Physiological Roles of Glutamate Signaling in Gut and Brain Function

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Some ingested nutrients have post-ingestive effects that modulate food intake and improve mood subconsciously. Here, we provide an overview of the positive post-ingestive effects of such nutrients, primarily L-glutamate, sugar, and lipids, with respect to behavior and brain function. We also discuss the mechanisms of brain activation resulting from signaling through the gut-brain axis. Recent studies have shown that rats prefer solutions paired with intragastric nutrients that have positive post-ingestive effects. Using functional magnetic resonance imaging (fMRI), we previously evaluated neural activation in response to ingested glucose, L-glutamate, and corn oil emulsion in rats and found that distinct forebrain regions were activated by these nutrients. Most of the areas activated by intragastric administration of L-glutamate were eliminated by abdominal vagotomy. On the other hand, the areas activated by intragastric administration of glucose were not affected by vagotomy. A behavioral study showed similar results for L-glutamate and glucose. These results indicate that brain activation in response to ingested nutrients occurs through distinct internal signals from the gut to the brain. Distinct regional and temporal activation in the brain determines the variety of post-ingestive behaviors and physiological responses.

Key words: post-ingestive effect; functional magnetic resonance imaging; L-glutamate; sugar; lipid

1. INTRODUCTION

The nutrients present in daily foods are necessary to maintain an adequate nutritional status for living things. For example, humans must take some kind of minerals, vitamins, and essential amino acids that cannot be generated de novo in the human body. Several nutrients, including L-glutamine, L-glutamate, glucose, and sucrose, have physiological effects such as protecting the gastric mucosa,

improving emotional state,

and supplying energy in the subconscious. These nutrients can also modulate subsequent behavior. All of these phenomena are termed post-ingestive effects.

Many researchers have investigated the post-ingestive effects of carbohydrates and lipids. Furthermore, some of these nutrients induce conditioned flavor preference (CFP) as described below and can lead to over-consumption, which is linked to addiction. Chronic intake of glucose and sucrose leads to over-consumption, increasing the risk of hyperglycemia. In a rodent model, chronic sucrose intake increases dopamine secretion in the shell region of the nucleus accumbens, which is related to reward and addiction. On the other hand, L-glutamate, a representative amino acid, induces preferable impression after ingestion via afferent vagal activation in the gut. Recently, we observed that an intragastric load of L-glutamate induced conditioned flavor preference in rats, which did not include the activation of the dopaminergic pathway. This finding is unlike those observed for glucose, sucrose, and lipids, as carbohydrate and lipid intake induce dopamine secretion in the nucleus accumbens.

In this review, we provide an overview of the positive post-ingestive effects of several nutrients, primarily L-glutamate, sugar, and lipids, with regard to behavior and brain function. We also discuss the mechanisms of brain activation and behavioral modulation resulting from internal signaling through the gut-brain axis.

2. POST-INGESTIVE EFFECTS ON SUBSEQUENT FEEDING BEHAVIOR AND EMOTIONAL STATE

The initial acceptance of foods largely depends on orosensory stimuli. After ingestion, animals can further learn to select foods through their post-ingestive factors. When ingested food or fluid has positive post-ingestive effects, animals can associate these positive effects with flavor and prefer to consume these foods. Flavor preference can be increased by repeatedly pairing certain foods with intragastric infusion of a nutrient solution. This paradigm is termed CFP. Behavioral studies have revealed that the intragastric infusion of carbohydrates, lipids, and alcohols induces CFP in rodents.

With regard to amino acids, we previously showed that an intragastric load of 60 mM monosodium L-glutamate (MSG) evoked CFP in rats. Isocaloric (60 mM) glucose and isotonic (60 mM) NaCl solution did not evoke CFP (Fig. 1), although 480 mM glucose solution did evoke CFP. Much higher concentrations of glucose lead to an increase in blood glucose and insulin, called as the caloric effect. Thus, these results indicate that the preference for the flavored solution paired with a gut infusion of MSG is due to neither caloric effect nor osmotic effect.

A progressive ratio is useful to assess the reinforcing properties of nutrients. Under a progressive ratio, successive food items within an episode of feeding become progressively more costly, e.g., there is an increase in the number of lever presses or the amount of licking required to obtain a constant amount of food. When rats repeatedly drink a glucose, sucrose, or ethanol solution with a reinforcement schedule under a progressive ratio, they become to pay more costs rather than water. In other words, chronic exposure to these

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solutions breaks down the balance between cost and benefit to allow the payment of greater costs to obtain the same benefits as before. Previous studies have shown that rats under a progressive ratio lick schedule of sucrose solution increase the number of licks, unlike the case for water intake. To our knowledge, however, there have been no studies on the reinforcing properties of L-glutamate. It would be interesting to compare the motivation for glucose and L-glutamate, as dopamine signaling, one of the crucial circuits involved in reward processing, is related to the postigestive effects of glucose but not L-glutamate.

The postigestive effects of carbohydrate and lipids also affect on the sleepiness and mood. The intragastric administration of carbohydrates and lipids has different effects in humans. An intragastric load of glucose induces a rapid increase in heart rate and energy expenditure, whereas lipids have a reduced or delayed effect. From 3- to 3.5-h after ingestion, subjects felt significantly sleepier after a lipid infusion compared to a saline infusion. Scores on a hedonic scale were also higher following saline and sucrose infusions than after the lipid infusion. These reports indicate that the postigestive nutrients could modulate the psychic state of humans as well as the feeding behavior.

3. FUNCTIONAL IMAGING OF THE POSTIGESTIVE NEURAL RESPONSE TO NUTRIENTS

To investigate the neural responses to ingested nutrients, we developed a functional magnetic resonance imaging (fMRI) technique in rats. One of the great advantages of fMRI is that the brain regions activated following nutrient stimulation in the gut can be investigated simultaneously. An intragastric load of 60 mM MSG or isocaloric glucose solution has been shown to activate distinct forebrain regions (Fig. 2). An intragastric load of MSG significantly activates the insular cortex, amygdala, and the hypothalamic regions, including the lateral hypothalamus, dorsomedial hypothalamus, and the medial preoptic area. On the other hand, an intragastric infusion of glucose activates the insular cortex, amygdala, nucleus accumbens, and the hypothalamic regions, including the lateral and ventromedial hypothalamus. We also investigated brain responses to an intragastric load of a corn oil emulsion, which activated the amygdala, lateral hypothalamus, hippocampus and the ventral tegmental area (Fig. 2). Behavioral studies have shown that ingested L-glutamate, glucose, and corn oil emulsion have positive postigestive effects with regard to CFP in rats. Based on the results of functional brain imaging and CFP studies, the brain regions commonly activated in response to the intragastric infusion of positive postigestive nutrients include the anterior cingulate cortex, insular cortex, amygdala, caudate-putamen, hippocampus, and the lateral hypothalamus. Thus, these regions should be related to CFP. The lateral hypothalamus and ventromedial hypothalamus are crucial areas for food intake, and the lateral hypothalamus is activated in response to glucose, L-glutamate, and corn oil emulsion. Only glucose activates the ventromedial hypothalamus. The lateral hypothalamus is related to the regulation of food intake, and there are glucose-sensitive neurons in the ventromedial hypothalamus. Touzani and Sclafani reported that lesions of the lateral hypothalamus diminish CFP by intragastric administration of glucose. The dopaminergic projections from the ventral tegmental area to the nucleus accumbens, amygdala, and the lateral hypothalamus are related to the preference for or addiction to ingested glucose and corn oil. Many studies have shown that sugar intake increases dopamine release in the nucleus accumbens shell region in rats, causing them to become addicted to sugar. A D2-like receptor antagonist has been shown to inhibit the reinforcing effects of corn oil in rats. On the other hand, intragastric infusion of L-glutamate does not activate the nucleus accumbens (Fig. 2), and
lesions of neurons in the ventral tegmental area do not affect the preference for L-glutamate in rats.65 These results show that the postingestive effects of L-glutamate differ from those of sugar and lipids.

Notably, fMRI also has the advantages of temporal and spatial resolution rather than the c-fos and electrophysiological studies. The time course of brain activation for different nutrients is different (Fig. 3). An intragastric load of 60 mM L-glutamate have been shown to activate the cortex, limbic regions, and the hypothalamus, primarily during the infusion period. Meanwhile, intragastric infusion of 60 mm glucose induces the long-term activation of more than 1 h.

Postigestive brain activation has also been investigated in human subjects. Lassman et al. found that intragastric administration of dodecanoic acid activates the brainstem, cingulate gyrus, hypothalamus, and the thalamus.16 The activation of these areas was abolished, however, by oral intake of dexloxiuglumide, a cholecystokinin (CCK)-1 receptor antagonist.

These reports indicate that the brain distinguishes ingested nutrients in the gastrointestinal tract. These temporal and regional differences of activation patterns could result in peculiar effects on postingestive behavior.

4. SIGNALING MECHANISMS OF THE GUT-BRAIN AXIS

How is postingestive information regarding nutrient intake conveyed to the brain? Ingested nutrients are digested and absorbed in the gastrointestinal tract. The afferent vagus nerve, which innervates the entire gastrointestinal tract and projects to the nucleus of the solitary tract, is then activated, or peripheral humoral factors such as insulin and glucagon-like peptide-1 (GLP-1) are released. In addition to absorption and metabolism, recent studies have indicated that the stomach, duodenum, and intestine contain chemosensing taste receptors and some kind of the G-protein coupling receptors (GPRs). The T1R receptor, which is related to the chemoreception of the sweet and the umami taste, and the T2R receptor, which is related to the chemoreception of the bitter taste, are both expressed in the gut.17,18 In addition, GPR120 exists in both the oral cavity and the gastrointestinal tract in rodents.19 Fatty acids interact with GPR120 to induce the release of circulating GLP-1.19 Free fatty acids also interact with GPR40 in the gastrointestinal tract and promote the secretion of GLP-120 and CCK.21 GLP-1 and CCK evoke c-fos positive immunoreactivity in several brain regions, including the amygdala and the periaqueductal gray matter.22-24 Intragastric infusion of glucose solution increases blood glucose, GLP-1, and insulin, and circulating GLP-1 acts on neurons in the nucleus of the solitary tract. Recently, we demonstrated that fluctuations in insulin following the intragastric administration of glucose correlate with the blood oxygenation level-dependent (BOLD) response in the amygdala, ventromedial hypothalamus, and nucleus accumbens.11

Electrophysiological studies have shown that intragastric and enteric delivery of amino acids and lipids both activate the afferent vagus nerve.25,26 The intraportal administration of amino acids also activates the afferent vagus nerve.27 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 to intragastric infusion of L-glutamate28 but does not affect CFP to intragastric infusion of carbohydrates in rats.29 Our previous fMRI study showed that total and abdominal vagotomy diminished L-glutamate-induced activation in the nucleus of the solitary tract and hypothalamus, whereas total vagotomy did not affect glucose-induced brain activation15 (Fig. 3). Instead, brain activation correlated with fluctuations in insulin following intragastric glucose infusion. These results from fMRI of vagotomized rats are consistent with postingestive behavior studies, indicating that internal signals in response to L-glutamate mainly involve the vagus nerve, whereas those in response to glucose at least partly involve insulin.

Finally, there are distinct postingestive pathway 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.

5. CONCLUSION

The postingestive effects of nutrients are important to maintain an adequate nutritional status and normal brain activity. The brain has a continuous monitoring system for nutritional status and, if necessary, controls feeding behavior to cause the intake of more or less nutrients. To achieve this, the brain must have the ability to detect ingested nutrients in the gut, integrate sensory information from food (e.g., appearance, smell, and taste) and postingestive information, evaluate this information, and modulate subsequent behaviors and physiological responses. In order to understand these mechanisms, future studies should focus on an integrated model of sensory information and postingestive internal signals.

In this review, we described the unique sensory mechanisms present in the gut and the postingestive effects of L-glutamate compared to those of glucose and lipids. Previous fMRI and behavioral studies in rodents have indicated that L-glutamate has positive postingestive effects through the affer-
ent vagus nerve but no reinforcing properties. Neural responses to l-glutamate on fMRI also imply possibility of physiological effects, e.g., thermoregulation and protection of the gastric mucosa.

REFERENCES