

DIGESTIVE PHYSIOLOGY OF THE PIG SYMPOSIUM: Detection of dietary glutamate via gut–brain axis^{1,2}

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ABSTRACT: Gustatory and visceral stimulation from food regulates digestion and nutrient use. Free L-glutamate (Glu) release from digested protein is responsible for umami taste perception in the gut. Moreover, monosodium Glu (MSG) is widely used as a flavor enhancer to add umami taste in various cuisines. Recent studies indicate that dietary Glu sensors and their signal transduction system exist in both gut mucosa and taste cells. Oral Glu sensing has been well studied. In this review, we focus on the role of Glu on digestion and absorption of food. Infusion of Glu into the stomach and intestine increase afferent nerve activity of the gastric and the celiac branches

of the vagus nerve, respectively. Luminal Glu also evokes efferent nerve activation of the abdominal vagus nerve branches simultaneously. Additionally, intragastric infusion of Glu activates the insular cortex, limbic system, hypothalamus, nucleus tractus solitaries, and amygdala, as determined by functional magnetic resonance imaging, and is able to induce flavor-preference learning as a result of postingestive effects in rats. These results indicate that Glu signaling via gustatory and visceral pathways plays an important role in the processes of digestion, absorption, metabolism, and other physiological functions via activation of the brain.

Key words: functional magnetic resonance imaging, monosodium L-glutamate, postingestive effect, vagus nerve

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doi:10.2527/jas2012-6021

INTRODUCTION

Chemical signals from potential foods are detected by specialized receptors throughout the body. These chemical receptors serve a variety of functions that ensure the nutritional health of an animal. At the periphery, the chemical senses of taste and smell provide important information on the nutrient value of a potential food and then help initiate digestion of that food. Other chemical senses in the digestive

tract are also involved in recognizing nutrients and stimulating release of hormones that aid in digestion and use. Finally, chemical sensors, including taste and smell sensors in the oral and digestive organs, may send messages to the brain, which processes them, compares them to stored prior information, and initiates behavioral, physiological, and neuroendocrine events that serve to ensure proper food use.

A primary chemical sense is the sense of taste. In the oral cavity, taste receptors have evolved to detect a relatively small number of primary taste qualities that presumably reflect nutritional needs of omnivorous animals. Sweet taste likely evolved to detect carbohydrate nutrients whereas salty taste detects the presence of the necessary mineral sodium. Sour taste may protect against ingestion of low pH foods, such as unripe fruits, and bitter taste acts to protect against poisons often found in plants.

In recent years, a fifth primary or basic taste, umami taste, has been recognized. This taste is thought to serve as a signal for dietary protein and AA. The prototypical umami taste stimulus is the L-glutamate (Glu), which

¹Based on a presentation at the preconference symposium titled “Gut Chemosensing: Integrating nutrition, gut function and metabolism in pigs” preceding the 12th International Symposium on Digestive Physiology of Pigs in Keystone, Colorado, May 29–June 1, 2012, with publication sponsored by Lucta S.A. (Barcelona, Spain), the American Society of Animal Science, and the *Journal of Animal Science*.

²The authors acknowledge A. Kitamura and T. Tsurugizawa for their substantial contribution to our research outcome. We also appreciate G. K. Beauchamp and S. Naoi who provided editorial advice.

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Received October 22, 2012.

Accepted January 10, 2013.

is typically added to foods as monosodium Glu (**MSG**). For over 100 yr MSG has been used as a seasoning and currently sales of MSG exceed 2.5 million t/yr with consumption increasing at a rate of several percent per year. That MSG is so widely used indicates that MSG plays not only a role as a sensory or taste stimulus but also may have additional physiological roles in digestion and food use. As an essential substrate in the intermediary metabolism, free Glu is present in most organs and tissues (skeletal muscles, brain, kidneys, and liver) in substantial concentrations (Giacometti, 1979; Young and Ajami, 2000). Glutamate plays an important role in energy metabolism and the metabolism of other AA, glutathione, and body proteins. In the brain, Glu, which is locally produced *de novo* from glucose and acts as a major excitatory neurotransmitter, and its activity regulates synaptic plasticity, learning, memory, motor activity, and neural development. Recent studies have revealed postingestive effects of Glu on various physiological functions such as digestion, nutrient absorption, metabolism, and energy homeostasis via brain activation. These effects may be mediated via luminal gut Glu sensors functionally linked to the afferent branches of the vagus nerve or via the afferent sensory nerves in the oral cavity. Moreover, Glu acts as a reinforcer after ingestion via vagal afferent activation in the gut. For example, we recently observed that an intragastric infusion of Glu induced conditioned flavor preference in rats (Uematsu et al., 2009, 2010).

In this review, we outline the physiological significance of dietary Glu for the maintenance of body homeostasis from the point of view of autonomic reflexes. We also describe the positive postingestive effects of several nutrients, primarily Glu, sugars, and lipids, with regard to behavior and brain functional changes.

GUSTATORY STIMULI REGULATE AUTONOMIC NERVE ACTIVITY

Taste receptor activation affects various visceral efferent nerve activities and functions. Salivary secretion is one of the taste-induced autonomic reflexes (Hector, 1999). The relative strengths of different stimuli inducing parotid salivary flow are citric acid (sour) > MSG (umami) > NaCl (salty) > sucrose (sweet) ≥ magnesium sulfate (bitter; Hodson and Linden, 2006). The role of saliva is not only to lubricate food for mastication and swallowing but also to initiate the digestion of nutrients (i.e., carbohydrates and fats) because it contains enzymes, such as amylase and lipase. In addition, there are various reports describing other taste-induced reflexes. Sweet taste stimulation with sucrose and glucose solution increases the efferent activity of the pancreatic and the hepatic vagus nerves in rats whereas a salty taste

solution containing a high concentration of NaCl suppresses such activity (Niijima, 1979, 1991a,c,d). In addition, sweet taste stimulation elicits insulin release before increasing plasma glucose concentrations, a process called cephalic-phase insulin release (Strubbe and Steffens, 1975; Louis-Sylvestre, 1976; Steffens, 1976). By contrast, sweet taste stimulation was observed to suppress vagal gastric efferent (**VGE**) activity and the efferent activity of the adrenal, pancreatic, and hepatic sympathetic nerves whereas salty taste stimulation was shown to increase these activities (Jiang and Niijima, 1986; Niijima, 1991c). Moreover, sweet taste signals stimulate gastric acid secretion via excitation of the vagus nerve (Ikuno and Sakaguchi, 1990).

Umami taste stimulation produced by a MSG solution was able to activate VGE activity and the efferent activity of the pancreatic and hepatic vagus nerves (Fig. 1; Niijima, 1991a,b, 2000) in association with an increase in insulin secretion (Niijima et al., 1990). However, it has been reported that MSG aqueous solution does not elicit cephalic-phase insulin release (Tonosaki et al., 2007), so further study will be necessary in the case of food intake with or without MSG to clarify the role of MSG in controlling insulin concentrations. Altogether, taste sensation induces reflexive production of salivary, gastric, and insulin secretions, which are important for energy metabolism, digestion of food, and absorption of nutrients.

GUT NUTRIENT STIMULI CONTROL AUTONOMIC NERVOUS SYSTEM ACTIVITY TO REGULATE METABOLISM

In the gastrointestinal (**GI**) tract, various nutrients are detected and absorbed through the luminal layer. Nutrients also regulate the activity of vagal afferent nerves and the release of GI peptides, including cholecystinin (**CCK**), peptide YY, glucagon-like peptide-1 (**GLP-1**), leptin, ghrelin, and others (Raybould

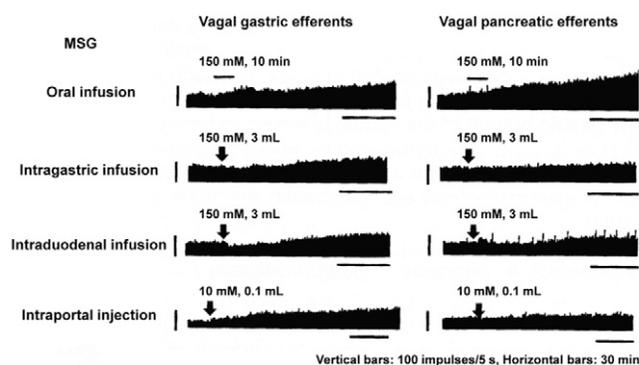


Figure 1. Reflex activation of vagal gastric and pancreatic nerve activity stimulated by monosodium L-glutamate (MSG) through oral (150 mM), intragastric (150 mM), intraduodenal (150 mM), and intraportal (10 mM) infusion. Reproduced from Niijima (2000) with permission.

et al., 2006; Rozengurt and Sternini, 2007; de Fonseka and Kaunitz, 2009; Kitamura et al., 2010).

It was thought for a long time that the vagal gastric afferents in the stomach could detect only gastric distension and not individual nutrients. However, we have previously reported that Glu evoked visceral sensations in the stomach (Nijima, 2000). This is important in the field of gastric nutrient perception because these data strongly indicate that chemical perception, in particular an AA-sensing system, exists in the gastric mucosa. Interestingly, among the 20 kinds of AA, Glu alone stimulates the rat vagal gastric afferents (VGA; Fig. 2; Uneyama et al., 2006). Luminal perfusion with the peripheral anesthetic lidocaine abolished the Glu-evoked VGA activation, indicating that this response is a chemical event within the gastric mucosa. Furthermore, the Glu response was blocked by depletion of serotonin (5-HT) and by inhibition of 5HT Type 3 (5-HT₃) receptors or nitric oxide (NO) synthase. The afferent response was also mimicked by luminal perfusion with an NO donor, such as sodium nitroprusside. In addition,

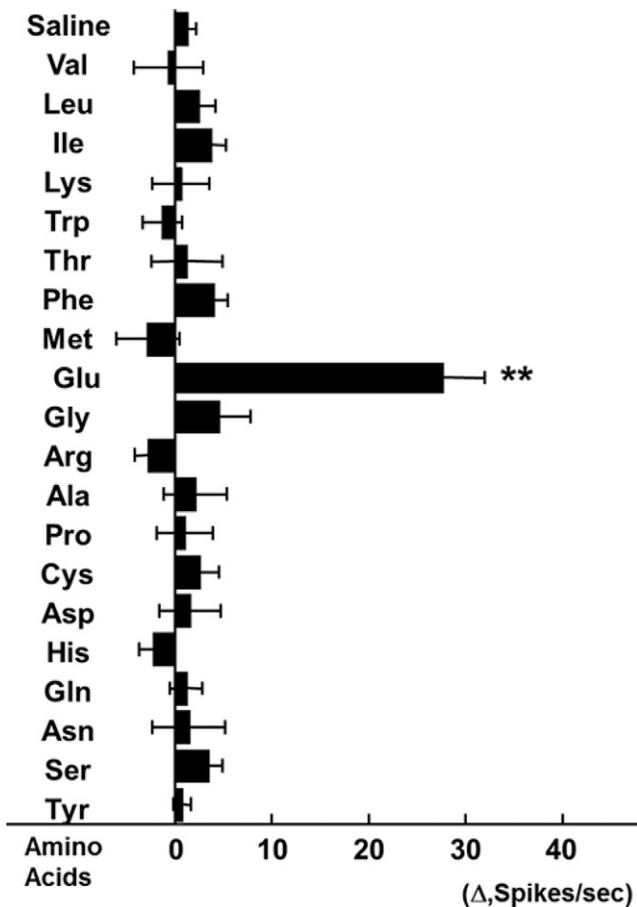


Figure 2. Gastric vagal afferent responses (changes of firing rate compare to baseline) to intragastric infusion of various AA solutions. Each aqueous solution (150 mM; 2 mL/rat) was intubated to rat stomach, and the mean value of discharge rate above baseline at 20 min was plotted. Each column and horizontal bar represents mean \pm SEM from 5 rats. ****** $P < 0.05$ vs. saline. Reproduced from Uneyama et al. (2006) with permission.

NO donor-induced afferent activation was abolished by 5-HT₃ receptor blockage (Uneyama et al., 2006). This finding strongly supports the possibility of intercellular communication in the rat gastric mucosa between mucosal cells and the vagus nerve with NO and 5-HT acting as stimuli. More than 90% of 5-HT throughout the body is localized in the enterochromaffin cells of the GI mucosa. Mucosal 5-HT from enterochromaffin cells serves a paracrine function by specifically recognizing Glu in the lumen of the stomach, which is similar to the role reported for the duodenal glucose sensing system.

The sensor for nutrients in the gut luminal layer may be an “intestinal sensor cell,” as originally proposed in the 1970s by Fujita et al. (1980). This hypothesis indicates that nutrient-sensing cells are distributed in the gastric antrum or duodenal mucosa and that when these cells interact with luminal nutrients, they release hormones in an endocrine or paracrine manner to transfer information about luminal nutrient content to other organs, including the brain via endocrine or vagal pathways. However, these cells involved in the gut nutrient perception system remained unidentified for a long time. Höfer et al. (1996) reported that taste-like cells similar to the taste cells in the oral cavity are distributed in the gastric and intestinal mucosa and they proposed that these taste-like cells represent the unknown sensor cells. Subsequently, with the development of molecular biology techniques in the field of taste research, several taste receptors responding to different AA have been identified. We now know that metabotropic Glu receptors, a calcium-sensing receptor, and a taste receptor [i.e., a heterodimer of taste receptor family 1 member 1 (T1R1) and T1R3, T1R1/T1R3] are all linked to AA sensation in the tongue. These same receptors are also candidates for luminal AA sensors. Although the molecule or molecules that sense Glu in the gastric mucosa is still unclear, intragastric infusion of MSG causes a vagovagal reflex, which increases VGE, as well as vagal pancreatic and celiac efferent activities (Fig. 1; Nijima, 2000; Kitamura et al., 2011). Interestingly, inosine 5'-monophosphate, another umami substance that enhances MSG binding to taste receptors and, thus, enhances umami taste intensity synergistically, also activates VGA and increases vagal celiac efferent activity (Kitamura et al., 2011). Because the coexistence of free Glu with dietary protein is very common in foods, these findings indicate that a Glu-sensing system in the stomach could contribute to the gastric phase of protein digestion and could integrate nutrient information in the brain by vagal afferent excitation.

In contrast to what occurs in the small intestine, there are many reports that intraduodenal infusion of AA or oligo-peptides alters vagal celiac afferent (VCA) activity. Sharma and Nasset (1962) observed an apparent increase in mesenteric afferent activity in either whole-

nerve or multifiber preparations from the GI tract after AA infusions in cats. Using a unitary recording technique in the nodose ganglion, Jeanningros (1982) subsequently revealed in detail the response of VCA to AA infusions in the cat small intestine. Their report described many sensors responsive to arginine, leucine, and other AA (Jeanningros, 1982). Recently, we reexamined the luminal AA sensitivity of VCA in rats. Intra-intestinal infusion of MSG, lysine, leucine, and other AA evoked excitatory responses in VCA (Nijijima et al., 2005). In contrast to these AA, intra-intestinal infusion of glycine, methionine, and certain other AA led to the depression of afferent nerve activity (Nijijima et al., 2005). In rats, duodenal infusions of protein hydrolysates also increased mesenteric afferent activity (Eastwood et al., 1998; Schwartz and Moran, 1998). Schwartz and Moran (1998) revealed that duodenal protein hydrolysates (e.g., peptone) stimulated celiac afferents, indicating that an AA sensor or oligopeptide sensor might exist in the rat duodenum. However, the mechanisms underlying such sensations are not fully understood, and further research is needed.

Changes in the vagal celiac afferent activity induce autonomic reflexes and regulate various visceral functions. Intra-intestinal infusions of MSG resulted in an increase in VGE, vagal pancreatic efferent activity (Nijijima, 1991b, 2000), and lysine evoked long-lasting enhancement of VGE activity (Nijijima et al., 2005). On the other hand, the intra-intestinal infusion of glycine inhibited VGE activity (Nijijima et al., 2005). In addition, introduction of a glucose solution into the intestine increased VCA activity; the sensing mechanism underlying glucose effects has been described in another review (Raybould, 2007). Glucose solution also suppressed sympathetic adrenal efferent activity and enhanced vagal pancreatic efferent activity (Nijijima et al., 2005). These observations support our hypothesis that vagal GI afferent signals regulate GI motility, metabolic control for homeostasis, and appetite for food (Mei, 1985; Schwartz, 2000).

BRAIN ACTIVATION AFTER GUT NUTRIENT STIMULATION

From recent studies, in addition to autonomic reflexes, the effects of ingested nutrients are processed in the forebrain, which determines whether food is good or not and subsequently regulates feeding behavior. To investigate which regions of the rat brain respond to ingested nutrients, we used a functional magnetic resonance imaging (fMRI) technique. The merit of fMRI is that activated areas in the whole brain can be investigated simultaneously by noninvasive means in a conscious animal. An intragastric load of 60 mM MSG or isocaloric (i.e., 60 mM) glucose solution has been shown to activate

distinct forebrain regions (Fig. 3; Tsurugizawa et al., 2008, 2009a). An intragastric load of MSG significantly activated several brain regions including the amygdala, lateral hypothalamus, dorsomedial hypothalamus, and medial preoptic area. On the other hand, an intragastric infusion of glucose activated the insular cortex, amygdala, nucleus accumbens (which is the terminal dopaminergic projection), and lateral and ventromedial hypothalamus. We also investigated brain responses to an intragastric load of corn oil emulsion, which activated the amygdala, lateral hypothalamus, hippocampus, and ventral tegmental area (Tsurugizawa et al., 2009b).

Behavioral studies also showed that ingested glutamate or glucose (60 mM in each) in water or corn oil emulsion have positive postingestive effects with regard to flavor preference learning in rats (Ackroff and Sclafani, 1994; Sclafani, 2007; Uematsu et al., 2009). In rodents and humans, the preference for the flavor of an ingested solution can be increased by repeatedly pairing it with ingestion or intragastric infusion of a nutrient solution. This paradigm is called conditioned flavor preference (CFP). Behavioral studies revealed that the intragastric infusion of carbohydrates, lipids, and alcohols induces CFP in rodents (Ackroff and Sclafani, 1994, 2001; Sclafani, 2007). In addition, we showed previously that an intragastric load of 60 mM MSG evoked CFP in rats. Isocaloric (i.e., 60 mM) glucose and isotonic (i.e., 60 mM) NaCl solution did not evoke CFP (Fig. 4; Uematsu et al., 2009, 2010) although 480 mM hypertonic glucose aqueous solution

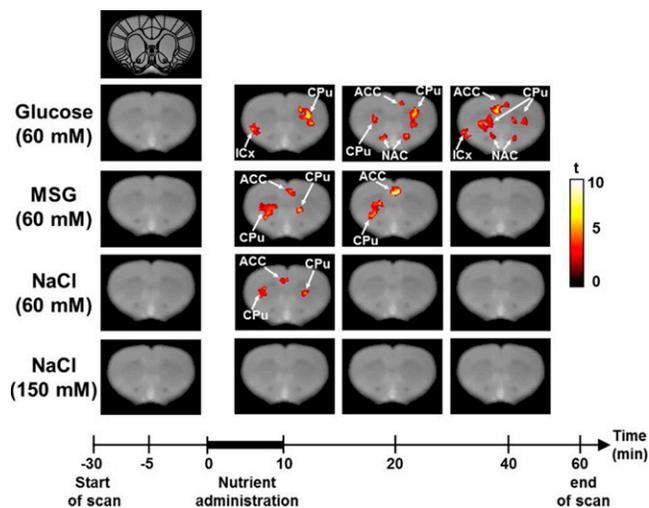


Figure 3. Activated area of rat forebrain specific to the stimulation of treatment with postoral nutrients [60 mM glucose, monosodium glutamate (MSG), and NaCl, and 150 mM NaCl] compared with common control images, which are averaged during 10 min before administration. Images (bregma + 2.0) depict activated brain regions at preadministration (–5 min), 10 min, 20 min, and 40 min after the onset of intragastric infusion. Upper figure is a template image overlaid with Paxinos Atlas. ACC = anterior cingulate cortex, CPu = caudate putamen, ICx = insular cortex, and NAC = nucleus accumbens. Color bar indicates *t*-value. Reproduced from Tsurugizawa et al. (2008) with permission.

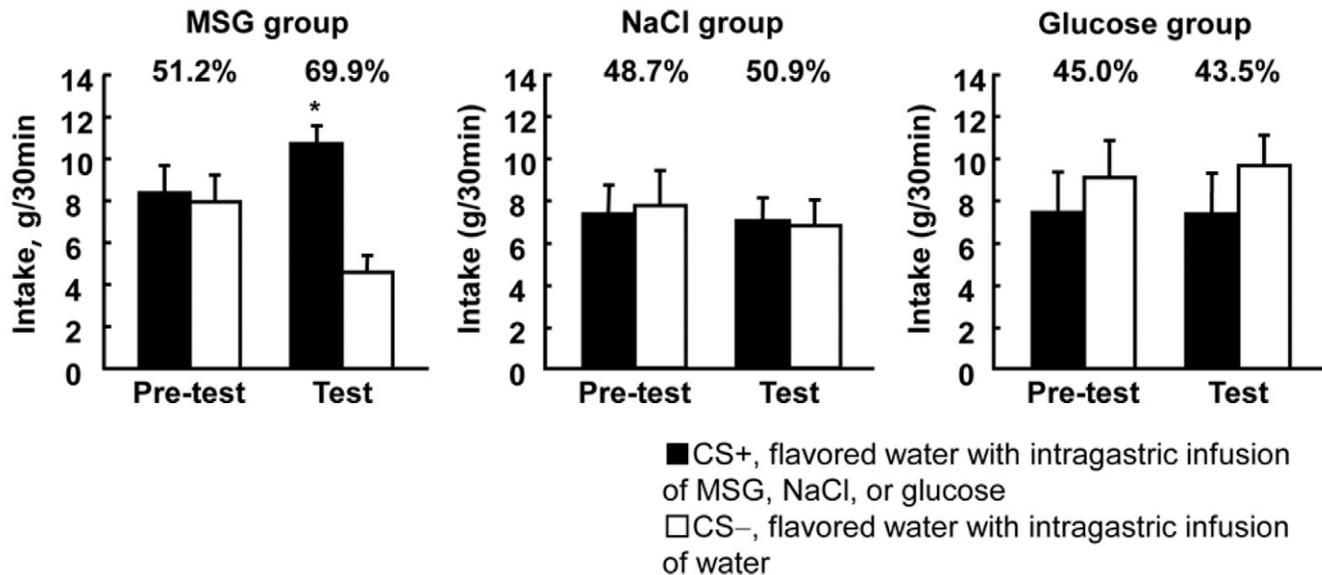


Figure 4. Mean intake of conditioned stimulus [■ conditioned stimulus (CS)+, flavored water with intragastric infusion of monosodium glutamate (MSG), NaCl, or glucose; and □ CS-, flavored water with intragastric infusion of water) solutions in the pretest and test periods. Each percentage number shows the selectivity of the CS+ solution intake. Mean percent intakes of the CS+ solution are shown above the bars. Reproduced from Uematsu et al. (2009) with permission.

did evoke CFP. Much greater concentrations of glucose lead 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 due to neither a caloric effect nor hyperosmotic effect. Based on the results of functional brain imaging and CFP studies, the brain regions commonly activated in response to the intragastric infusion of either glutamate or glucose in water (60 mM) or corn oil emulsion include the anterior cingulate cortex, insular cortex, amygdala, caudate-putamen, hippocampus, and lateral hypothalamus (Tsurugizawa et al., 2009a,b). Therefore, these regions should be related to CFP. In particular, the lateral hypothalamus is an important area regulating food or liquid intake. A previous report revealed that lesions of the lateral hypothalamus diminished CFP induced by intragastric infusion of glucose (Touzani and Sclafani, 2002). The glucose-sensitive neurons that exist in the ventromedial hypothalamus are activated as the intracellular glucose levels increase. Dopaminergic projections from the ventral tegmental area to the nucleus accumbens, amygdala, and lateral hypothalamus are related to the preference for, or addiction to, ingested glucose-like sugars and corn oil. Some studies showed that sugar intake increased dopamine release in the nucleus accumbens shell region in rats, reportedly causing them to become addicted to all sugars (Mark et al., 1994). On the other hand, intragastric infusion 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 (Shibata et al.,

2009). These results show that the postingestive effects of Glu differ from those of sugars and lipids.

Another advantage of fMRI is that it has better temporal resolution than an alternative monitoring technique, c-fos labeling. The time course of brain activation is different for Glu and for glucose, as revealed by fMRI (Fig. 5; Tsurugizawa et al., 2008). An intragastric infusion of 60 mM Glu induced vagal

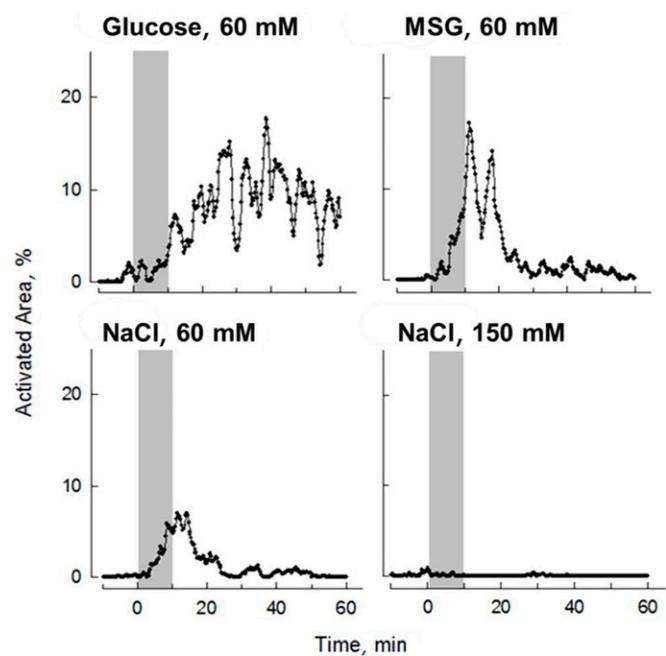


Figure 5. Chronological variation of the percent changes in significantly activated area in rats. Horizontal axis is elapsed time after the onset of infusion. Reproduced from Tsurugizawa et al. (2008) with permission. MSG = monosodium L-glutamate.

afferent activation in most of the brain during the infusion period. In contrast, intragastric infusion of 60 mM glucose induced long-term activation lasting more than 1 h. These different temporal and regional activation patterns in the brain are due to distinctive signaling pathways between the gut and brain and they result in distinctive effects on postingestive behavior.

SIGNALING MECHANISMS OF THE GUT–BRAIN AXIS PROMOTE CONTROL OF METABOLISM

Ingested food is digested and absorbed in free form as nutrients in the GI tract. The afferent vagus nerve, which innervates the entire GI tract and projects to the nucleus of the solitary tract (NTS), is activated by each of these nutrients. In parallel, peripheral humoral factors, such as insulin and GLP-1, are released. In addition to the process of absorption and metabolism in the gut, recent studies have indicated that the stomach, duodenum, and intestine express localized chemosensing taste receptors in the luminal layer and other G protein-coupled receptors. The T1R receptors, which are responsible for the chemoreception of the sweet and umami tastes, and the family of taste receptor family 2 (T2R) receptors, which mediate the chemoreception of the bitter taste, are both expressed in the gut (Dyer et al., 2005; Rozengurt, 2006). A fatty acid receptor, G protein-coupled receptor 120 (GPR120), exists in both the oral cavity and the GI tract, and these acids interact with it to induce the release of circulating GLP-1 (Hirasawa et al., 2005). Free fatty acids also interact with another receptor, GPR40, in the GI tract to promote secretion of GLP-1 (Itoh et al., 2003) and CCK (Beardshall et al., 1989). Glucagon-like peptide-1 and CCK evoke c-fos positive immunoreactivity in several brain regions, including the amygdala (Wang et al., 1998; Baggio et al., 2004; Viltart et al., 2006). Intragastric infusion of glucose solution increases blood glucose concentrations, GLP-1, and insulin. Circulating GLP-1 also acts on neurons in the NTS. Recently, we demonstrated that fluctuations in insulin after the intragastric administration of glucose correlate with fMRI responses in the amygdala, ventromedial hypothalamus, and nucleus accumbens (Tsurugizawa et al., 2009a).

Electrophysiological studies have shown that intragastric and enteric delivery of AA and lipids both activate the afferent vagus nerve, as described previously (Jeanningros, 1982; Mei and Garnier, 1986; Eastwood et al., 1998; Randich et al., 2000; Nijijima et al., 2005). Intraportal administration of AA also activates afferent vagus nerve responses (Nijijima and Meguid, 1995). 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 abdominal vagotomy eliminates CFP in response to intragastric infusion of Glu (Uematsu et al., 2010) but does not affect CFP response to intragastric infusion of carbohydrates in rats (Sclafani and Lucas, 1996). An fMRI study showed that total and abdominal vagotomy diminished Glu-induced activation in the NTS and hypothalamus whereas total vagotomy did not affect glucose-induced brain activation (Tsurugizawa et al., 2009a). Instead, brain activation was correlated with fluctuations in insulin after intragastric glucose infusion (Tsurugizawa et al., 2009a). These results from fMRI studies of vagotomized rats are consistent with postingestive 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. Finally, there are distinct postingestive effects in response to different nutrients, resulting in the activation of forebrain regions. The spatial and temporal patterns of brain activation could link postingestive behavioral and physiological effects underlying the maintenance of homeostasis after a meal.

TRIAL OF BOTH L-GLUTAMATE AND L-GLUTAMINE SUPPLEMENTATION TO PIGLETS

Weaning is a critical period for the piglet, because of major changes in diet and in physical environment. Diarrhea is the most serious problem during and after weaning (Hampson, 1986). As described previously, additional Glu has a potential to modulate the negative consequences of this dietary change from liquids to solids and to increase gut health. Furthermore, it has been reported that dietary Glu prevented diarrhea during intragastric tube feeding of rats (Manso et al., 2012). Our preliminary study indicated that a reasonable supplement for weaning piglets would contain Glu and L-glutamine. Piglets were weaned at 21 d of age and supplemented Glu and L-glutamine mixture with different levels (i.e., 0 to 1.2%) until 42 d of age. Addition of 0.3 to 0.8% of the Glu and L-glutamine mixture into the weaning diet induced a significant reduction of the diarrhea index and an increase in the feed conversion rate. These results indicate that dietary Glu improves intestinal function in the piglets.

SUMMARY AND CONCLUSIONS

Glutamate plays important physiological roles in the perception of umami taste, visceral information, and regulation of endocrine-exocrine systems and excitatory neurotransmission. In our series of studies reviewed here, we showed that dietary Glu also stimulates Glu sensors in the stomach and intestines, producing local effects on gut function. Moreover, via the release of

signaling molecules, NO and 5-HT, the presence of Glu in the gut leads to activation of the vagal afferent nerve, which in turn modulates a number of target areas in the brain. In addition, we described the postingestive effects of Glu and showed that they were different from those elicited by glucose and lipids. Previous fMRI and behavioral studies in rodents have indicated that Glu has positive postingestive effects through the vagal afferent nerve that controls digestion and appetite for food. However, Glu does not have the same reinforcing properties of addictive substances, such as sugars and alcohol. Altogether, these findings indicate that dietary Glu influences numerous physiological functions, indicating a broad, integrative role for dietary Glu in body homeostasis.

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