum both exogenous (labeled) CEL and CML are present in bound form, although their actual levels are small compared

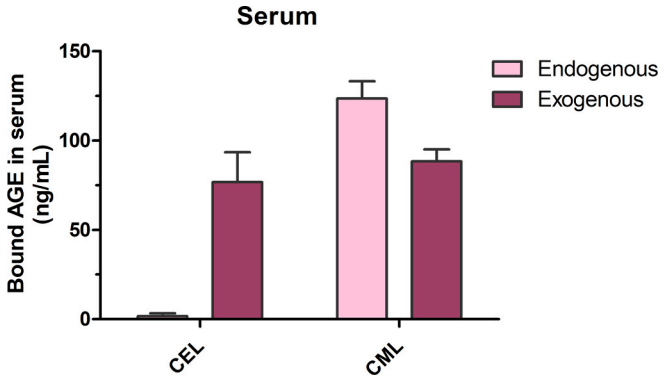

Fig. 4. Serum concentration of bound- endogenous and exogenous AGEs in rats 2 h after oral gavage administration of an exogenous LMM AGE mixture at 10 mg/kg BW each.

to the levels of the free form of these LMM AGEs in these compartments. The results presented in Fig. 5 show that a portion of both endogenous and exogenous bound AGEs was also detected in the compartments of the small intestines (with luminal content), possibly related to some bound endogenous AGEs originally present in residual luminal content, and some free endogenous and exogenous LMM AGEs that may be converted to bound AGEs during gastrointestinal passage. Fig. 6 indicates that low levels of bound exogenously administered labeled CML and CEL were detected especially in the kidneys, where the levels originating from exogenously added CEL and CML were 5.1- and 2.1-fold higher than the levels of bound CEL and CML originating from endogenous sources. Beyond this, the other organs contained mainly bound CEL and CML that originated from endogenous formation (Fig. 6).

4. Discussion

In recent years, growing evidence has indicated that the intake of foods rich in AGEs, such as baked foods, grilled foods, and highly processed products, can pose potential risks to both healthy individuals and patients with AGE related diseases such as diabetes and kidney diseases (Akıllıoğlu & Gökmen, 2019; Liang et al., 2020). The absorption, distribution, metabolism and excretion of AGEs are fundamental to understanding their adverse impacts. In this study, the bioavailability and biodistribution of a mixture of four selected LMM AGEs and the contribution of exogenous exposure to the internal AGE exposome was quantified in rats. The simultaneous dosing of multiple labeled LMM AGEs enabled a direct comparison between the different AGEs and provided insight in the differences in the relative contribution of these orally administered AGEs to the total AGE pool in the various tissues. This comparison revealed significant differences in their absorption and accumulation profiles, providing novel insights into how the different orally administered AGEs interact and contribute to the overall AGE level in the body.

Recently, a few studies reported on the bioavailability of exogenously administered versus endogenously formed LMM AGEs in both animals and humans. A common method involves altering the dietary AGE content or administering a pure AGE solution and monitoring the concentration of the respective AGE in different tissues or quantify urinary levels in order to demonstrate oral systemic bioavailability and a contribution of exogenously administered AGEs to the body exposome (Perkins et al., 2019; Yuan et al., 2023). In the past decade, studies also applied isotopic labeling as method to differentiate between exogenous and endogenous AGEs (Tessier et al., 2016; Tessier et al., 2021; Xu et al., 2013). While these studies provided practical value in indicating potential trends, the results from studies on single AGEs cannot be directly and simply compared to conclude on differences between different AGEs. Our study is the first to quantify the endogenous and exogenous levels of a series of selected LMM AGEs in rats following a single dose of a mixture. While this combined exposure facilitates comparisons between the individual AGEs studied, showing remarkable differences, the data from the combined exposure in the present study can be compared to data available from experiments with single compounds. For CML, previous studies reported comparable levels of CML in the serum of rats as what was observed in the present study, upon a similar dose level of unlabeled CML administered by oral gavage (Yuan et al., 2023). In the same report, the accumulation of CML was particularly noted in the kidney, in line with its role as an important target organ for AGE-mediated toxicity (Thornalley et al., 2003). In contrast to the literature studies where long term exposure of mice to CML or bound-CML significantly increases CML accumulation in the brain (Rabbani & Thornalley, 2018; Tessier et al., 2016; Yuan et al., 2022), limited increase in the brain level of the four LMM AGEs was observed in the short duration of our research. This may be related to the time required for the hydrophilic substances to cross the blood-brain barrier (Pulgar, 2019). Overall, the results reveal consistent outcomes between our labeled mixture exposure approach and those from single CML exposure in previous studies (Xu et al., 2013; Yuan et al., 2023). For the other compounds in this study, such data of biodistribution for comparison are

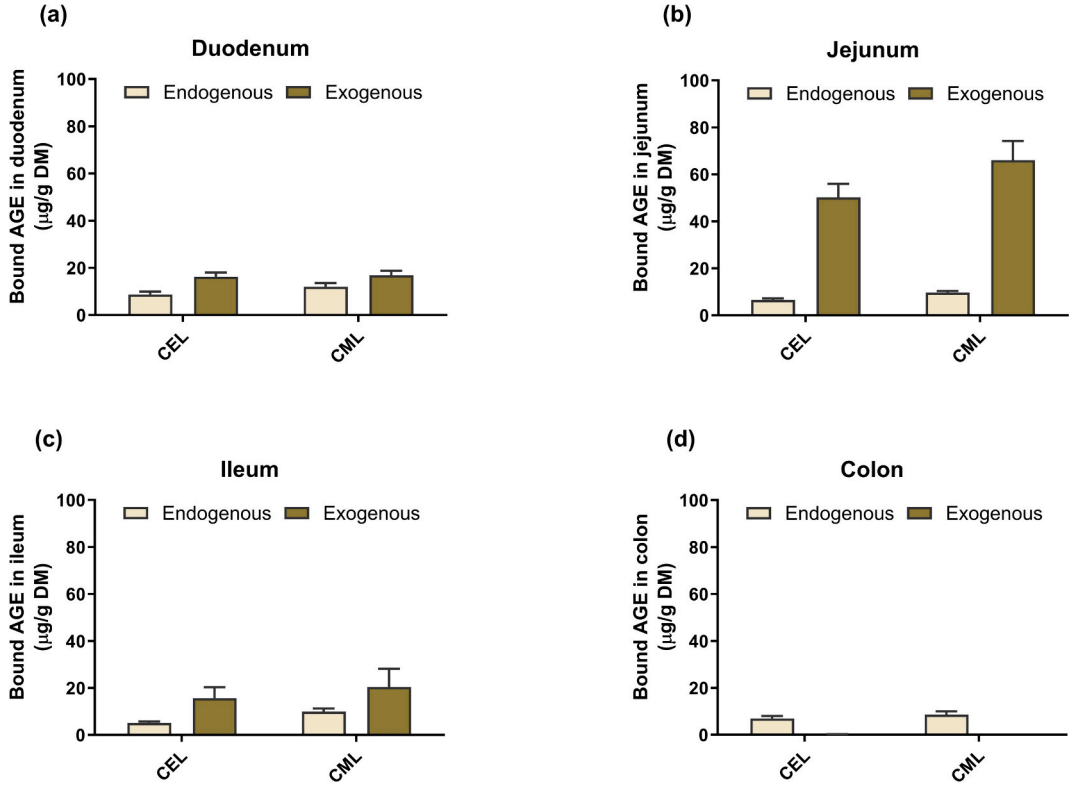

Fig. 5. Concentration of bound- endogenous and exogenous LMM AGEs in different segments of the gastrointestinal tract in rats 2 h after oral gavage administration of an exogenous LMM AGE mixture at 10 mg/kg BW each for (a) duodenum, (b) jejunum, (c) ileum, and (d) colon.

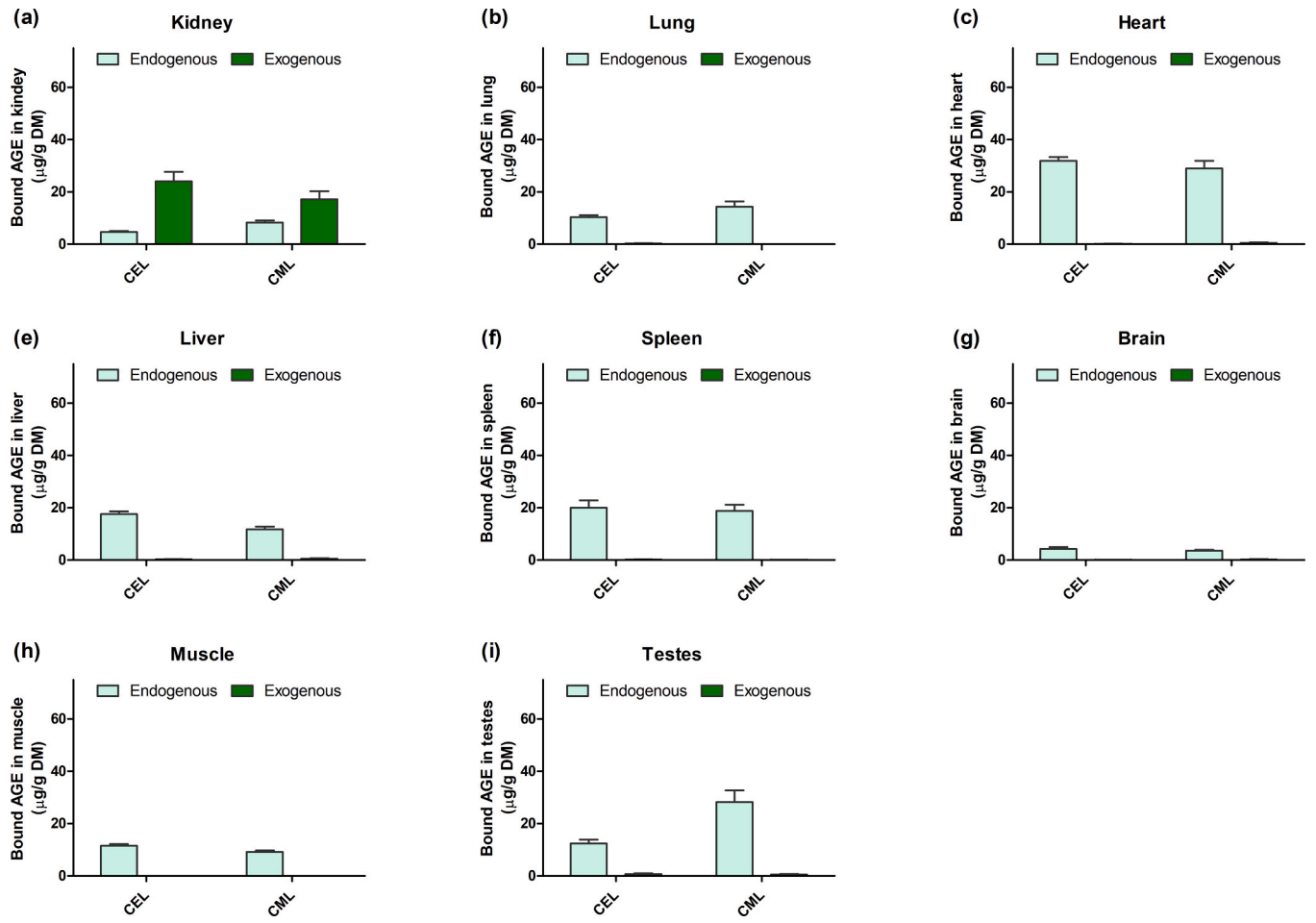

Fig. 6. Concentrations of bound- endogenous and exogenous AGEs in rats in different organs and tissues after oral gavage administration of an exogenous LMM AGE mixture at 10 mg/kg BW each in (a) kidney, (b) lung, (c) heart, (d) liver, (e) spleen, (f) brain, (g) muscle, (h) testes.

not available. Our study facilitates comparison of the in vivo fate of the LMM AGEs studied. For instance, 2 h post oral administration, the serum concentrations of CML and CEL were comparable, whereas, in spite of the comparable dose, the concentration of GALA was nearly two-fold higher than those of CML and CEL, and the serum level of pyrraline was less than 10 % of those of CEL and CML. A further analysis (Fig. S2) revealed significant correlations between organ AGE levels and serum levels of the exogenously administered AGEs, especially for testes (r^2 = 0.98), lungs (r^2 = 0.94), and brain (r^2 = 0.92). In most tissues, the level of CEL was highest, followed by CML and GALA, whereas the accumulation of pyrraline in various organs was considerably minimal, potentially attributable to its restricted bioavailability or rapid metabolism. For the excretion, it was found that the urinary elimination of the four different AGEs varied, with amounts less than the values of up to 30 % and 50 % reported previously for dietary CML and pyrraline (Förster et al., 2005), which may be attributed to the limited 2 h monitoring period in the present study, compared to 24 h urinary collection in these other studies (Yuan et al., 2023). Pyrraline was found at markedly lower levels in tissues compared to other free AGEs, such as CML, CEL, and GALA. This may be attributed to its limited intestinal absorption, in line with results previously obtained in in vitro Caco-2 transport studies, in which pyrraline showed the lowest permeability among the tested free AGEs (Li et al., 2025). In addition, its physicochemical features—such as molecular size and polarity—may limit passive transport. Its susceptibility to complexation with chyme could further limit its bioavailability. Besides, it is also possible that pyrraline undergoes faster metabolic conversion or elimination, further contributing to its reduced systemic exposure. New Approach Methodologies (NAMs) have been extensively applied to predict bioavailability, employing in vitro cell models and computational models to assess drug distribution and metabolism in the human body. Our previous research studying the intestinal transport of LMM AGEs in a Caco-2 intestinal transwell model, revealed that GALA exhibited the highest apparent permeability coefficient (Papp) value, followed by CML, CEL, and pyrraline (Li et al., 2025). A further analysis revealed that there is a strong correlation between the Papp value obtained in this previous study for the four model LMM AGEs and their serum concentration observed in the present study at 2 h post dosing (r^2 = 0.936) (Fig. S3). This correlation could also be used to obtain an indication about the serum concentration 2 h post dosing for AGEs that have not been subjected to in vivo experiments but for which Papp values from Caco-2 transport experiments are available. Given the previously noted correlations between serum and organ concentrations of AGEs (Fig. S2), it is even feasible to infer clues regarding the levels within certain tissues.

Given that the average human daily exposure to CML is 0.03–0.35 mg/kg bw (Hellwig et al., 2024; Zhang et al., 2024), and to pyrraline approximately 0.5 mg/kg bw (based on a body weight of 60 kg) (Hellwig & Henle, 2012), the gavage dose used in this study is 50-fold higher than typical human intake and provides an exaggerated model of human exposure. By converting to a physiologically relevant dose, the high administered dose can be used to further investigate the contribution of dietary intake to the endogenous AGEs pool. Assuming i) comparable dietary exposure to CEL, ii) the tissue levels of CEL and CML to vary linear with the dose, and iii) limited species differences in the toxicokinetics of these LMM AGEs, an intake of CML and CEL from dietary sources of 0.2 to 0.5 mg per AGE/kg BW (Zhang et al., 2024) (i.e. 50- and

20- fold lower than the dose level of the present study), would result at 2 h post dietary intake in free exogenous levels of dietary CEL in the kidney and lung that amount to 59.8 % and 149.5 % and to 45.2 % and 112.90 % of the corresponding endogenous level, while the bound CEL would amount to 10.2 % and 25.53 % and to 0.10 % and 0.24 % of the endogenous bound AGE levels these tissues (Table S1 and S2). For CML the levels of free dietary CML in the kidney and lung at a dose of 0.2 and 0.5 mg/kg BW would amount to 25.02 and 62.54 % and to 1.25 % and 3.13 % of the corresponding endogenous level, while the bound CML would amount to 4.12 % and 10.29 % and to 0 % of the endogenous bound CML levels in these tissues (Table S1 and S2). It is important to note that this extraction protocol retains non-covalently associated LMM AGEs, which may be associated with the protein pellet through reversible interactions. Consequently, the contribution of dietary AGEs from a regular diet on the endogenous exposome is lower than that of the endogenously formed AGEs but could in some organs reach levels that are not negligible. To complete the picture, full concentration time curves, experiments at different dose levels and repeated dose exposures will enable full evaluation of the risks associated with the accumulation of AGEs in the body due to long-term consumption of dietary AGEs.

Although a portion of the endogenously detected AGEs may be subject to washout beyond 12 h post-administration, our data are unlikely to be substantially affected by this process. Based on the AGE levels reported for standard rodent chow (van Dongen et al., 2021) and assuming a daily intake of 10 g chow, the intake of LMM AGEs can be estimated at approximately 139 μg/kg bw/day for free CML and 22 μg/kg bw/day for free CEL. Compared with the administered AGE dose of 10 mg/kg bw, the dietary contribution (including both free and bound forms) is at least one order of magnitude lower. In combination with the 12 h wash out period, it appears reasonable to assume that AGEs present in the standard diet would have a negligible influence on the ratio of endogenous versus exogenous AGEs. Nevertheless, some residual AGEs may persist in tissues, which could slightly overestimate endogenous levels. Given that complete avoidance of dietary AGE exposure is challenging in practice and that prolonged fasting may affect nutrient absorption and raise ethical concerns, this limitation has been acknowledged. Future studies that provide reliable data on tissue background levels will help clarify the distinction between endogenous and exogenous sources.

Oral gavage dosing of pure compounds in this study was used to achieve the most accurate dose administration, however, it is worth to consider that this differs from administration in the diet given that the food matrix may influence bioavailability. However, if dietary components were to reduce bioavailability, this would lower the contribution of dietary LMM AGEs to the total exposome. This implies that dosing of the pure compounds via oral gavage provides the highest possible bioavailability and thus the highest possible contribution to the total exposome. The fact that even under this dosing regimen the contribution of exogenous LMM AGEs to the overall exposome appeared to be limited, reinforces the conclusion that dietary AGEs play a minor role in the total AGE exposure. While dietary AGEs also occur in protein-bound forms (HMM AGEs) sometimes, they are hydrolyzed during digestion and ultimately absorbed as LMM AGEs, which were therefore used in this study to reflect the systemically available forms. In addition, the applied fasting period of 14 h total was chosen to stabilize endogenous AGE levels and minimize dietary interference, prolonged fasting may alter gastrointestinal physiology, including reduced enzymatic activity and slowed intestinal transit. These changes could potentially affect the absorption and distribution of orally administered AGEs. However this would have resulted in relatively higher bioavailability of the exogenously administered AGEs and even under these conditions their contribution to the total exposome appeared to be limited, supporting the overall conclusion of the study.

Moreover, while male Sprague Dawley rats were used in this study to minimize variability related to hormonal cycles, it should be noted that both rat strain, species and sex could potentially influence the metabolism and disposition of AGEs (Liu et al., 2016; Tessier et al., 2016). Further research exploring the effects of different strains, species and sexes would help to further strengthen and refine our understanding of AGE metabolism.

In the present study, we focused on evaluating the early absorption and systemic exposure of representative free AGEs based on available data indicating that plasma concentrations peak within a few hours after ingestion (Alamir et al., 2013; Helou et al., 2022; Yuan et al., 2023). Given that gastrointestinal transit in rats is reported to take approximately 1–2 h to reach the cecum and 4–6 h to reach the colon (Dalziel et al., 2016), the selected 2-h sampling window that is appropriate for capturing peak plasma concentrations (Cmax) of AGEs is likely insufficient to detect AGE accumulation in the distal gut, such as the colon. Besides, urinary and fecal excretion would have required collection over extended time periods, which was beyond the scope of the present study given tissue were to be collected at 2 h post doing. Previous reports have demonstrated that renal clearance is a significant pathway for removing dietary AGEs, with half-lives varying but beyond 10 h depending on their physicochemical properties and degree of protein binding (Chaudhuri et al., 2018; Chen et al., 2020; Koschinsky et al., 1997). Future studies extending sampling to 6 h or beyond would be necessary to evaluate colonic exposure or retention and urinary excretion.

5. Conclusion

In conclusion, our study employed a labeled LMM AGE mixture, to study the bioavailability and tissue distribution of four LMM AGEs in a way that enabled mutual comparison. Altogether, the results demonstrate that dietary AGEs increase serum AGE levels, with the absorption order being GALA>CEL>CML>pyrraline. The levels of the LMM AGEs in the lungs, testes, and brain exhibit significant correlations with serum levels of the corresponding AGE. The kidney appears to be the primary target organ for the accumulation of free AGEs. For the majority of tissues and organs, at a dose level of 10 mg/kg BW for each AGE in the mixture, exogenous free AGEs predominate two hours post oral administration over endogenous AGEs. Based on the results obtained it was estimated that at levels of normal human dietary intake the contribution of dietary AGEs to the endogenous exposome is lower than that of the endogenously formed AGEs but can especially in kidneys and lungs reach levels that are not negligible. Taken together, this study confirmed the bioavailability of free AGEs in the body and revealed distinct tissue biodistribution patterns among different AGEs, providing more insights for further investigation into their biological significance.

Abbreviation

AGEs	Advanced glycation end products
BW	body weight
GALA	Glycolic acid-lysine-amide
CML	N-ε-(carboxymethyl)lysine
CEL	N-ε-(carboxyethyl)lysine
HMM	High molecular mass
LMM	Low molecular mass
NAMs	New Approach Methodologies
TCA	Trichloroacetic acid
Papp value	Apparent permeability coefficient value.

CRediT authorship contribution statement

Xiyu Li: Writing – original draft, Visualization, Investigation, Data curation, Conceptualization. **Yaxin Sang:** Writing – review & editing, Supervision, Funding acquisition. **Xiaohan Liu:** Writing – review & editing, Investigation. **Sebastiaan Wesseling:** Writing – review & editing, Methodology. **Wouter Bakker:** Writing – review & editing, Methodology. **Ivonne M.C.M. Rietjens:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.foodres.2025.117672.

Data availability

Data will be made available on request.

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