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Review

Brain activation by the umami taste substance monosodium L-glutamate via gustatory and visceral signaling pathways, and its physiological significance due to homeostasis after a meal

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ABSTRACT

Monosodium L-glutamate (MSG) elicits a unique taste sensation termed umami and is widely used as a flavor enhancer in various cuisines. In addition, recent studies have suggested the existence of receptors for L-glutamate (Glu) and transduction molecules in the gut mucosa as well as in the oral cavity. The gastric afferent vagal nerve responds specifically to luminal stimulation by Glu in the stomach and regulates autonomic reflexes. The intragastric infusion of MSG also activates several brain areas (insular cortex, limbic system, and hypothalamus) and is able to induce flavor-preference learning in rats. These results suggest that Glu signaling via the gustatory and visceral pathways plays an important role in digestion, absorption, metabolism, and other physiological functions by activating the brain.

Contents

1. Introduction

The main function of teeth is to masticate food. Not only does mastication render food easier to swallow but it also has other important functions. One of these functions is to help generate the sensory properties that make food palatable, particularly taste, smell, and texture, to promote recognition of whether or not the ingested food contains required nutrients. These in turn help promote the digestion processes. Humans are omnivorous, and our teeth pattern has evolved to help us eat a wide variety of food. From the viewpoint of dentition, it is quite interesting to compare what our ancestors ate to the contemporary diets we consume, which consists of highly palatable processed and cooked foods that require much less chewing and are of smaller portions because of highly efficient digestibility of macronutrients.

Humans started to use fire for cooking food 2 million years ago, which resulted in the improvement of the sterility and palatability of food. Moreover, people discovered how to grow food, which led to

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a much more constant food supply. The digestibility of cooked food, particularly their usable carbohydrate content, markedly increased from 6% to almost 100%.

Today, animal products that are rich sources of protein are easily available and are usually highly palatable, in part, because of their ability to impart an attractive umami taste sensation. However, excessive intake of animal products can have deleterious effects. It may compromise people's ability to maintain a metabolic homeostasis, thereby leading to an increase in the incidence of lifestyle-related diseases such as hyperlipidemia, diabetes, and arteriosclerosis.

In recent years, in addition to the standard basic tastes (sweet, sour, salty, and bitter), the umami taste has been categorized as a fifth basic taste. The typical umami taste is because of monosodium L-glutamate (MSG), which is used for seasoning many foods across many cultures. Today, its consumption exceeds 2.5 million tons per year and is continues to increase by several percents per year. This widespread and increasing use of MSG strongly suggests that in addition to its oral sensory flavoring role, MSG also plays both physiological and nutritional roles in metabolism. To support this suggestion, we reviewed and summarized recent research articles documenting the role of MSG in gut–brain communication and its place in a healthy diet and lifestyle.

2. Role of chemical senses in the ingestion, digestion, and absorption of food

The chemical senses, olfaction and taste, provide important sensory cues for conscious recognition of food. These senses also play important roles in the digestion of food by recognizing nutrients in the alimentary tract, because there are taste receptors not only in the oral cavity but also in the digestive tract. These receptors serve to recognize nutrients and thereby to control and modulate food digestion and nutrient absorption, which maintains nutrient homeostasis, including that of glucose and free fatty acids, in both the blood and the brain.

Food intake is episodic; humans eat meals and then do not eat for a considerable time. Nevertheless, concentrations of electrolytes in the blood and brain, pH, osmotic pressure, glucose levels, and the concentrations of amino acids are all maintained at relatively constant levels throughout the day. The senses of taste, smell, and vision help maintain this complex control. Partly based on innate responses and past experiences, these senses allow us to determine whether a substance is an acceptable food and what nutrients may be present in the food. For example, the taste profile of a food item permits us to determine the following: whether the food is sweet, and thus likely to contain carbohydrate as an energy source; whether it is salty, and thus contains electrolytes such as sodium; or whether it has an umami taste, indicative of presence of amino acids and proteins. Once the food is identified as nutritious, it is masticated along with saliva. Saliva contains electrolytes, digestive enzymes such as α-amylase that digests starch to maltose, and other nutrients including up to 20 different amino acids derived from dietary protein derivatives. The alimentary bolus is then swallowed. In order to detect the taste and flavor of food, the concentration of nutrients in the food must be greater than that in saliva. For this reason, foods that are rich in nutrients but do not have strong smell or taste components are very bland in flavor and do not stimulate the appetite or cause satiation. For example, cooked rice has little flavor and is not generally eaten alone; instead it is eaten along with other food or flavoring.

Recent research has shown that the amino acid L-glutamate (Glu) has multiple physiological functions. It is an essential substrate for intermediary metabolism; free Glu is present in most organs and tissues (skeletal muscles, brain, kidneys, and liver) in substantial concentrations [1,2]. Moreover, Glu plays an important role in energy metabolism and in the synthesis of other amino acids, glutathione, and body proteins. In the brain, Glu acts as a major excitatory neurotransmitter, and its activity regulates synaptic plasticity, learning, memory, motor activity, and neural development. In the oral cavity, Glu in food elicits the unique taste sensation termed umami, which is generally believed to be indicative of the presence of dietary proteins and stimulates palatability and ingestion of food.

In addition to the gustatory roles of Glu in the umami taste sensation, recent studies have shown the post-ingestion effects of Glu on various physiological processes such as digestion, nutrient absorption, metabolism, and energy homeostasis through brain activation. These effects may be mediated via the Glu sensors in the luminal gut, which are 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. We recently observed that intragastric infusion of Glu conditioned flavor preference in rats [3,4].

In the next sections, we have described the physiological significance of dietary Glu in the maintenance of body homeostasis from the viewpoint of autonomic reflexes. We have also described the positive post-ingestion effects of several nutrients, primarily Glu, sugars, and lipids, with regard to behavior and brain function.

3. Gustatory stimuli regulate autonomic nerve activity

Taste sensations affect various visceral efferent nerve activities and functions. Salivary secretion is one of the known taste-induced autonomic reflexes [5]. The relative strengths of different parotid salivary flow-inducing stimuli are in the following order: citric acid (sour) > MSG (umami) > NaCl (salty) > sucrose (sweet) ≥ magnesium sulfate (bitter) [6]. 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. There are various reports describing other taste-induced reflexes. Sweet taste stimulation with sucrose or glucose solutions increases the efferent activity of the pancreatic and the hepatic branches of the vagus nerve in rats, whereas a salty solution containing a high concentration of NaCl suppresses this activity [7–10]. Sweet taste stimulation elicits insulin release before increasing the plasma glucose levels, a process known as cephalic-phase insulin release [11–13]. 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 [9,14]. Moreover, sweet taste signals stimulate gastric acid secretion via vagus nerve excitation [15]. Umami taste stimulation by MSG solution activated VGE activity and the efferent activity of the pancreatic and hepatic vagus nerves (Fig. 1) [10,16,17], in association with an increase in insulin secretion [18]. However, it has been reported that an MSG aqueous solution does not elicit cephalic-phase insulin release [19]; therefore, further study of intake of food with or without MSG is necessary to clarify this issue. Overall, taste sensation induces the reflex production of salivary, gastric, and insulin secretions, which are important for energy metabolism and for the digestion and absorption of food.

4. 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

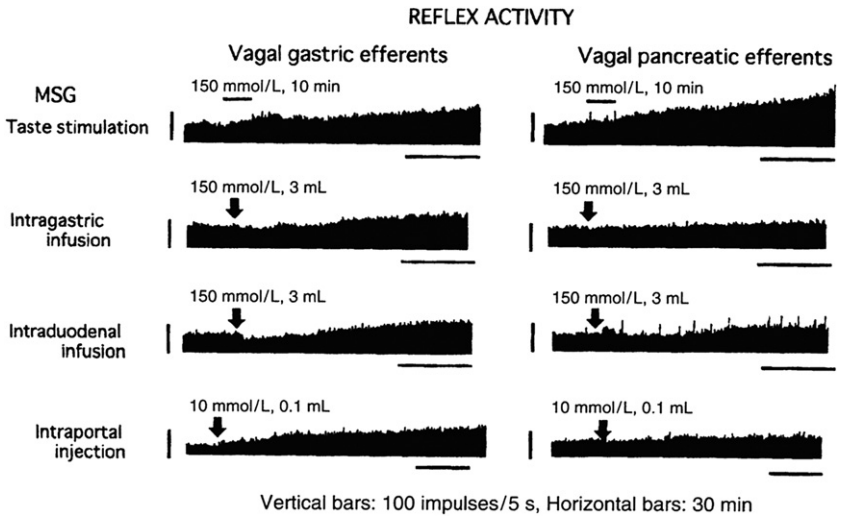

Fig. 1. Reflex activation of vagal gastric and pancreatic nerve activity stimulated through oral, gastric, intestinal, and hepatoportal glutamate sensors. Reproduced from Niijima [17].

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 others [20–23].

It was long believed that the VGEs in the stomach could detect only gastric distension and not individual nutrients. However, we have shown that Glu evokes visceral sensations in the stomach [17]. This report is important in the field of gastric nutrient perception because this finding strongly suggests that a chemical perception system, particularly for sensing the presence of amino acids, exists in the gastric mucosa. Interestingly, among the 20 kinds of amino acids, Glu alone stimulates the rat vagal gastric afferents (VGA) (Fig. 2) [24]. Luminal perfusion with the peripheral anesthetic lidocaine abolished Glu-evoked VGA activation, indicating that this response is a chemical event occurring within the gastric mucosa. Furthermore, the Glu response was blocked by depletion of serotonin (5-HT) and by inhibition of 5-HT Type 3 (5-HT_3) receptors or nitric oxide (NO) synthase. The afferent response was also mimicked by luminal perfusion with a NO donor such as sodium nitroprusside. In addition, NO donor-induced afferent activation was abolished by 5-HT_3 receptor blockage [24]. This finding strongly suggests that in the rat gastric mucosa, communication exists between the mucosal cells and the vagus nerve endings, which uses NO and 5-HT as stimuli. More than 90% of 5-HT present throughout the body is localized in the enterochromaffin (EC) cells of the GI mucosa. The mucosal 5-HT from EC cells apparently serves a paracrine function by specifically recognizing Glu in the lumen of the stomach, similar to the role reported in the duodenal glucose sensing system.

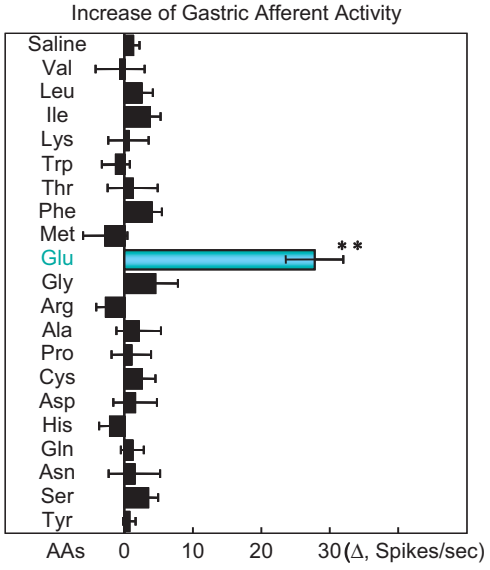

Fig. 2. Vagal gastric afferent (VGA) responses to intragastric infusion of various amino acid solutions. Each aqueous solution (150 mmol/L, 2 mL/rat) was intubated into rat stomach, and the mean value of discharge rate above baseline at 20 min was plotted. Each column and horizontal bar represents mean ± SEM from 5 rats. $^{**}p < 0.05$ vs. saline (Kruskal–Wallis test). Reproduced from Uneyama et al. [24].

The sensing of nutrients in the gut luminal layer can be envisioned to be mediated by the "intestinal sensor cells," as originally proposed in the 1970s by Fujita et al. [25] Their hypothesis proposes that nutrient-sensing cells are distributed in the gastric antrum or the 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 the endocrine or vagal pathways. However, the cells involved in the gut nutrient perception system are not well understood. In 1996, Höfer et al. reported that taste bud-like cells, similar to the taste buds in the oral cavity are distributed in the gastric and intestinal mucosa; they proposed that these taste bud-like cells represent the unknown sensor cells [26]. Subsequently, with the development of molecular biology techniques in the field of taste research, several kinds of taste receptors responding to individual amino acids have been identified. We now know that metabotropic Glu receptors (mGluRs) [24], calcium-sensing receptors (CaSRs) [27], and taste receptor (T1R1/T1R3, the heterodimer of two 7-transmembrane receptor molecules called T1R1 and T1R3) [28] are all linked to amino acid sensation in the tongue. These receptors are also candidates for luminal amino acid sensors. Although the molecule(s) that senses Glu in the gastric mucosa is still unknown, intragastric infusion of MSG causes a vago–vagal reflex, which increases VGE as well as vagal pancreatic and celiac efferent activities (Fig. 1) [17,29]. Interestingly, inosine 5′-monophosphate, which enhances MSG binding to the receptor and thereby synergistically enhances the umami taste; it also activates VGA and increases vagal celiac efferent activity [29]. Assuming that the concentration of free Glu is positively correlated with the concentration of dietary protein, these findings suggest that a Glu-sensing system in the stomach

could contribute to the gastric phase of protein digestion and could convey nutrient information to the brain via vagal afferent excitation.

In contrast to what occurs in the small intestine, many reports suggest that intraduodenal infusion of amino acids or oligopeptides alters vagal celiac afferent (VCA) activity. Sharma and Nasset observed an apparent increase in the mesenteric afferent activity in either the whole-nerve or the multifiber preparations from the GI tract following amino acid infusions in cats [30]. Using a unitary recording technique in the nodose ganglion, Jeannigros and colleagues have reported in detail the response of VCA to amino acid infusions in the small intestines of cats. Their report described many sensors responsive to arginine, leucine, and other amino acids [31,32]. Recently, we reexamined the luminal amino acid sensitivity of VCA in rats. Intraintestinal infusion of MSG, lysine, leucine, and other amino acids evoked excitatory responses in VCA [33]. In contrast to these amino acids, intraintestinal infusion of glycine, methionine, and certain other amino acids led to the depression of afferent nerve activity [33]. In rats, duodenal infusions of protein hydrolysates also increased mesenteric afferent activity [34,35]. Schwartz et al. reported that duodenal protein hydrolysates (e.g., peptone) stimulated celiac afferents, indicating that an amino acid sensor or oligopeptide sensor may exist in the rat duodenum [35]. 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. Intraintestinal infusions of MSG resulted in an increase in VGE and vagal pancreatic efferent activity [16,17]; further, lysine evoked long-lasting enhancement of VGE activity [33]. On the other hand, the intraintestinal infusion of glycine inhibited VGE activity [33]. In addition, introduction of glucose solution into the intestine increased VCA activity. The sensing mechanism underlying glucose effects has been described in another review [36]. Glucose solution also suppressed sympathetic adrenal efferent activity and enhanced vagal pancreatic efferent activity [33]. These observations support our hypothesis that the vagal GI afferent signals regulate GI motility, metabolic control for homeostasis, and appetite for food [37,38].

5. Brain activation after gut nutrient stimulation

From recent studies, we understand that in addition to the autonomic reflexes, the effects of ingested nutrients are first processed in the forebrain to determine whether food is good or not and subsequently regulate the next step of 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 activates areas in the whole brain, and the patient can be simultaneously and non-invasively investigated in a conscious state. An intragastric load of 60 mM MSG or isocaloric (60 mM) glucose solution has been shown to activate distinct forebrain regions (Fig. 3) [39,40]. An intragastric load of MSG significantly activated several brain regions, including the amygdala, lateral hypothalamus, dorsomedial hypothalamus, and the medial preoptic area. On the other hand, an intragastric infusion of glucose activated the insular cortex, amygdala, nucleus accumbens (which is the terminal of the dopaminergic projection), and the 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 the ventral tegmental area [41].

Behavioral studies have shown that ingestion of either glutamate or glucose (60 mM each) in water or corn oil emulsion has positive post-ingestion effects that can condition flavor preferences in rats [3,42,43]. 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 known as conditioned flavor preference (CFP). Behavioral studies have shown that intragastric infusion of carbohydrates, lipids, and alcohols induces a CFP in rodents [42–44]. In addition, we have previously shown that an intragastric load of 60 mM MSG evoked a CFP in rats. Although isocaloric (60 mM) glucose and isotonic (60 mM) NaCl solution did not

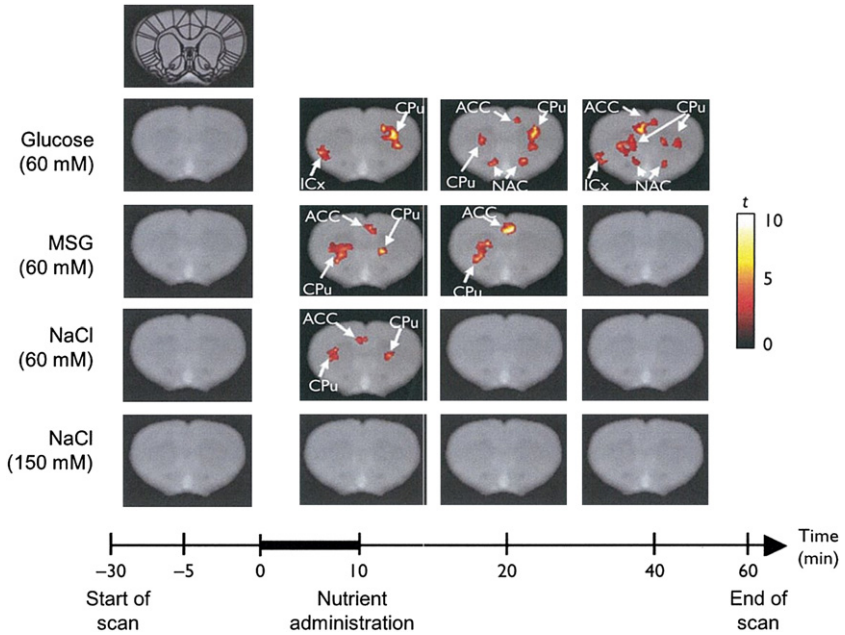

Fig. 3. Activated area of the rat forebrain specific to the stimulation with post-oral nutrients (60 mM glucose, MSG and NaCl, and 150 mM NaCl) compared to common control images, which are averaged during the 10 min before administration. T-map images (bregma +2.0) depict activated brain regions before administration (−5 min) and 10 min, 20 min, and 40 min after the onset of intragastric infusion. The upper figure is a template image overlaid with Paxinos Atlas. ACC; anterior cingulate cortex, CPu, caudate putamen; ICx, insular cortex; NAC, nucleus accumbens. Color bar, *t* value. Reproduced from Tsurugizawa et al. [39].

evoke a CFP (Fig. 4) [3,4], 480 mM hypertonic glucose aqueous solution did evoke a CFP. Much higher 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 because of neither a caloric effect nor a hyperosmotic pressure effect. On the basis of the results of functional brain imaging and CFP studies, we showed that the brain regions were commonly activated in response to the intragastric infusion of either glutamate and glucose in water (60 mM), and corn oil emulsion activated the anterior cingulate cortex, insular cortex, amygdala, caudate-putamen, hippocampus, and the lateral hypothalamus [40,41]. Thus, we believe that these regions may be associated with CFP. The lateral hypothalamus is a particularly important area associated with food or liquid intake. A previous report has shown that lesions of the lateral hypothalamus diminished the CFP induced by intragastric infusion of glucose [45]. The glucose-sensitive neurons that exist in the ventromedial hypothalamus are activated as intracellular glucose levels increase. The dopaminergic projections from the ventral tegmental area to the nucleus accumbens, amygdala, and the lateral hypothalamus are associated to the preference for, or addiction to, ingested glucose-like sugars and corn oil. Some studies have shown that sugar intake increases dopamine release in the nucleus accumbens shell region of rats, likely causing them to become addicted to sugars [46]. 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 [47]. These results indicate that the post-ingestion 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. Thus, fMRI studies have revealed that the time course of brain

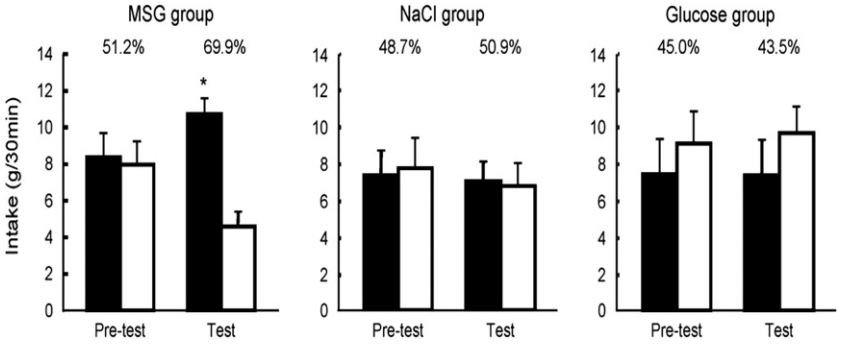

Fig. 4. Mean intake of conditioned stimulus (■CS+, flavored water paired with intragastric infusion of MSG, NaCl, or glucose; □CS−, flavored water paired with intragastric infusion of water) solutions in the pre-test and test periods. Mean percent intakes of the CS+ solution are shown above the bars. Reproduced from Uematsu et al. [3].

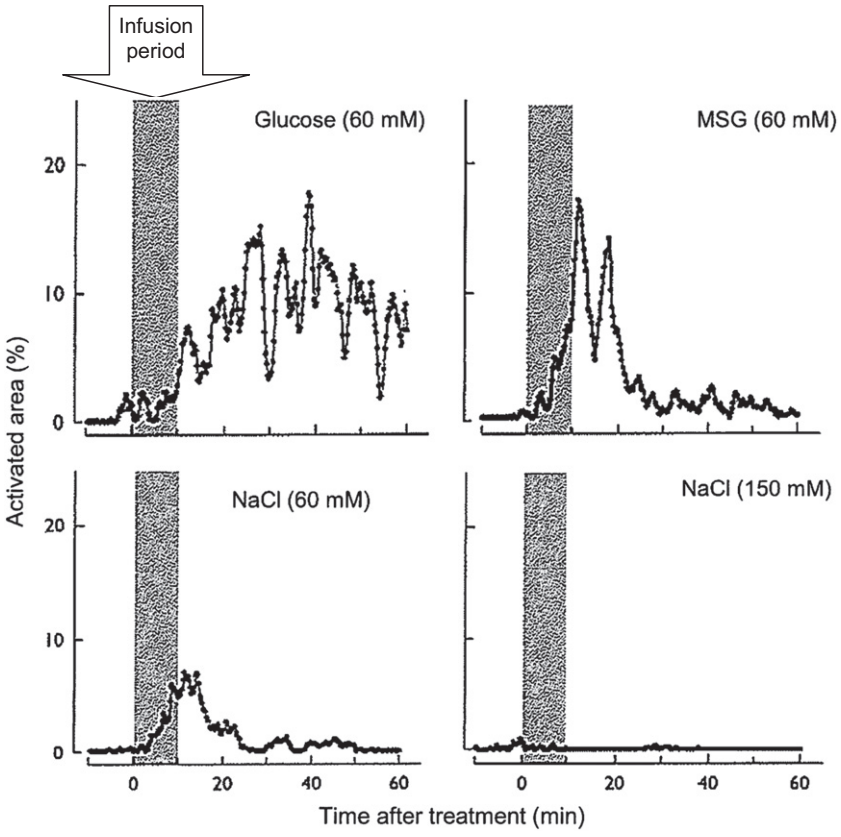

Fig. 5. Variation over time of the percent changes in significantly activated brain areas in rats. The horizontal axis represent the time elapsed after the onset of infusion. The infusion period is represented by the gray bar. Reproduced from Tsurugizawa et al. [39].

activation is different for Glu and for glucose (Fig. 5) [39]. An intragastric infusion of 60 mM Glu induced the vagal afferent activation to elicit functional fMRI signal changes in most parts of the brain during the infusion period alone. In contrast, intragastric infusion of 60 mM glucose induces long-term activation lasting more than 1 h. These different temporal and regional activation patterns in the brain are caused by distinctive signaling pathways between the gut and brain, and they result in distinctive effects on post-ingestion behavior.

6. Signaling mechanisms of the gut–brain axis promote metabolic control

Ingested food is broken down into individual nutrients, which are absorbed 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 nutrient. Simultaneously, 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 identified localized chemosensing taste receptors, including G-protein-coupled receptors (GPCR), in the luminal layer of the stomach, duodenum, and intestine. The T1R receptors, which are responsible for recognition of the sweet and umami tastes, and the family of T2R receptors, which mediate the recognition of the bitter tastes, are both expressed in the gut [48,49]. In both the oral cavity and the GI tract, GPR120 interacts with free fatty acids to induce the release of circulating GLP-1 [50]. Free fatty acids also interact with GPR40 in the GI tract and promote the secretion of GLP-1 [51] and CCK [52]. GLP-1 and CCK evoke c-fos-positive immunoreactivity in several brain regions, including the amygdala [53–55]. Intragastric infusion of glucose solution increases blood glucose levels, GLP-1, and insulin. Circulating GLP-1 also acts on neurons in the NTS. Recently, we showed that fluctuations in insulin following the intragastric administration of glucose correlate with fMRI responses in the amygdala, ventromedial hypothalamus, and nucleus accumbens [40].

Electrophysiological studies have shown that intragastric and enteric delivery of amino acids and lipids both activate the afferent vagus nerve as described above [32–34,56,57]. The intraportal administration of amino acids also activates the afferent vagus nerve response [58]. These reports indicate that the afferent vagus nerve is important for the transmission of information about nutrients in the gut to the brain. Interestingly, behavioral studies have shown that abdominal vagotomy eliminates the CFP in response to intragastric infusion of Glu [4] but does not affect the CFP response to intragastric infusion of carbohydrates in rats [59]. An fMRI study showed that both total and abdominal vagotomy diminished Glu-induced activation in the NTS and hypothalamus, whereas total vagotomy did not affect glucose-induced brain activation [40]. Instead, brain activation correlated with fluctuations in insulin following intragastric glucose infusion [40]. These results from fMRI studies of vagotomized rats are consistent with post-ingestion 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. The distinct post-ingestion effects in response to different nutrients result in the activation of forebrain regions. The spatial and temporal patterns of brain activation could link post-ingestion behavioral and physiological effects due to maintenance of homeostasis after a meal.

7. Conclusions

Glu plays important physiological roles in the perception of umami taste, in visceral information and regulation of endo–exocrine systems, and in excitatory neurotransmission. In our series, we have shown that dietary Glu also stimulates Glu sensors in the stomach and intestines, thereby 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 the activation of the vagal afferent nerve and consequently to the activation of a number of target areas in the brain. In addition, we have described the post-ingestion effects of Glu compared to those of glucose and lipids. Previous fMRI and behavioral studies in rodents have indicated that through the vagal afferent nerve, Glu exerts positive post-ingestion effects on the control of digestion and appetite for food, but no reinforcing properties such as the addictive behavior observed with sweets and alcohol intake. Together, these findings indicate that dietary Glu influences numerous physiological functions, suggesting a broad, integrative role for dietary Glu in body homeostasis. Recently, the newly developed method for investigating brain functional changes using a functional MRI after nutrient presentation to the gut has helped confirm the results obtained using the older technique of c-fos expression studies in rats [60]. Together, through chemical recognition of individual nutrients by using and non-invasive treatments in animals in a conscious state, this research approach to the study of gut–brain communication promises to provide important insights into mechanisms underlying food selection and utilization.

Conflict of interest

No potential conflicts of interest are disclosed.

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