Forum Minireview

New Therapeutic Strategy for Amino Acid Medicine: Effects of Dietary Glutamate on Gut and Brain Function

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Abstract. The gustatory and visceral stimulation from food regulates digestion and nutrient utilization, and free glutamate (Glu) release from food is responsible for the umami taste perception that increases food palatability. The results of recent studies reveal a variety of physiological roles for Glu. For example, luminal applications of Glu into the mouth, stomach, and intestine increase the afferent nerve activities of the glossopharyngeal nerve, the gastric branch of the vagus nerve, and the celiac branch of the vagus nerve, respectively. Additionally, luminal Glu evokes efferent nerve activation of each branch of the abdominal vagus nerve. The intragastric administration of Glu activates several brain areas (e.g., insular cortex, limbic system, and hypothalamus) and has been shown to induce flavor-preference learning in rats. Functional magnetic resonance imaging of rats has shown that the intragastric administration of Glu activates the nucleus tractus solitarius, amygdala, and lateral hypothalamus. In addition, Glu may increase flavor preference as a result of its postingestive effect. Considering these results, we propose that dietary Glu functions as a signal for the regulation of the gastrointestinal tract via the gut–brain axis and contributes to the maintenance of a healthy life.

Keywords: monosodium L-glutamate, vagus nerve, autonomic reflex, postingestive effect, functional magnetic resonance imaging, amino acid

1. Introduction

L-Glutamate (Glu) is the most abundant amino acid and has multiple functions in the body. As an essential substrate in intermediary metabolism, free Glu is present in most organs and tissues (e.g., skeletal muscles, brain, kidneys, and liver) in substantial concentrations (1, 2). Glu plays an important role in energy metabolism and in the synthesis of other amino acids, glutathione, and proteins. In the central nervous system, Glu is the dominant excitatory neurotransmitter, and the activity of this neurotransmitter regulates synaptic plasticity, learning, memory, motor activity, and neural development. In the oral cavity, the Glu in foods elicits a unique taste that is known as umami, and this taste is generally believed to serve as a signal for protein ingestion.

In addition to the gustatory roles of Glu, recent studies have revealed the postingestive significance of Glu for various physiological functions, such as digestion, absorption, metabolism, and energy homeostasis, through brain activation. These effects may be mediated via the gastrointestinal (GI) Glu sensors that are functionally linked to the afferent vagus nerve or that may be mediated via the afferent sensory nerves in the oral cavity (Fig. 1). Moreover, Glu acts as a reinforcer after ingestion via vagal afferent activation in the GI tract. For example, we recently observed that an intragastric administration of Glu induced conditioned flavor preference in rats (3, 4).

In this review, we describe the physiological significance of dietary Glu for the maintenance of digestion and absorption from the point of view of autonomic reflexes. We also describe the positive postingestive effects of several nutrients, such as Glu, sugar, and lipids, in terms of behavior and brain function.
sorbed through the luminal mucosa. Nutrients also regulate the activity of the vagal afferent nerves and the release of GI peptides, including cholecystokinin (CCK), peptide YY, glucagon-like peptide-1 (GLP-1), leptin, ghrelin, and other peptides (5 – 8).

For many years, it has been believed that the vagal gastric afferents in the stomach detect gastric distension and not individual nutrients. However, we previously reported that Glu evoked visceral sensations in the stomach (9). This report suggests that chemical perception, specifically as an amino acid-sensing system, exists in the gastric mucosa. Interestingly, among the 20 amino acids, only Glu stimulated the rat vagal gastric afferents (VGA) (Fig. 2) (10). Furthermore, this Glu response was blocked by the depletion of serotonin (5-HT) and by the inhibition of 5-HT3 receptors or the nitric oxide (NO) synthase enzyme. The afferent response was also mimicked by a luminal perfusion or an intravenous injection with the NO donor. In addition, this NO donor-induced afferent activation was abolished by 5-HT3-receptor blockage or the depletion of 5-HT (10, 11). This finding strongly supports the possibility of intercellular communication in the rat gastric mucosa between mucosal cells and the vagus nerve through the use of NO and 5-HT. Greater than 90% of the 5-HT in the body is localized in the enterochromaffin (EC) cells of the GI mucosa. The physiological role of the mucosal 5-HT that is released from EC cells serves a paracrine function by specifically recognizing Glu in the lumen of the stomach, and this function is similar to the role of 5-HT that has been reported for duodenal glucose sensing.

Currently, three candidate Glu receptors have been identified in the gut: the heterodimer T1R1/T1R3 and the metabotropic Glu receptors type 1 (mGluR1) and type 4 (mGluR4). T1R1 and T1R3 are located in the epithelial cells of the stomach and small intestine (12). In the jejunum of a fed rat, T1R1 and T1R3 are colocalized in the epithelial cells and Paneth cells (13). mGluR4 is localized at low expression levels in the rat jejunum (14). In contrast, mGluR1 is located in the chief cells (pepsinogen-secreting cells) of the rat stomach (15). In addition, some mGluRs and amino acids sensors are expressed in gastric mucosal cells using cell fractions isolated from rats (16, 17). The cellular transduction molecules of the Glu receptors that are involved in taste, including α-gastducin, transducin, phospholipase C β2, protein kinase C βII, and transient receptor poten-
tial channel M5, are also coexpressed in these chief cells (12–14), which indicates the presence of a complete receptor transduction machinery. Although the molecule that senses Glu in the gastric mucosa has not been identified, the intragastric administration of monosodium Glu (MSG) causes a vago-vagal reflex, which increases vagal gastric efferent (VGE) and the level of vagal pancreatic and celiac efferent activities (9, 18) and the sympathetic efferent pathways that innervate adrenal medulla, kidney, and the white adipose tissue (18, 19). In addition, adding MSG to protein-rich meals accelerates gastric emptying in healthy volunteers (20). Interestingly, MSG does not affect gastric emptying when added to an isocaloric carbohydrate meal or to water (20), suggesting that Glu acts as a modulator of gastric motility and that the effect of Glu is linked to the properties of the ingredients (protein levels) of the diet. Furthermore, the addition of MSG to a liquid diet prevents the incidence of diarrhea during repetitive intragastric tube feeding (21). Assuming that free Glu always coexists with dietary protein, these findings suggest that a Glu-sensing system in the stomach contributes to the gastric phase of protein digestion and integrates nutrient information in the brain. In addition, the application of Glu to foods might be useful for the elderly and for patients with dyspepsia or anorexia.

In contrast to the results of studies in the small intestine, several papers report that the intraduodenal administrations of amino acids or oligopeptides alter vagal celiac afferent (VCA) activity. For example, Sharma and Nasset observed an apparent increase in the mesenteric afferent activity in whole-nerve or multifiber preparations from the GI tract following amino acid infusions in cats (22). Using a unitary recording technique in the nodose ganglion, Jeannigros and colleagues revealed the response of the VCA to amino acid infusions in the feline small intestine. The previous reports by these authors have described many sensors that are responsive to arginine, leucine, and other amino acids (23, 24). Recently, we re-examined the luminal amino acid sensitivity of the VCA in rats. Intraintestinal administration of MSG, lysine, and leucine evoked excitatory responses in the VCA (25). In contrast to the administration of these amino acids, the intraintestinal administrations of glycine and methionine led to the depression of afferent nerve activity (25). In rats, the duodenal administrations of protein hydrolysates also increased mesenteric afferent activity (26, 27). Moreover, duodenal protein hydrolysates (e.g., peptone) have been shown to stimulate the VCA via the oligopeptide transporter PepT1 (28). PepT1 is localized to the apical membrane of enterocytes and is highly expressed along the length of the small intestine (29), suggesting that PepT1 is a main transporter for the uptake of peptone in the intestine.

Changes in VCA activity induce autonomic reflexes and regulate visceral functions. The intraintestinal administration of MSG resulted in an increase in VGE activity, vagal pancreatic efferent activity (9, 30), and lysine-evoked long-lasting enhancement of VGE activity (25). In contrast, the intraintestinal administration of glycine inhibited VGE activity (25). In addition, the introduction of a glucose solution into the intestine increased VCA activity; the sensing mechanism responsible for these glucose effects has been described in a previous review (31). A glucose solution has also been shown to suppress sympathetic adrenal efferent activity and enhance vagal pancreatic efferent activity (25). These observations support the hypothesis that vagal GI afferent signals regulate GI motility, metabolic activity, and food intake (32, 33).

3. Brain activation by gut nutrient stimulation

Recent studies suggest that, in addition to the autonomic reflex, the effects of ingested nutrients are processed in the forebrain to determine the next feeding behavior. To investigate the regions of the rat brain that respond to ingested nutrients, we used a functional magnetic resonance imaging (fMRI) technique. Using fMRI, the activated areas of the brain can be investigated simultaneously. An intragastric administration of 60 mM MSG or an isocaloric (60 mM) glucose solution has been shown to activate distinct forebrain regions (Fig. 3) (34, 35). An intragastric administration of MSG significantly activated several brain regions, including the amygdala, lateral hypothalamus, dorsomedial hypothalamus, and the medial preoptic area. In contrast, an intragastric administration of glucose activated the insular cortex, amygdala, nucleus accumbens (which is the terminal region of dopaminergic projections), and the lateral and ventromedial hypothalamus. Interestingly, inosine monophosphate (IMP), which is another umami substance, activated several brain regions; however, MSG and IMP activated distinct brain regions (36). We also investigated the brain responses to an intragastric administration of a corn oil emulsion, which activated the amygdala, lateral hypothalamus, hippocampus, and ventral tegmental area (37).

Behavioral studies have also shown that ingested Glu, glucose, and corn oil emulsions have positive postigestive effects on the flavor preferences in rats (3, 38, 39). In rodents and humans, the preference for the flavor of an ingested solution can be increased by repeatedly pairing the solution with ingestion or the intragastric administration of a nutrient solution. This paradigm is known as conditioned flavor preference (CFP). Behavioral studies have revealed that the intragastric administration of
carbohydrates, lipids, and alcohols induces CFP in rodents (38 – 40). In addition, we have previously shown that an intragastric administration of 60 mM MSG evokes CFP in rats. In contrast, isocaloric (60 mM) glucose and isotonic (60 mM) NaCl solution did not evoke CFP (Fig. 4) (3, 4); however, a 480 mM glucose solution did evoke CFP. In addition, greater concentrations of glucose led to an increase in blood glucose and insulin. These results indicate that the preference for the flavored solution paired with a gut infusion of MSG is not due to a caloric effect or an osmotic effect. Functional brain imaging and CFP studies have shown that the brain regions that are commonly activated in response to the intragastric administration of Glu, glucose, and corn oil emulsions in—
include the anterior cingulate cortex, insular cortex, amygdala, caudate-putamen, hippocampus, and lateral hypothalamus (35, 37). Thus, these brain regions should be related to CFP. In particular, the lateral hypothalamus is an important area for food or liquid intake. A previous report revealed that lesions of the lateral hypothalamus diminished the CFP that was induced by the intragastric administration of glucose (41). The glucose-sensitive neurons that are present in the ventromedial hypothalamus are activated as the intracellular glucose levels are increased. The dopaminergic projections from the ventral tegmental area to the nucleus accumbens, amygdala, and lateral hypothalamus are involved in the preference for, or the addiction to, ingested glucose and corn oil. Several studies have shown that sugar intake increases dopamine release in the nucleus accumbens shell region in rats, and this leads to a sugar addiction (42). In addition, a D2-like receptor antagonist has been shown to inhibit the reinforcing effects of corn oil in rats. In contrast, the intragastric administration of Glu does not activate the nucleus accumbens (Fig. 3), and lesions of neurons in the ventral tegmental area do not affect the preference for Glu in rats (43). These results suggest that the postigestive effects of Glu differ from those of sugar and lipids.

Another advantage of fMRI is that this technique has better temporal resolution than an alternative monitoring technique, c-fos labeling. The time course of the brain activation is different for Glu and for glucose, as revealed by fMRI (34). An intragastric administration of 60 mM Glu induced activation in the majority of the brain during the administration period. In contrast, an intragastric administration of 60 mM glucose induced long-term activation that lasted longer than 1 h. These different temporal and regional activation patterns in the brain are due to distinctive signaling pathways between the gut and the brain. In addition, these patterns result in distinctive effects on postigestive behavioral modulation.

4. Signaling pathway of the gut–brain axis

Ingested nutrients are digested and absorbed in the GI tract. Next, the afferent vagus nerve, which innervates the GI tract and projects to the nucleus tractus solitarius (NTS), is activated, or peripheral humoral factors, such as insulin and GLP-1, are released. The intragastric administration of a glucose solution increases blood glucose, GLP-1, and insulin. Circulating GLP-1 acts on neurons in the NTS. Recently, we demonstrated that fluctuations in insulin after the intragastric administration of glucose correlate with the blood oxygenation level-dependent (BOLD) responses in the amygdala, ventromedial hypothalamus, and nucleus accumbens (35). Electrophysiological studies have shown that the intragastric and enteric delivery of amino acids and lipids activate the afferent vagus nerve, as described above (24 – 26, 44, 45). The intraportal administration of amino acids also activates the afferent vagus nerve (46). These reports indicate that the afferent vagus nerve is important for the transmission of gut nutrient information to the brain. Interestingly, behavioral studies have shown that an abdominal vagotomy eliminates CFP in response to the intragastric administration of Glu (4) but does not affect CFP response to the intragastric administration of carbohydrates in rats (47). The results of our previous fMRI study revealed that a total abdominal vagotomy reduced the level of Glu-induced activation in the NTS and hypothalamus, whereas a total vagotomy did not affect the level of the glucose-induced brain activation (35). Instead, the level of brain activation correlated with the fluctuations in insulin after an intragastric glucose administration (35). These results from fMRI studies in vagotomized rats are consistent with those of postigestive behavior studies, indicating that internal signals in response to Glu mainly involve the vagus nerve, whereas those in response to glucose at least partly involve insulin.

Lastly, there are distinct postigestive effects in response to different nutrients that result in the activation of forebrain regions. The spatial and temporal patterns of this brain activation may be used to link postigestive behavioral and physiological effects.

5. Conclusion

Glu plays an important role in the perception of the umami taste, intermediary metabolism, and excitatory neurotransmission. In one series of studies, we showed that dietary Glu also stimulates the Glu sensors in the stomach and intestines, producing local effects on GI function. Moreover, via the release of the signaling molecules NO and 5-HT, the presence of Glu in the GI tract leads to the activation of the vagal afferent nerve and, consequently, induces the vago-vagal reflexes and the activation of a number of target areas in the brain. In addition, we described the postigestive effects of Glu compared to those of glucose and lipids. The results of previous fMRI and behavioral studies in rodents have indicated that Glu has positive postigestive effects through the vagal afferent nerve but that Glu does not exhibit reinforcing properties. Altogether, these findings suggest that dietary Glu influences numerous physiological functions, contributing to the maintenance of a healthy life.
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