The Roles of Dietary Glutamate in the Intestine

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Keywords

Amino acid · Metabolism · Nutrient chemosensing

Abstract

Glutamate (Glu), either as one of the amino acids of protein or in free form, constitutes up to 8–10% of amino acid content in the human diet, with an intake of about 10–20 g/day in adults. In the intestine, postprandial luminal Glu concentrations can be of the order of mM and result in a high intramucosal Glu concentration. Glu absorbed from the intestinal lumen is for a large part metabolized by enterocytes in various pathways, including the production of energy to support intestinal motility and functions. Glu is the most important fuel for intestinal tissue, it is involved in gut protein metabolism and is the precursor of different important molecules produced within the intestinal mucosa (2-oxoglutarate, L-alanine, ornithine, arginine, proline, glutathione, γ -aminobutyric acid [GABA]). Studies in adult humans, pigs, piglets or preterm infants indicate that a large proportion of Glu is metabolized in the intestine, and that for the usual

range of Glu dietary intake (bound Glu and free Glu including added Glu as a food additive in normal amounts up to 1 g/day), circulating Glu is tightly maintained at rather low concentrations. Systemic blood levels of Glu transiently rise when high doses monosodium glutamate (>10–12 g), higher than normal human dietary consumption, are ingested and normalize within 2 h after the offset of consumption. Glu is also involved in oral and post oral nutrient chemosensing that involves gustatory nerves and both humoral and neural (vagal) gut-brain pathways with an impact on gut function and feeding behavior. Glu functions as a signaling molecule in the enteric nervous system and modulates neuroendocrine reflexes in the gastrointestinal tract. The oral taste sensation of Glu involves its binding to the oral umami taste receptors that triggers the cephalic phase response of digestion to prepare for food digestion. Glu is sensed again in the gut, inducing a visceral sensation that enhances additional gut digestive processes through the visceral sense (vago-vagal reflex).

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Introduction

Glutamate (Glu) is a non-essential amino acid, and the most important excitatory neurotransmitter in the central nervous system and in the periphery. In the gut, dietary Glu is extensively metabolized as a major energy substrate, plays a role in amino acid metabolism and in the disposal of dietary protein, and is the precursor of different important biologically active molecules. In the gut and other tissues Glu, including the dietary-derived fraction, also plays a role in sensory, neurotransmission, and different regulatory processes.

Origin of Dietary Glu in the Gut

Glu, either in a bound form (as one of the amino acids of protein sequences) or in a free form, constitutes up to 10% of amino acids content in the average human diet.

Glu is among the most abundant amino acids (8–10%) found in dietary proteins and as such naturally occurs in foods with high protein content (meats, seafood, stews, soups, and sauces) [1]. Free dietary Glu, either naturally present in some products or produced by fermentation by bacteria (*coryneform* bacteria, *lactobacilli* bacteria) in fermented foods, also occurs in many foods consumed by humans (seaweeds, cheeses, fermented beans, tomatoes, mushrooms, cured ham, scallops, tuna, green peas, fish and soy sauces, beef, yeast extract, hydrolyzed vegetable proteins and autolyzed yeast extract, human and cow's milk) [2–6]. In addition, free dietary Glu is provided as salts of sodium, potassium, calcium, or magnesium used in foods, and in particular monosodium glutamate (MSG) with the most prominent flavor enhancing capacity and umami potency is used to enhance the flavor and palatability of foods [7–11].

Total dietary Glu intake that comprises protein-associated Glu and free Glu is about 10–20 g/day in adults with different origins and dietary habits [12–14]. In the total Glu intake from various dietary sources, MSG dietary consumption represents a relatively small fraction (5–10%) [15]. Food intake data in the USA and Europe indicate an average daily consumption of food-added MSG of 0.6 g, with a range of 0.3–1.0 g/day and an intake of about 2.0 g/day for high consumers [12, 16–18]. In East and Southeast Asian countries, MSG intakes are 2–3 times higher when compared to those reported in the USA and Europe with an intake of 1.5–3.0 g/day in Taiwan, 1.1–1.6 g/

day in Japan and 1.6–2.3 g/day in South Korea [12, 13, 19]. The health impact of the consumption of free Glu salts has been addressed elsewhere [20].

In addition to the dietary origin, free Glu is produced by the gut microbiota (*lactobacilli* bacteria) in the large intestinal lumen [6]. Moreover, both prokaryotes and eukaryotes synthesize γ -aminobutyric acid (GABA), a major inhibitory neurotransmitter of the CNS, through the decarboxylation of Glu by glutamate decarboxylase (GAD) and genes encoding GAD are present in the gut microbiota (*Lactobacillus*, *Bifidobacterium*) than can synthesize GABA from Glu in the distal intestinal lumen. Commensal *Bifidobacterium dentium* produce GABA via enzymatic decarboxylation of glutamate by GadB and daily oral administration of this specific *Bifidobacterium* strain induced the production of GABA [21].

Glu Metabolism in the Gut

Glu is an important nutrient in the maintenance of intestinal mucosal activity. Glu is the most important fuel for intestinal tissue, it is involved in gut protein metabolism and is the precursor of different important molecules produced within the intestinal mucosa (2-oxoglutarate, L-alanine, ornithine, arginine, proline, glutathione, GABA) [22]. In the intestine, Glu is taken up from the lumen or is produced in the epithelium from glutamine through glutaminase activity. The gastrointestinal tract is the route for the penetration of ingested dietary Glu into the body. Intestinal mucosal tissue is exposed to a high concentration of Glu from the diet and postprandial luminal Glu concentrations can easily be in the order of millimolars, which may accordingly result in a high intramucosal Glu concentration [23]. However, as the gastrointestinal tract has a very high capacity for using Glu, most of the luminal Glu is metabolized within the gut to other amino acids, such as alanine, or utilized as a source of energy within intestinal epithelial cells, and under the usual conditions of intake, the transfer of dietary Glu in the portal vein is low and Glu concentration in peripheral blood is low (10–50 μ M) compared to other amino acids [24–26].

Glu absorbed from the intestinal lumen is for a very large part metabolized by enterocytes in various pathways, including the production of energy to support intestinal motility and functions [27–31]. After transport from the intestinal lumen across the apical membrane of the intestinal enterocyte, Glu catabolism occurs in

the cytosol and mitochondria by transamination by aspartate aminotransferase, alanine aminotransferase, branched chain aminotransferase, and glutamate dehydrogenase which are expressed along the intestine [32–34]. These metabolic pathways include transamination of glutamate to alanine and aspartate, as well as the formation of other metabolites (α -ketoglutarate, γ -aminobutyrate, urea, and glutathione). Glu undergoes transamination with pyruvate generating 2-oxoglutarate oxidized in the tricarboxylic acid cycle generating malate, pyruvate, and NADH and FADH₂ is used to promote ATP synthesis, and L-alanine exported through the hepatic portal vein to the liver. Glu is a major energy substrate in the gut and approximately 35% of the total energy consumption of intestinal mucosal cells is derived from dietary Glu oxidized to CO₂ [27, 35–38]. Most of the glutamine (55–70%), Glu (52–64%), and aspartate (52%) are oxidized to carbon dioxide in the intestine [27, 35, 39, 40]. In the neonate, the GI tract also preferentially uses dietary glutamine and Glu as respiratory fuels and dietary Glu is almost completely oxidized in the mucosal cells of the intestine as an energy source for growth and function [41]. One of the consequences of gut Glu metabolism is that plasma Glu levels are not strongly affected by dietary Glu and circulating Glu is tightly maintained at rather low concentrations [42].

Studies with adult humans, pigs, piglets or preterm infants indicate that a large proportion of Glu is metabolized in the intestine and that the usual range of Glu dietary intake (bound Glu and free Glu including added Glu as a food additive in normal amounts up to 1 g/day MSG) has a relatively small impact on Glu plasma levels. In healthy adults, about 96% of the enterally delivered L-Glu is removed by the splanchnic bed on the first pass [43, 44]. In premature human infants on enteral feeding, some 74% of Glu is removed in the first pass [45]. In premature infants, splanchnic extraction is the major fate of dietary Glu, which is not a significant gluconeogenic substrate in these infants [30]. These studies in premature infants and adults indicate that about 75–80% of the dietary Glu intake is metabolized in first-pass by splanchnic tissues and that a large proportion above 80% of this Glu is oxidized to CO₂. Taken together, the rapid metabolism and use of Glu in the intestine explains why normal dietary consumption of MSG has no major effect on plasma Glu concentration [46]. In young piglets fed a high-protein, milk-based formula, 95% of the dietary glutamine, Glu, and aspartate are used *in vivo* by the gastrointestinal tract [29, 40] and 5% of enteral Glu appeared in portal blood [28].

In piglets, about 90% of the dietary Glu is metabolized by the gut and 50% of this fraction is converted to CO₂ [28, 40].

Under usual levels of intake (1–2 g/day), the majority of ingested MSG is actively metabolized in the intestine and the concentration in blood remains low (about 10–50 μ M). Only with high doses of MSG (i.e. >10–12 g), at levels higher than usual human dietary consumption, do systemic blood levels of Glu transiently rise, particularly when ingested without food or if MSG is administered by parenteral routes, and these elevated plasma levels normalize within 2 h after the offset of consumption [24, 26, 47, 48]. The concurrent consumption of sucrose, starch, gelatin, or ingesting MSG with foods, blunts for a part the plasma increase that is reduced by up to several times in relation to an increase in the gut metabolism through transamination of Glu with other metabolites [48–50]. When MSG was added at 15, 40, and 45 mg/kg (total, 100 mg/kg/day) respectively to the breakfast, lunch, and dinner meals, plasma Glu concentrations slightly but significantly increased after lunch and dinner, but the circadian variations of plasma glutamate were small (between 32 and 53 μ M) and varied significantly as a function of the time of day, indicating that Glu is actively metabolized in the gut [46]. In adult pigs, transient portal and arterial increase in Glu concentration was observed when the diet was supplemented with 10 g MSG, but the most part of MSG was metabolized in the gut [51]. In post-weaning pigs, dietary supplementation with 4% MSG (2 g MSG/kg BW/day) results in a transient, approximately 75% increase in circulating Glu levels at 1 h after feeding but the resulting concentrations in plasma remain low [52]. In piglets, an increase in Glu concentrations was observed in portal and arterial blood plasma when a basal milk formula, administered enterally at a rate of 510 μ mol/kg/h was supplemented with high MSG level (1,250 μ mol/kg/h) [53]. In these piglets when the dietary intake is increased 3–4 fold, a main part of the dietary Glu intake is metabolized by the gut, either for the generation of ATP or for conversion into other amino acids. Apart from CO₂, most of the end-products of Glu metabolism are predictably non-essential amino acids and when the dietary Glu intake is increased 3-fold, the net intestinal production of glutamine, aspartate, and ornithine increased significantly by 4.8, 4.0, and 2.7-fold, respectively [54]. In freely moving rats, MSG at 4 g/kg (40% solution) given by gavage induced an increase in plasma Glu compared to control rats receiving a 40% sucrose solution (10 mL/kg) [55].

Role of Glu in Oral and Visceral Sensation and in Regulatory Processes within the Gut

Glu is involved in the oral and post oral nutrient chemosensing that involves gustatory nerves, and both humoral and neural (vagal) gut-brain pathways with an impact on gut function, feeding behavior and food preferences [56, 57].

Glutamate functions as a signaling molecule in the enteric nervous system and modulates neuroendocrine reflexes in the gastrointestinal tract [58, 59]. Multiple glutamate receptors and transporters have been found in the gastrointestinal tract, enteric nervous system, and pancreatic tissues [60–63]. Amino acid taste receptors (T1R1/T1R3) and metabotropic glutamate receptors (mGluR1/mGluR4) are candidates for the umami taste receptor in the mouth [56]. The stomach and intestine have also specific glutamate recognizing systems in the epithelial mucosa. The primary receptor types (T1R1 + T1R3, mGluR4, and mGluR1) are found in the stomach and intestine, and both stomach and duodenal MSG can elicit mucosal responses [56, 64]. There is a large distribution and function of the major glutamate receptors along the brain gut axis [65]. Analysis of Group III mGlu receptor expression shows the presence of mGlu 4, 6, 7, and 8 receptors not only in the brain but also along the gastrointestinal tract where they are involved in several neural function and digestive processes [66]. L-Glu receptors are also involved in sensory and secretory functions of enteroendocrine cells of the gut where both the taste receptor (T1R1/T1R3) and metabotropic mGluR1 and 4 glutamate receptors are identified [67].

The taste and oral sensations of Glu include its binding to the oral umami taste receptor that participates in the signaling of the cephalic phase response of digestion, which consists of a series of autonomic reflexes, such as salivation related to food mastication and swallowing, to prepare for food digestion. Glu is sensed again in the gut, inducing a visceral sensation that enhances additional gut digestive processes through the visceral sense (vago-vagal reflex). Intragastric Glu inhibits food intake more potently than most other proteinogenic amino acids in rats [68]. Ingestion of MSG induces gastric distension and promotes gastric emptying and greater postprandial elevations of several indispensable amino acids in plasma in humans [69, 70]. Flavor preference conditioning using intragastric MSG infusions in water-restricted rats shows a 70% preference for a conditioned stimuli flavor paired with intragastric self-infusion of 60 mM (1%) MSG over a conditioned stimuli flavor paired with intragastric water [71, 72]. Post-oral MSG sensing is not restricted to

gastric sensing for the learned response as flavor preference conditioning using intragastric or intraduodenal MSG infusions in rats shows that both water-restricted and food-restricted rats acquired a significant conditioned stimuli preference for a flavor paired with intragastric or intraduodenal self-infusions of 60 mM MSG [73]. Further evidence for post oral MSG conditioning is provided by the finding that P2X2/P2X3 knockout mice, which do not taste MSG orally, acquired a preference for a flavor mixed into a 150 mM MSG solution [73–75].

There is a vagal transmission of post oral MSG sensing. Gut vagal stimulation by gastric or intestinal Glu appears to mediate post oral MSG learning. Only MSG-induced gastric vagal afferent responses to intragastric amino acids and intragastric infusions of MSG, but not other amino acids or sodium chloride, was reported to stimulate gastric vagal afferent activity [76]. Rats with total abdominal vagotomy, unlike those with hepatic vagotomy or sham surgery, failed to learn a preference for a conditioned flavor stimulus paired with intragastric self-infusions of 60 mM MSG but not with glucose. MSG administration induces a reflex activation of vagal gastric intestinal, hepatoportal and pancreatic nerve activity through oral, gastric, intestinal, and hepatoportal glutamate sensors [59].

In addition, the high Glu concentration in the intestinal microenvironment and in the microenvironment of Peyer's patches could participate in the oral tolerance to food antigens by a tonic inhibitory effect on the intestinal naïve T cells that become hypo-responsive to several stimuli and favor Th2/Treg differentiation [23].

Conclusion

Dietary Glu has numerous roles in the intestine, being involved in energy metabolism, in the synthesis of important bioactive molecules, and in sensory and signaling pathways. It is remarkable to note that although Glu represents close to 10% of amino acid content in the average human diet and that postprandial Glu concentrations in the intestinal luminal can be in the order of millimolars, the largest proportion of ingested Glu is actively metabolized in the intestinal mucosa and under usual levels of Glu intake, Glu concentration in the peripheral blood remains low (about 10–50 μ M) and transiently increase only with a high dose of Glu intake. Glu also appears as an important player in taste and oral sensations, and significant progress has been made during the last decades in the identification of Glu receptors in the gut, their signaling pathways, and their role in the control of different functions.

Ethics Statement

The author has no ethical conflicts to disclose.

Disclosure Statement

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References

- 1 Rangan C, Barceloux DG: Food additives and sensitivities. *Dis Mon* 2009;55:292–311.
- 2 Hac LR, Long ML, Bush MJ: The occurrence of free L-glutamic acid in various food. *Food Technol* 1949;3:351–355.
- 3 Yamaguchi S, Ninomiya K: Umami and food palatability. *J Nutr* 2000;130(4S suppl):921S–926S.
- 4 Jinap S, Hajeb P: Glutamate. Its applications in food and contribution to health. *Appetite* 2010;55:1–10.
- 5 Skypala IJ, Williams M, Reeves L, Meyer R, Venter C: Sensitivity to food additives, vaso-active amines and salicylates: a review of the evidence. *Clin Transl Allergy* 2015; 5:34.
- 6 Mazzoli R, Pessione E: The neuro-endocrinological role of microbial glutamate and GABA signaling. *Front Microbiol* 2016;30:1934.
- 7 Bellisle F: Effects of monosodium glutamate on human food palatability. *Ann N Y Acad Sci* 1998;855:438–441.
- 8 Chaudhari N, Landin AM, Roper SD: A metabotropic glutamate receptor variant functions as a taste receptor. *Nat Neurosci* 2000;3:113–119.
- 9 Li X, Staszewski L, Xu H, Durick K, Zoller M, Adler E: Human receptors for sweet and umami taste. *Proc Natl Acad Sci U S A* 2002;99: 4692–4696.
- 10 Nelson G, Chandrashekar J, Hoon MA, Feng L, Zhao G, et al: An amino-acid taste receptor. *Nature* 2002;416:199–202.
- 11 Zhang Y, Venkatasamy C, Pan Z, Liu W, Zhao L: Novel umami ingredients: umami peptides and their taste. *J Food Sci* 2017;82:16–23.
- 12 Giacometti T: Free and bound glutamate in natural products; in Filer LJ Jr, Garattini S, Kare MR, Reynolds WA, Wurtman RJ (eds): *Glutamic Acid: Advances in Biochemistry and Physiology*. New York, Raven Press, 1979, pp 25–34.
- 13 Maga JA, Yamaguchi S: Flavor potentiators. *Crit Rev Food Sci Nutr* 1983;18:231–312.
- 14 Briguglio M, Dell'Osso B, Panzica G, Malgarelli A, Banfi G, Zanaboni Dina C, Galentino R, Porta M: Dietary neurotransmitters: a narrative review on current knowledge. *Nutrients* 2018;10:pii:E591.
- 15 Brosnan JT, Drewnowski A, Friedman MI: Is there a relationship between dietary MSG and [corrected] obesity in animals or humans? *Amino Acids* 2014;46:2075–2087.
- 16 Rhodes J, Titherley AC, Norman JA, Wood R, Lord DW: A survey of the monosodium glutamate content of foods and an estimation of the dietary intake of monosodium glutamate. *Food Addit Contam* 1991;8:663–672.
- 17 Geha RS, Beiser A, Ren C, Patterson R, Greenberger PA, Grammer LC, Ditto AM, Harris KE, Shaughnessy MA, Yarnold PR, Corren J, Saxon A: Review of alleged reaction to monosodium glutamate and outcome of a multicenter double-blind placebo-controlled study. *J Nutr* 2000;130(4S suppl):1058S–1062S.
- 18 Beyreuther K, Biesalski HK, Fernstrom JD, Grimm P, Hammes WP, Heinemann U, Kempster O, Stehle P, Steinhart H, Walker R: Consensus meeting: monosodium glutamate – an update. *Eur J Clin Nutr* 2007;61:304–313.
- 19 Lee EH, Lee DI: A study of intake of monosodium glutamate in Korea. *Korean J Environ Health Soc* 1986;12:75–85.
- 20 Henry-Unaeze HN: Update on food safety of monosodium L-glutamate (MSG). *Pathophysiology* 2017;24:243–249.
- 21 Pokusaeva K, Johnson C, Luk B, Uribe G, Fu Y, Oezguen N, Matsunami RK, Lugo M, Major A, Mori-Akiyama Y, Hollister EB, Dann SM, Shi XZ, Engler DA, Savidge T, Versalovic J: GABA-producing *Bifidobacterium dentium* modulates visceral sensitivity in the intestine. *Neurogastroenterol Motil* 2017;29:e12904.
- 22 Hou Y, Wu G: L-glutamate nutrition and metabolism in swine. *Amino Acids* 2018;50: 1497–1510.
- 23 Xue H, Field CJ: New role of glutamate as an immunoregulator via glutamate receptors and transporters. *Front Biosci (Schol Ed)* 2011;3:1007–1020.
- 24 Stegink LD, Filer LJ Jr, Baker GL, Bell EF: Plasma glutamate concentrations in 1-year-old infants and adults ingesting monosodium L-glutamate in consommé. *Pediatr Res* 1986; 20:53–58.
- 25 Divino Filho JC, Hazel SJ, Furst P, Bergstrom J, Hall K: Glutamate concentration in plasma, erythrocyte and muscle in relation to plasma levels of insulin-like growth factor (IGF)-I, IGF binding protein-1 and insulin in patients on haemodialysis. *J Endocrinol* 1998;156: 519–527.
- 26 Graham TE, Sgro V, Friars D, Gibala MJ: Glutamate ingestion: the plasma and muscle free amino acid pools of resting humans. *Am J Physiol Endocrinol Metab* 2000;278:E83–E90.
- 27 Windmueller HG, Spaeth AE: Intestinal metabolism of glutamine and glutamate from the lumen as compared to glutamine from blood. *Arch Biochem Biophys* 1975;171:662–672.
- 28 Reeds PJ, Burrin DG, Jahoor F, Wykes L, Henry J, Frazer EM: Enteral glutamate is almost completely metabolized in first pass by the gastrointestinal tract of infant pigs. *Am J Physiol* 1996;270(3 pt 1):E413–E418.
- 29 Reeds PJ, Burrin DG, Stoll B, Jahoor F: Intestinal glutamate metabolism. *J Nutr* 2000; 130(4S suppl):978S–982S.
- 30 Hay's SP, Ordonez JM, Burrin DG, Sunehag AL: Dietary glutamate is almost entirely removed in its first pass through the splanchnic bed in premature infants. *Pediatr Res* 2007;62: 353–356.
- 31 Blachier F, Boutry C, Bos C, Tomé D: Metabolism and functions of L-glutamate in the epithelial cells of the small and large intestines. *Am J Clin Nutr* 2009;90:814S–821S.
- 32 Burrin DG, Stoll B, Chang X, Van Goudoever JB, Fujii H, Hutson SM, Reeds PJ: Parenteral nutrition results in impaired lactose digestion and hexose absorption when enteral feeding is initiated in infant pigs. *Am J Clin Nutr* 2003;78:461–470.
- 33 Suryawan A, Hawes JW, Harris RA, Shimomura Y, Jenkins AE, Hutson SM: A molecular model of human branched-chain amino acid metabolism. *Am J Clin Nutr* 1998;68:72–81.
- 34 Sweatt AJ, Wood M, Suryawan A, Wallin R, Willingham MC, Hutson SM: Branched-chain amino acid catabolism: unique segregation of pathway enzymes in organ systems and peripheral nerves. *Am J Physiol Endocrinol Metab* 2004;286:E64–E76.
- 35 Windmueller HG, Spaeth AE: Identification of ketone bodies and glutamine as the major respiratory fuels in vivo for postabsorptive rat small intestine. *J Biol Chem* 1978;253:69–76.
- 36 Windmueller HG, Spaeth AE: Respiratory fuels and nitrogen metabolism in vivo in small intestine of fed rats. Quantitative importance of glutamine, glutamate, and aspartate. *J Biol Chem* 1980;255:107–112.

- 37 Reeds PJ, Burrin DG: Glutamine and the bowel. *J Nutr* 2001;131(9 suppl):2505S–2508S; discussion 2523S–2524S.
- 38 Burrin DG, Stoll B: Metabolic fate and function of dietary glutamate in the gut. *Am J Clin Nutr* 2009;90:850S–856S.
- 39 Windmueller HG, Spaeth AE: Metabolism of absorbed aspartate, asparagine, and arginine by rat small intestine in vivo. *Arch Biochem Biophys* 1976;175:670–676.
- 40 Stoll B, Burrin DG, Henry J, Yu H, Jahoor F, Reeds PJ: Substrate oxidation by the portal drained viscera of fed piglets. *Am J Physiol* 1999;277:E168–E175.
- 41 Jacobi SK, Odle J: Nutritional factors influencing intestinal health of the neonate. *Adv Nutr* 2012;3:687–696.
- 42 Watford M: Net interorgan transport of L-glutamate in rats occurs via the plasma, not via erythrocytes. *J Nutr* 2002;132:952–956.
- 43 Matthews DE, Marano MA, Campbell RG: Splanchnic bed utilization of glutamine and glutamic acid in humans. *Am J Physiol* 1993;264:E848–E854.
- 44 Battezzati A, Brillion DJ, Matthews DE: Oxidation of glutamic acid by the splanchnic bed in humans. *Am J Physiol* 1995;269(2 pt 1):E269–E276.
- 45 Riedijk MA, de Gast-Bakker DA, Wattimena JL, van Goudoever JB: Splanchnic oxidation is the major metabolic fate of dietary glutamate in enterally fed preterm infants. *Pediatr Res* 2007;62:468–473.
- 46 Tsai PJ, Huang PC: Circadian variations in plasma and erythrocyte concentrations of glutamate, glutamine and alanine in men on a diet without and with added monosodium glutamate. *Metabolism* 1999;48:1455–1460.
- 47 Walker R, Lupien JR: The safety evaluation of monosodium glutamate. *J Nutr* 2000;130:1048S–1052S.
- 48 Stegink LD, Filer LJ, Baker GL: Plasma glutamate concentrations in adult subjects ingesting monosodium L-glutamate in consommé. *Am J Clin Nutr* 1985;42:220–225.
- 49 Wen CP, Hayes KC, Gershaff SN: Effects of dietary supplementation of monosodium glutamate on infant monkeys, weanling rats, and suckling mice. *Am J Clin Nutr* 1973;26:803–813.
- 50 Tarasoff L, Kelly MF: Monosodium L-glutamate: a double-blind study and review. *Food Chem Toxicol* 1993;31:1019–1035.
- 51 Blachier F, Guihot-Joubrel G, Vaugelade P, Le Boucher J, Bernard F, Duée P, Cynober L: Portal hyperglutatememia after dietary supplementation with monosodium glutamate in pigs. *Digestion* 1999;60:349–357.
- 52 Rezaei R, Knabe DA, Tekwe CD, Dahanayaka S, Ficken MD, Fielder SE, Eide SJ, Lovering SL, Wu G: Dietary supplementation with monosodium glutamate is safe and improves growth performance in postweaning pigs. *Amino Acids* 2013;44:911–923.
- 53 Janeczko MJ, Stoll B, Chang X, Guan X, Burrin DG: Extensive gut metabolism limits the intestinal absorption of excessive supplemental dietary glutamate loads in infant pigs. *J Nutr* 2007;137:2384–2390.
- 54 Burrin DG, Janeczko MJ, Stoll B: Emerging aspects of dietary glutamate metabolism in the developing gut. *Asia Pac J Clin Nutr* 2008;17(suppl 1):368–371.
- 55 Monno A, Vezzani A, Bastone A, Salmons M, Garattini S: Extracellular glutamate levels in the hypothalamus and hippocampus of rats after acute or chronic oral intake of monosodium glutamate. *Neurosci Lett* 1995;193:45–48.
- 56 Sclafani A, Ackroff K: Role of gut nutrient sensing in stimulating appetite and conditioning food preferences. *Am J Physiol Regul Integr Comp Physiol* 2012;302:R1119–R1133.
- 57 Uneyama H, Kobayashi H, Tonouchi N: New functions and potential applications of amino acids. *Adv Biochem Eng Biotechnol* 2017;159:273–287.
- 58 Chandrashekar J, Hoon MA, Ryba NJ, Zuker CS: The receptors and cells for mammalian taste. *Nature* 2006;444:288–294.
- 59 Nijima A: Reflex effects of oral, gastrointestinal and hepatportal glutamate sensors on vagal nerve activity. *J Nutr* 2000;130(suppl):971S–973S.
- 60 Kirchgessner AL: Glutamate in the enteric nervous system. *Curr Opin Pharmacol* 2001;1:591–596.
- 61 Fan MZ, Matthews JC, Etienne NM, Stoll B, Lackeyram D, Burrin DG: Expression of apical membrane L-glutamate transporters in neonatal porcine epithelial cells along the small intestinal crypt-villus axis. *Am J Physiol Gastrointest Liver Physiol* 2004;287:G385–G398.
- 62 Iwanaga T, Goto M, Watanabe M: Cellular distribution of glutamate transporters in the gastrointestinal tract of mice: an immunohistochemical and in situ hybridization approach. *Biomed Res* 2005;26:271–278.
- 63 Li T, Ghishan FK, Bai L: Molecular physiology of vesicular glutamate transporters in the digestive system. *World J Gastroenterol* 2005;11:1731–1736.
- 64 Akiba Y, Watanabe C, Mizumori M, Kaunitz JD: Luminal L-glutamate enhances duodenal mucosal defense mechanisms via multiple glutamate receptors in rats. *Am J Physiol Gastrointest Liver Physiol* 2009;297:G781–G791.
- 65 Filpa V, Moro E, Protasoni M, Crema F, Frigo G, Giaroni C: Role of glutamatergic neurotransmission in the enteric nervous system and brain-gut axis in health and disease. *Neuropharmacology* 2016;111:14–33.
- 66 Julio-Pieper M, O'Connor RM, Dinan TG, Cryan JF: Regulation of the brain-gut axis by group III metabotropic glutamate receptors. *Eur J Pharmacol* 2013;698:19–30.
- 67 Nguyen CA, Akiba Y, Kaunitz JD: Recent advances in gut nutrient chemosensing. *Curr Med Chem* 2012;19:28–34.
- 68 Jordi J, Herzog B, Camargo SM, Boyle CN, Lutz TA, Verrey F: Specific amino acids inhibit food intake via the area postrema or vagal afferents. *J Physiol* 2013;44:911–923.
- 69 Kusano M, Zai H, Hosaka H, Shimoyama Y, Nagoshi A, Maeda M, Kawamura O, Mori M: New frontiers in gut nutrient sensor research: monosodium L-glutamate added to a high-energy, high-protein liquid diet promotes gastric emptying: a possible therapy for patients with functional dyspepsia. *J Pharmacol Sci* 2010;112:33–36.
- 70 Boutry C, Matsumoto H, Airinei G, Benamouzig R, Tomé D, Blachier F, Bos C: Monosodium glutamate raises antral distension and plasma amino acid after a standard meal in humans. *Am J Physiol Gastrointest Liver Physiol* 2011;300:G137–G145.
- 71 Uematsu A, Tsurugizawa T, Kondoh T, Torii K: Conditioned flavor preference learning by intragastric administration of L-glutamate in rats. *Neurosci Lett* 2009;451:190–193.
- 72 Uematsu A, Tsurugizawa T, Uneyama H, Torii K: Brain-gut communication via vagus nerve modulates conditioned flavor preference. *Eur J Neurosci* 2010;31:1136–1143.
- 73 Ackroff K, Sclafani A: Flavor preferences conditioned by post-oral infusion of monosodium glutamate in rats. *Physiol Behav* 2011;104:488–494.
- 74 Ackroff K, Sclafani A: Flavor preferences conditioned by intragastric monosodium glutamate in mice. *Chem Senses* 2013;38:759–767.
- 75 Ackroff K, Sclafani A: Flavor preferences conditioned by oral monosodium glutamate in mice. *Chem Senses* 2013;38:745–758.
- 76 Uneyama H, Nijima A, San Gabriel A, Torii K: Luminal amino acid sensing in the rat gastric mucosa. *Am J Physiol Gastrointest Liver Physiol* 2006;291:G1163–G1170.