Physiological Significance of Glutamate Signaling in Gut-Brain Communication

Takashi KONDOH1,2, Hruda Nanda MALLICK1,3 and Kunio TORII1*

1Institute of Life Sciences, Ajinomoto Co., Inc., 1–1 Suzuki-cho, Kawasaki-ku, Kawasaki 210-8681, Japan
2AJINOMOTO Integrative Research for Advanced Dieting, Graduate School of Agriculture, Kyoto University, Kitashirakawaoiwake-cho, Sakyo-ku, Kyoto 606-8502, Japan
3Department of Physiology, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110029, India

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L-Glutamate is involved in the perception of umami taste, intermediary metabolism, and excitatory neurotransmission. In addition, recent studies have uncovered a variety of physiological roles for dietary glutamate, as evidenced by the fact that intragastric glutamate infusions induce flavor preference learning in rats. Moreover, glutamate increases digestive juice secretion and gastric emptying of protein-rich meals. Glutamate levels in blood and brain remain stable all day long even after the food intake since most of glutamate absorbed is oxidized in the mucosa of the small intestine as a primary energy source. Chronic ad libitum ingestion of glutamate solution contributes to reducing weight gain, fat deposition, and plasma leptin levels in comparison to ingestion of water. Glutamate receptors and their cellular transduction molecules have recently been identified in gut epithelial cells. Stimulation of gut glutamate receptors enhances the apical expression of glutamate transporters and also triggers the release of nitric oxide. Nitric oxide in turn induces gut serotonin release, which increases vagal afferent inputs to different brain regions. Notably, three brain areas, i.e., the medial preoptic area, the dorsomedial nucleus of the hypothalamus, and the habenular nucleus are activated by intragastric glutamate infusions. Total subdiaphragmatic vagotomy abolishes this response. Consistent with the above, vagotomy specifically reduces the overall intake of glutamate. Taken together, these findings contribute to the growing body of evidence indicating that glutamate signaling via dedicated taste and gut receptors influences multiple physiological functions including gut secretion, motility, digestion, absorption, metabolism and energy homeostasis.

Key words: monosodium L-glutamate; glutamate receptor; vagus nerve; gut-brain communication; energy homeostasis

INTRODUCTION

The sense of taste provides information concerning the presence of nutritive or toxic substances in foods and guides behavior for ingestion or rejection. After swallowing, digestion and nutrient absorption take place in the gut, while sensations of hunger and satiety originate in the neuronal circuits in the brain. Nutritional stimuli in the gut release hormones into the systemic circulation and activate the vagus and splanchnic nerves, which are key components of the gut-brain axis (10, 41). Brain regions that regulate homeostasis, such as the caudal brainstem and the hypothalamus, receive inputs from a variety of sources, including forebrain structures involved in reward processes (3). Neuroendocrine signals arising from the gastrointestinal (GI) tract are also integrated in these brain regions, and contribute to homeostatic regulation. However, the precise mechanisms supporting gut-brain communication remain poorly understood.

L-Glutamate is the most abundant amino acid in our body (approximately 2% of body weight) and is found in both free and protein-bound forms (27). Specific actions of glutamate are mediated by the free, rather than the bound, form through the activation of glutamate-specific receptors (ionotropic and metabotropic receptors). Glutamate is involved in the perception of umami taste, intermediary metabolism and excitatory neurotransmission. In the central nervous system, glutamate is the dominant excitatory neurotransmitter and regulates important neuronal-related functions such as synaptic plasticity, learning, memory, motor activity, and neural development (50).

Although glutamate is typically classified as a non-essential amino acid, dietary glutamate is known to be required (indispensable) in the intermediary metabolism in the small intestine (42, 43). In addition, recent studies...
have uncovered new roles for dietary glutamate in gut-brain axis activation and energy homeostasis (23–28, 44, 51–54). This review focuses on these recent findings concerning postingestive mechanisms of dietary glutamate involved in the gut-brain communication.

**GLUTAMATE (UMAMI) TASTE: A MARKER OF DIETARY PROTEIN INTAKE**

Glutamate is the most abundant amino acid in plant and animal proteins (15). Although proteins in general do not elicit any specific taste sensations, glutamate in free form elicits a unique taste termed “umami” (one of the five basic tastes) (58–60). Preference for monosodium L-glutamate (MSG) solutions reflects protein intake levels (49), leading to the hypothesis that umami taste produced by glutamate is a marker of dietary protein intake. However, it is unlikely that such “protein sensing” would depend exclusively on glutamate taste in the mouth, since only free, not protein-bound, glutamate activates glutamate receptors. In addition, the free glutamate content of natural foods does not depend on their protein content. For example, tomatoes are high in free glutamate, but not in protein-bound glutamate (15, 60). Therefore, the total glutamate content in foods (i.e., free + protein-bound forms) is a more plausible index of protein intake levels. On the other hand, the amount of free glutamate released after protein digestion may contribute significantly to the protein-related signal.

**VISCERAL MECHANISMS**

Gut epithelial cells express receptors for umami, sweet, and bitter substances that are indistinguishable from those found in the oral cavity (6, 21, 31–33, 44, 57). The downstream elements found to be required for glutamate taste transduction in the oral cavity are also co-expressed in gut cells, suggesting that such “taste-like” receptors expressed in the apical membrane of the gut epithelium are involved in GI functions such as digestion, absorption, metabolism, secretion and motility. Here we describe the existence of a glutamate-sensing system in the gut linked to glutamate absorption and activation of vagal afferent fibers that transmits food-related signals to the brain.

**Gastrointestinal glutamate receptors**

Gut epithelium consists of a variety of cells including brush cells, enteroendocrine cells and enterocytes. GI brush cells have been called a variety of names including “brush”, “tuft”, “tufted”, “caveolated”, “fibrilovesicular” or “solitary chemosensory” cells (5). In any event, GI brush cells have a structure similar to lingual taste cells. Several studies have been performed to identify the location of chemoreceptors in the gut epithelium; so far, however, the results have been inconsistent. For example, Höfer et al. (17) found expression of taste-like cells in tufted cells, while Dyer et al. (12), Wu et al. (57), Jang et al. (21) and Margolskee et al. (33) reported taste receptors in the enteroendocrine cells. In addition, Mace et al. (32) reported T1Rs in enterocytes. Therefore, identification of epithelial chemosensory cells that express receptors for nutrients needs to be further clarified in future experiments.

Currently, three candidate glutamate receptors have been identified in the gut, i.e., the heterodimer T1R1/T1R3 and the metabotropic glutamate receptors type 1 (mGluR1) and type 4 (mGluR4). The T1R1 and T1R3 proteins are found in epithelial cells of the stomach, small intestine, and colon (6). In the jejunum of a fed rat, T1R1 and T1R3 are co-localized in enterocytes, solitary chemoreceptor cells and Paneth cells (31). The mGluR4 is found at low expression levels in the rat jejunum (32). In contrast, mGluR1 is located in chief cells (pepsinogen-secreting cells) of the rat stomach (44). The cellular transduction molecules of taste glutamate receptors, including α-gustducin, transducin, phospholipase C β2, protein kinase C β1 and transient receptor potential channel M5 are also co-expressed in these cells (6, 31, 32), indicating the presence of a complete receptor transduction machinery. These findings suggest that taste-like gut glutamate receptors might detect free glutamate on the luminal side of the gut, and provide this information to adjacent cells and nerve terminals.

**Glutamate transporters and absorption**

The intestinal absorption of glutamate presumably occurs for the most part in the epithelial cells lining the mucosa, namely enterocytes. Glutamate is transported from the intestinal lumen across the apical membrane to cytosol mainly via the high affinity X^-AG system and to a lesser extent by the low affinity B^0 system (8). Studies with pig and mice tissue show that the excitatory amino acid carrier-1 (EAAC-1) is the most abundant glutamate transporter among the four proteins capable of inducing X^-AG system activity in the intestine (14, 20).

Stimulation of the T1R1/T1R3 receptor activates an intracellular signaling cascade involving α-gustducin, transducin, phospholipase C β2 and protein kinase C β1, which eventually leads to increased EAAC-1 expression in the apical membrane, thereby facilitating glutamate absorption (32). After absorption, most of the glutamate is used for energy production since glutamate is the single

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most important energy source in the intestinal mucosa \((42, 43)\). The remaining glutamate units are used for the biosynthesis of amino acids (aspartate, alanine, proline), glutathione or proteins. Therefore, glutamate levels in the blood and brain remain stable for several hours following food intake \((2, 26, 61)\).

Adding glutamate to an intestinal perfusate induces rapid internalization of T1R1, T1R3 and transducin \(\beta II\) \((32)\), suggesting the presence of a dynamic regulatory system mediating glutamate absorption. Interestingly, this glutamate absorption system acts to coordinate the regulation of apical transporters for glucose and oligopeptides reciprocally through a common enterocytic pool of protein kinase \(\mathrm{C}\) \(\beta II\) \((32)\). This intracellular network may be important for the control of energy supply to the body.

**Hormonal release**

The gastrointestinal tract is the largest endocrine organ of the body. Hormones released into the systemic circulation from the gut in response to nutritional stimuli form a key component of gut-brain communication \((10)\). Gut peptides such as cholecystokinin, glucagon-like peptide-1, oxyntomodulin, pancreatic polypeptide, and peptide YY \(_{3-36}\) reduce food intake and are thought to act as satiety signals and meal terminators \((10)\). Typically, the appetite-modifying actions of most of these peptides are partly reduced or completely abolished after vagotomy, suggesting an important role for the vagus nerve on appetite control and energy homeostasis \((10)\).

Although glutamate stimulates the vagus nerve through the release of bioactive substances such as nitric oxide and serotonin in the stomach \((36)\), there is no direct evidence indicating that dietary glutamate stimulates hormonal release from the gut into the circulation. This is in sharp contrast to the case of sweet receptor stimulation, despite the fact that the T1R1/T1R3 umami receptor shares common intracellular signaling pathways to T1R2/T1R3 sweet receptor. It remains to be clarified whether gut peptide release can be triggered after glutamate ingestion.

**Activation of vagal afferent fibers**

The vagus nerve is the major neuroanatomical link between the GI tract and the brain. Signals detected in the abdominal regions are transmitted to the nucleus of the solitary tract (NST) in the caudal brainstem via the three vagal branches, i.e., the hepatic, gastric and celiac branches. Each branch carries both afferent and efferent fibers. As vagal afferents do not project directly into the lumen, their activation by luminal signals depends on the release of secondary substances from the mucosal epithelium \((41)\).

The administration of MSG solution into the stomach, duodenum and portal vein activates vagal afferents of the gastric, celiac, and hepatic branches, respectively \((36)\), suggesting the existence of glutamate-sensing mechanisms in the stomach, small intestine and hepato-portal region.

Of the three vagal components, gastric afferents respond specifically to MSG; i.e., no response is elicited by infusing any of the other amino acids or NaCl into the stomach \((54)\). These MSG-specific responses cannot be explained by activation of T1R1/T1R3 because, at least in rodents, it functions as a broadly tuned \(\ell\)-amino acid receptor \((35)\). The activation of gastric afferents by MSG is observed in a concentration-dependent manner and includes the release of bioactive substances such as nitric oxide and serotonin \((54)\). As vagal afferents express the type 3 serotonin receptor \((5\text{-HT}_3\text{R})\) \((41)\), serotonin possibly binds to \(5\text{-HT}_3\text{Rs}\) located on gastric afferent terminals. Moreover, the vagal afferents do not respond to the intravenous administration of MSG \((54)\), implying that vagal activation by luminal glutamate administration is initiated in the GI tract since any leakage into the circulation would in principle have no effects. Anatomical and immunohistochemical evidence reveals that serotonin-immunoreactive cells are found in the stomach, particularly in the superficial part of the mucosal epithelium and at the base of the fundic glands \((18)\). \(5\text{-HT}_3\text{R}\)-immunoreactivity is localized to the neck of the fundic glands. Nitric oxide synthase 1 (NOS1) or neuronal NOS-immunoreactive cells of bipolar shape in the stomach are found in the lamina propria, where a dense network of neuronal cells is present. These findings suggest that complex cellular events mediate glutamate signaling in the stomach.

In contrast to gastric afferents, hepatic afferents respond, in either excitatory or inhibitory way, to all amino acids delivered into the portal vein \((37)\). These results suggest the existence of different mechanisms responsible for detecting amino acids between the stomach and the hepato-portal region. Again, glutamate enhances activity of hepatic afferents, but the mechanism of activation remains to be elucidated.

**Effects of vagotomy on MSG ingestive behavior**

Experiments using 30-min one-bottle acceptance tests have demonstrated the importance of the vagus nerve to MSG ingestive behavior. Ingestion of MSG solutions \((240–600 \text{ mM})\) is clearly reduced after selective abdominal vagotomy \((24, 26)\). The strengths of the
vagotomy-induced reductions are as follows: subdiaphragmatic total vagotomy (TVX) = gastric vagotomy > celiac vagotomy > hepatic vagotomy = intact controls. Since the effects of gastric vagotomy are comparable to those of TVX, the glutamate signal appears to be mediated mainly via the gastric branches that innervate both the stomach and the proximal duodenum (4). This is further confirmed by experiments employing partial vagotomy of the gastric branches: selective transection of either the right or left branches of the gastric vagus shows moderate (approximately 50%) reduction of MSG ingestion compared to bilateral transections (27). The vagotomy-induced reduction of MSG intake does not result from aversive sensations arising from the gut since intake of proline (a sweet amino acid) is unaffected by TVX (28).

The abdominal vagus nerve carries both afferent and efferent fibers. Dominant fibers in the vagal efferent are cholinergic (parasympathetic) nerve fibers (4). If the behavioral changes after vagotomy depend on parasympathetic innervation, blockade of cholinergic transmission by atropine, an antagonist of muscarinic acetylcholine receptors, would alter the behavior. As shown in Fig. 1, intraperitoneal administration of a large dose of atropine does not modify MSG ingestive behavior. These results indicate that parasympathetic innervation and cholinergic activity are not involved in vagotomy-induced changes in MSG ingestion.

If nonvagal neural inputs to the brain have any significant roles, transection of these nonvagal nerves would also alter the behavior. Surprisingly, bilateral transections of taste nerves (chorda tympani, glossopharyngeal nerve, and their combination) or the splanchnic nerve do not affect MSG ingestive behavior (27). Thus, taste nerves in the mouth and splanchnic visceral afferents seem to provide a minor contribution to glutamate ingestive behavior. Altogether, the above results suggest that the vagus nerve, especially its gastric afferent fibers, play crucial roles in the transmission of glutamate signals to the brain that promote MSG ingestion.

Glutamate intake and gut microflora

Recent data suggest that the modulation of gut microbiota affects host metabolism and has an impact on energy storage (9). An important and yet unresolved question is to what extent the gut microbiota are involved in the process of nutrient absorption (8). The first described mechanism relates to the harvesting of energy from ingested foods. Chronic ingestion of 1% MSG solution for 15 weeks in rats fed a high-fat diet increased the number of Lactobacillus slightly but significantly without altering the composition of microbiota in the cecum (our unpublished observations). This raises the possibility that dietary glutamate reduces weight gain (see below) in part by influencing the microbiota in the gut. Further studies are needed on this topic.

Luminal glutamate and positive reinforcement

Postingestive consequences are important factors determining long-term preferences for foods and fluids. Conditioned flavor preference paradigms (1, 46) are frequently used to evaluate the hedonic value of flavorful substances associated with the postoral effects of nutrients. In these associative learning experiments, changes in preference for flavored solutions (the cue acting as the conditioned stimuli) paired with intragastric infusions of a test solution (the nutrient acting as the unconditioned stimuli) are tested, so that orosensory receptors are bypassed. If the nutrient infusions have positive impacts on animals, preference for the flavored solution is increased compared to other flavors paired with intragastric water infusions (control). To date, enhanced flavor preference induced by intragastric infusions of highly caloric substances (carbohydrates,
long-chain fatty acids and ethanol) has been demonstrated (46). However, the influence of postingestive effects produced by umami substances on this paradigm have not been addressed. In a recent report (53), rats implanted with chronic intragastric cannulae were trained (conditioned) to drink either an orange or grape-flavored solution (conditioned stimulus; CS+) paired with intragastric infusions of a test solution (MSG, NaCl, or glucose at 60 mM) or a second flavored solution (CS−) paired with intragastric infusion of water. After this conditioning phase, the MSG group showed significantly higher intake and preference for the CS+ over the CS− solution during two-bottle preference tests. Neither NaCl nor glucose infusions produced significant increases in preferences. The MSG effect can be explained neither by Na+ nor by caloric load. A glutamate-specific signaling mechanism involving gut glutamate receptor stimulation and vagal activation is a plausible explanation for the behavioral effects observed. Based on these results, it is emphasized that postingestive MSG could be rewarding to animals even at a low caloric concentration (60 mM MSG and 60 mM glucose solution contain 32.6 cal/g and 43.2 cal/g, respectively).

**BRAIN MECHANISMS**

Given that the ingestion of diets containing large amounts of either protein or glutamate does not lead to appreciable changes in plasma glutamate levels (2, 25, 48, 61), the brain is unlikely to monitor protein intake via meal or diet-related variations in plasma glutamate. However, luminal glutamate content, that should rise once proteins are digested, may well reflect protein ingestion, and thus constitute a reliable signal of protein intake. Under such circumstances, the stimulation of gut glutamate receptors by luminal glutamate following protein digestion, and the subsequent activation of afferent vagal fibers, might constitute a primary mechanism by which the brain senses protein ingestion.

**Forebrain activation by intragastric nutrient administration**

The vagal afferent fibers project to the caudal part of the NST, which in turn projects to numerous areas in the brain (4). Some of these brain areas might be responsive to luminal glutamate through activation of vagal afferents. Functional magnetic resonance imaging (fMRI) studies in anesthetized rats indicate that intragastric administration of nutritive substances [glucose, MSG and NaCl at 60 mM which correspond to the most preferred concentration of MSG by rats (24–26)] activates a number of brain areas, including the cortex, basal ganglia, limbic system, and hypothalamus (23, 26–28, 51). All of these regions receive vagal information through the NST (4). Notably, three areas of the brain (the medial preoptic area, dorsomedial nucleus of the hypothalamus, and habenular nucleus) are activated only by MSG, while the nucleus accumbens is activated only by glucose. The amygdala is activated by both glucose and MSG. The medial preoptic area and dorsomedial nucleus of the hypothalamus have both been proposed as playing a role in thermoregulation (7, 11, 29), while the habenular nucleus, especially the lateral habenula, participates in affective decision-making by influencing the activity of midbrain dopaminergic and serotonergic neurons (34). The amygdala is a key structure in the evaluation of the biological significance of foods (38, 40). Such findings suggest that luminal glutamate may play a role in energy homeostasis, thermoregulation, reward processing, and emotional behavior.

In addition to these findings, the brain activation induced by intragastric glutamate, but not by intragastric glucose, is abolished after the TVX (52). These results suggest that gut luminal glutamate is “sensed” in the brain by a signal provided by the afferent vagus, which is critical for the transmission of glutamate signals to the brain.

**Cerebral blood flow changes by intraduodenal glutamate administration**

Changes in cerebral blood flow are physiological events associated with brain activation (30). Infusion of isotonic MSG solution (150 mM) into the duodenum of awake and non-fasted rats enhances overall cerebral blood flow as measured by T1-weighted MRI, with the responses peaking around 20–40 min after the start of the infusion, with flow levels decreasing with respect to baseline levels after 60 min of the start of the infusion (27). In contrast, isotonic glucose (300 mM) infusions reduce blood flow with peaking at 80 min. Neither isotonic NaCl (150 mM) nor water infusions produced significant effects. These results suggest that MSG response is ascribed neither to Na+ nor caloric load but to glutamate. Importantly, the MSG-induced response is completely abolished after the TVX (27), suggesting the crucial role of the vagus nerve in the generation of cerebral blood flow responses by luminal glutamate.

**PHYSIOLOGICAL SIGNIFICANCE**

**Secretion of digestive juices**

A growing body of evidence suggests that taste stimulation by glutamate enhances secretion of digestive
HT3R. Vagal decentralization (“Heidenhain” pouch) intravenous injection of granisetron, an antagonist of 5-

1. Vagal decentralization (“Heidenhain” pouch) intravenous injection of granisetron, an antagonist of 5-

2. In dogs

3. The stomach (isolated from the Pavlov pouch) of conscious

4. Pepsinogen from vagally innervated (“Pavlov”) small

5. Dependently potentiates secretion of acid, fluid and

6. An amino acid-rich diet (but not a glutamate diet) dose-

7. Activation, or both. In support of this idea, adding MSG to

8. Gut, central mediation upon efferent nerve (vagus)

9. Different factors such as local effects of glutamate in the

10. Stimulation is partially mediated via stimulation of 5-

11. -independent pathways. Gastric secretion by glutamate

12. Administration of MSG alone in the main stomach did not

13. Gastric secretion in the Pavlov gastric pouch. Adding NaCl (140 mM) to the amino acid-rich diet

14. showed no effect on diet-induced gastric secretion. These results suggest that glutamate, but not Na+, potentiates

15. Gastric secretion via both serotonin-dependent and

16. -HT3R. Vagal decentralization (“Heidenhain” pouch) partly reduced the potentiating effects of dietary MSG.

17. Administration of MSG alone in the main stomach did not

18. Gastric emptying while that of quinine (bitter and aversive taste) decreases it in rats (19). Adding MSG (umami and

19. palatable taste) to protein-rich meals also accelerates gastric emptying in healthy volunteers (62). Interestingly,

20. MSG produces no such effects on gastric emptying when

21. Added to an isocaloric carbohydrate meal or to water (62),

22. Suggesting that glutamate acts as a modulator of gastric

23. Motility and its effect is linked to the properties of the ingredients (protein levels) of the diet. Enrichment of

24. Protein-rich diets with glutamate may be useful for the elderly, for patients with dyspepsia and anorexia, and

25. Other individuals susceptible to delayed gastric emptying.

26. Food intake, weight gain, fat deposition and plasma

27. Leptin levels

28. Obesity increases the risk of lifestyle-related diseases such as type II diabetes, hypertension, hyperlipidemia,

29. Cardiovascular disease, and ischemia. Often, susceptible individuals want alternative treatments in order to avoid

30. Medication or forced exercise. Ingestion of functional foods or ingredients is an attractive method to prevent

31. Body fat accumulation and its effects. Since MSG is a flavor palatability enhancer (58–60), the effects of MSG

32. On food intake and body weight are of growing interest.

33. Using behavioral experiments with two drinking bottles, Kondoh & Torii (25) have recently reported on

34. The effects of MSG on body energy homeostasis. In fact, rats given free access to two drinking bottles, with one

35. Containing a 1% (w/v) MSG solution (the most preferred concentration for most rat strains) and the other plain

36. Water, showed a high preference (93–97%) for the MSG solution. Interestingly, rats ingesting the MSG solution

37. Showed smaller weight gain compared to rats ingesting no MSG solution (water only) (25). Abdominal fat mass and

38. Plasma leptin levels are also lower in rats ingesting MSG solution. Naso-anal length, lean mass, food and caloric

39. Intakes, blood pressure, blood glucose, and plasma levels of insulin, triglyceride, total cholesterol, albumin and

40. Glutamate did not differ between the two groups. After

41. One year of ingesting MSG solution, the reduced plasma

42. ammonia is an additional merit of MSG ingestion for health.

43. Food intake, weight gain, fat deposition and plasma

44. Leptin levels

45. Hedonics of taste influences gastric emptying of ingested foods. For example, addition of saccharin (sweet

46. And palatable taste) on mash food increases gastric emptying while that of quinine (bitter and aversive taste)

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since food and total caloric intake are unaffected by MSG ingestion (23, 25, 28). In support of this possibility, ingestion of MSG solution enhances diet-induced thermogenesis (47, 56). Conceivably, such effects of MSG might involve activation of the peripheral and central nervous systems such as the afferent vagal branches in the gut, the afferent sensory nerves in the oral cavity, and possibly the activation of the medial preoptic area and dorsomedial nucleus of the hypothalamus, the areas activated by intragastric MSG (26–28, 51) and known to be involved in thermoregulation (7, 11, 29).

In nursing homes for the elderly, addition of 300 mg MSG with or without flavor to the cooked meal for 16 weeks did not lead to higher overall energy intake at lunch, and neither did it increase body weight (13). Interestingly, both the MSG group and flavor + MSG group showed an average 0.7–0.8 kg reduction in body weight (0.1 kg increase in the control group). The MSG group also showed an average 0.7 kg reduction in body fat (0.1 kg increase in the control group). Unfortunately, plasma leptin was not measured in this experiment. These results suggest that MSG might also reduce body weight and body fat mass in humans without changing caloric intake. Enhanced thermogenesis may be involved in the MSG effects on energy homeostasis.

CONCLUSION

Glutamate plays an important role in the perception of umami taste, intermediary metabolism, and excitatory neurotransmission. The discovery of new physiological roles for dietary glutamate in gut-brain axis activation and energy homeostasis adds a new dimension to glutamate function. In one series of studies, we showed that dietary glutamate stimulates glutamate receptors in the stomach and intestines, producing local effects on gut function. Moreover, via the release of the signaling molecules nitric oxide and serotonin, the presence of glutamate in the gut leads to the activation of the afferent vagus nerve and, consequently, of a number of target areas in the brain. Some effects of MSG on gut function (secretion and motility) may be regulated by the brain. In another study, it was shown that the chronic intake of a palatable solution of MSG reduces weight gain (development of obesity), fat deposition, and plasma leptin levels in growing rats, most likely through an enhancement of energy expenditure. MSG also reduces the levels of the toxic waste metabolite, ammonia, in the blood. Glutamate levels in the blood and brain remain stable all day long even after food intake since most of the glutamate absorbed is oxidized in the mucosa of the small intestine as an energy source. Altogether, these findings indicate that dietary glutamate influences numerous physiological functions, suggesting a broad, integrative role for dietary glutamate in body homeostasis. Manipulation of glutamate signaling in the mouth and gut may be an effective strategy for preventing obesity, metabolic syndrome, dyspepsia and anorexia. Adding dietary glutamate to our food habits may thus increase quality of life.

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