Current Topics

Physiology and Pharmacology of the Gut Nutrient Perception

Physiological Roles of Dietary Free Glutamate in Gastrointestinal Functions

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The appropriate recognition of nutrients in gastrointestinal tract has an important role in the maintenance of healthy body functions. Perception of nutrients in gastrointestinal tract influences not only the regulation of gastrointestinal functions such as digestion and absorption, but also the subsequent formation of ingestive behaviors and food preferences. Glutamate is widely distributed amino acids, approximately 15–45% in the dietary protein as the total of free- and bound-forms. To note is that, glutamate is implicated in numerous physiological and metabolic functions in the body as a nutrient, in addition, free glutamate in the food is also known as the source of umami, one of the five basic taste. Taste is basically perceived on the tongue in the oral cavity *via* the specific taste sensors (receptors and/or transporters), however, the recent studies suggest the functional roles of taste sensors in the regulation of gastrointestinal tract. Interestingly, we recently found the presence of specific glutamate-sensing systems in the lumen of the stomach. In addition, we have been vigorously studying the physiological roles of dietary free glutamate in the body through experimental animals and human. In this topic, we review the beneficial roles of dietary free glutamate in the regulation of gastrointestinal functions and propose some application of the benefits for the clinical gastrointestinal disorders.

Key words glutamate; gastrointestinal tract; chemosensing; taste; nutrition

1. INTRODUCTION

When you are hungry and eat something delicious, you must feel deep satiety soon. In this process to feel satiety, tasting with tongue alone is not enough. First, you have to “taste” with gustatory sensors on the tongue in the oral cavity during the masticatory process, then the smaller pieces of foods chewed-up enter the stomach, and the stomach starts digesting the contents by sensing the volume, the hardness and the ingredients. Partially digested contents are properly pushed out to the intestine and the subsequent digestion, such as protein to amino acids, fat to fatty acid and carbohydrate to sugars, enable these nutrients to be sensed and absorbed in the intestine. Absorption and/or sensing of nutrients in the gastrointestinal tract convey the nutrient information *via* neuronal (vagus nerve) and endocrine (gastrointestinal hormone secretion) pathways to the brain. Thus, “Satiety” should be considered as a kind of highly-integrated feeling recognized by brain after processing the visceral sensation (which metabolically modulates the blood levels of absorbed nutrients finely within the normal range) and the subsequent information of nutrient sufficiency from the peripheral tissues.

Umami is one of the five basic taste, induced solely and synergistically by free glutamate and 5'-mononucleotides such as inosine 5'-monophosphate (IMP) and guanosine 5'-monophosphate (GMP). Now, for umami sensing, several receptors such as taste receptor (T1R1/T1R3 heterodimer) and metabotropic glutamate receptors (mGluR1 and mGluR4) are proposed in the taste bud on the tongue. These umami substances are widely distributed in the vegetables, meats, and fishes, and especially concentrated in the traditional food materials such as dried seaweed “kombu”, tomato, cheese, soy sauce, dried mushroom and dried fishes. For example, in

Japan, umami-taste dishes are considered as traditional, delicious, relaxed foods and daily intake of free glutamate is estimated to be more than 1.6 g per person. Thus cooking using these “umami” food materials is the best shortcut to have delicious dishes, leading to enough “satisfaction”.

“Eat well, be well, and live better” through the food is our final goal. To accomplish this, we are vigorously studying to clarify the mechanisms of “eating behavior” from a variety of aspect. Especially, we are now focusing on the physiological roles of free glutamate in the regulation of gastrointestinal functions. Recently, we proposed the presence of glutamate sensing and the following signaling pathway in the stomach. In this topic, we show previous and new findings of dietary free glutamate in the regulation of gastrointestinal functions and then propose some applications of the benefits for the clinical gastrointestinal disorders.

2. THE ESSENTIAL REQUIREMENT OF UMAMI PREFERENCES FOR PROTEIN INTAKE

A number of researchers have reported that mammals other than humans such as rat, cat, pig and cow, can perceive umami taste (Naim *et al.*, 1978,³⁾ Ohara *et al.*, 1979⁴⁾). Our previous studies have indicated that the taste preference is influenced by the levels of ingested dietary protein (Fig. 1) (Mori *et al.*, 1991²⁾). When the protein intake in diet is restricted to deficient levels around 0–5%, rats favor more salty (NaCl) and sweet (glycine) rather than umami taste (monosodium glutamate; MSG) solution. However, as protein intake in diet increases, the taste preference to these solution changes gradually. Interestingly, at 20% protein in diet, rats favor more umami taste solution rather than NaCl solution or glycine solution. These results lead us to hypothesize that a preference for umami taste is linked somehow to the

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Fig. 1. Changes of Preference to NaCl (Open Triangle), Glycine (Open Circle) and MSG (Closed Square) under the Restriction of Protein Intake in Rats

Male SD rats were received diet containing stepwise increasing doses of egg protein for the indicated periods and the preferences to three taste solutions (150 mM NaCl, 500 mM glycine and 150 mM MSG) were determined. Figure was cited from Torii *et al.* (Torii *et al.*, 1987⁶⁾).

body requirement to operate metabolism of ingested dietary protein.

3. GLUTAMATE SENSING SYSTEM IN THE STOMACH

Gastrointestinal tract has important roles in the digestion of dietary protein and the following absorption of amino acids. Especially, stomach contributes most to digest protein by secreting gastric acid from parietal cells and pepsinogen from chief cells. Recently, we have reported that luminal application of glutamate into the stomach stimulates the firing activity in the afferent fibers from gastric branch of vagus nerve (Fig. 2) (Uneyama *et al.*, 2006⁷⁾). In the mechanism of this glutamate-sensing, serotonin, serotonin receptor type 3 and nitric oxide are involved. To note is that, other amino acids failed to have the same effect, although, all the amino acids respond in the intestine. Thus, among the 20 dietary amino acids which compose body proteins, glutamate alone could evoke the nutrient information from the stomach to the brain. As postprandial gastric acid and pepsinogen secretions are mainly vagus-regulated, our results strongly suggest that luminal umami glutamate stimulates gastric digestive functions *via* vago-vagal reflex. In addition, using immunohistochemistry, we have reported that mGluR1 is located at the apical membrane of chief cells and possibly parietal cells (San Gabriel *et al.*, 2007⁵⁾). The functional analysis to prove the physiological role of mGluR1 has not finished yet, however, it is possible that luminal glutamate acts on glutamate sensing receptor and/or transporter located on the gastric mucosa, then directly regulates gastric functions without connecting *via* cephalic phase.

4. PHYSIOLOGICAL SIGNIFICANCE OF LUMINAL GLUTAMATE TO REGULATE GASTRIC FUNCTIONS

Vasilevskaia *et al.*, have compared the effect of luminal umami taste flavor (glutamate+IMP) on dietary meat-stimulated postprandial gastric juice secretion using the Pavlov-

Fig. 2. Luminal Sensing of Glutamate Results in the Activation of Rat Gastric Afferent Vagus Nerve *via* NO, Serotonin (5-HT) and Serotonin Receptor Type 3 (5-HT₃R)

Each amino acid aqueous solution (150 mmol/l, 2 ml) was applied to the stomach, and the mean activation rate above baseline at 20 min was plotted. Each column and the horizontal bar represents mean $\pm$ S.E.M. $**p < 0.05$ vs. saline (Kruskal-Wallis test).

pouched dogs (Vasilevskaia *et al.*, 1993⁸⁾). The flavor supplementation caused rapid and prolonged increase in the meat-stimulated postprandial gastric juice secretion compared with control diet and the total juice volume was approximately 1.6-fold higher. We also found that glutamate stimulates gastric acid and pepsinogen secretion using acute rat gastric fistula model (unpublished results). Similar result was observed in clinical study by Kochetkov *et al.* (Kochetkov *et al.*, 1992¹⁾). They determined the effect of free glutamate supplementation into daily hospital meals on gastric secretion and appetite in patients with chronic atrophic gastritis. These patients suffer from loss of appetite, because gastric acid secreting parietal cells and pepsinogen secreting chief cells are almost lost by atrophy due to *Helicobacter pylori* infection, aging or autoimmune gastritis, and they lack enough digestion, *i.e.*, gastric dyspepsia (Fig. 3). Interestingly, the intake of the daily meals supplemented with free glutamate for 24 d improved the basal and maximal gastric acid secretion and appetite in these patients. This is consistent with our recent finding that diet with preferable amount of MSG supplementation for 3 months decreased gastritis and gastric atrophy induced by *Helicobacter pylori* in experimental gerbil model (in preparation). Thus, it is speculated that glutamate-induced gastric mucosal protection/repair might be involved in the improvement of gastric acid secretion in patients with chronic atrophic gastritis, leading to recovery of the appetite loss. Concerning the other gastric functions, Zai *et al.*, reported that supplementation with 0.5% free glutamate increased the delayed gastric emptying rate induced by protein-rich liquid diets in humans using the breath test with the stable isotope (¹³C-acetate) (Zai and Kusano, 2006⁹⁾). Based on these basic and clinical evidences, we propose that free glutamate has a potent power to improve gastric digestive function by modulating gastric secretions, mucosal protective factors and motility. Thus, it is quite promising that free glutamate supplementation should be useful for the patients with gastric problem such as functional dyspepsia, chronic atrophic gastritis and maldigestion, and for the elderly peoples insufficient in digestion.

Fig. 3. Pathogenesis of Gastric Atrophy

Pathogenic factors such as *H. pylori* infection, autoimmune antibody to parietal cells and aging, influence gastric mucosal differentiation, then reduce the number of acid-secreting parietal cells and pepsinogen-secreting chief cells, (i.e., atrophy), resulting in the insufficient digestion, called as "dyspepsia."

5. PERSPECTIVE

This year is 100th anniversary for the discovery of sodium glutamate as umami taste by Dr. Kikunae Ikeda in 1908. During this century, many scientific findings for glutamate were clarified in terms of oral taste and nutritional function. In addition to these aspects, for the next 100 years, we propose the gastric umami taste sensing system which modulates gastrointestinal functions leading to better digestion of the food. Because, in taste field, umami, a taste sense of free glutamate, is considered as a marker for protein intake, we hope that palatability for umami taste should mean some physiological requirement for protein digestion. We should care much about umami taste palatability and hopefully utilize the preference for better understanding of gastrointestinal condition, to eat well and live well in our healthy life.

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