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Perceived Palatability and Appetite for Protein by Umami Taste Derived from Glutamate

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Abstract

About a century ago, a new tastant, umami taste substance (L-glutamate) was discovered in Japan with a motivation to improve the poor nutritional status of Japanese people by supplying affordable delicious flavors. Since then, Japanese physiologists have been leading the taste research to establish the taste of free L-glutamate as the fifth basic taste (umami taste), in addition to sweet, bitter, sour and salty taste. Taste physiologsts have presented the hypothesis that the umami taste is a sensory marker for protein intake, like as salty taste is that for mineral intake. Evidence has now accumulated that free glutamate is sensed by taste receptors on the tongue as well as in the gastrointestinal tract, leading to protein digestion and absorption, as well as perceived palatability and appetite. Analytical food technology has revealed that a high level of free glutamate is contained in seasonings used worldwide, including soy, fish and oyster sauces, and tomato ketchup, or food stuffs such as tomato and cheese. We are dedicated to bringing the nutritional and physiological benefits of glutamate for human health through incorporation of umami taste to worldwide food culture. In this review, we will introduce our recent findings about the nutritional and physiological significance of the umami taste in protein intake and utilization.

Keywords: Umami taste substances; Monosodium glutamate; Visceral information; Protein digestion

Introduction

The pleasant sensory qualities of traditional Western cuisine derive mainly from animal fat, whereas traditional Japanese cuisine contains less fat and relies more on "dashi" (Japanese broth) to enhance food palatability. Early in the last century (1908), a Japanese scientist, Kikunae Ikeda at Tokyo Imperial University noticed that an unidentified taste quality, distinct from the four basic tastes (sweetness, saltiness, sourness and bitterness), was present in palatable foods. He found this taste most clearly in soups rich in "dashi" prepared from Japanese sea tangle (*kombu*), which has traditionally been used in Japanese cuisine, and he discovered the salts of an amino acid, glutamic acid, as an umami taste substance. The year after his discovery, sodium salt of glutamic acid (monosodium glutamate: MSG) became commercially available as the first umami taste seasoning in the world [1].

We maintain our daily life activities through taking essential nutrients from the outside world via the taste sensation. The essence of taste is the signal of the intake of nutrients and avoidance of harmful substances. In particular, appetite and palatability are strongly influenced by the nutritional status of the body. For example, in laboratory animals, hypoglycemia by insulin injection induces an increase in the preference of sweet taste, and the decrease of plasma sodium concentration by adrenalectomy can increase the palatability of salty foods [2,3]. In the field of taste physiology, it has been thought that sweet taste is the signal of energy intake (glucose and glucogenic amino acids), salty taste is the signal of minerals (sodium and potassium), sour taste is the signal of harmful food decomposition (organic acids), bitter taste is the signal of poison and pharmacologically active substances (plant alkaloids). The last basic taste, umami taste has been thought to be the signal of protein intake (amino acids) [4,5].

We can easily understand the above laboratory evidence from our daily experience. When hungry, we are attracted to sweet foods as they increase the blood glucose level and to salty dishes when we lose minerals through sweat during hard exercise. Scientific reports mentioned that palatability and pleasantness for sweet or salty taste are affected in hunger or exercise as well [6,7]. Regarding the preference for umami taste, animal experimental data has shown that a preference for umami is linked somehow to the body's requirement to operate metabolism of ingested dietary protein (Figure 1). In this experiment,

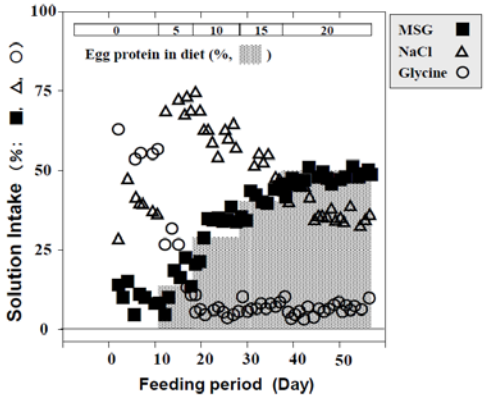

Figure 1: Physiological significance of taste in the body nutrient homeostasis Relationship between protein intake and umami taste preference.
Changes in taste preference for umami taste (150 mM MSG: ■), salty taste (150 mM NaCl: ■) and sweet taste (500 mM Glycine: ○) in fed with various contents of protein diets (0-20%). Data was quoted from Torii et al. [8].

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rats received a diet containing stepwise increasing doses of egg protein for the indicated periods, and the preferences to three taste solutions (NaCl, glycine and MSG) were determined. When the protein content in diet is restricted to deficient levels around 0-5%, rats favor a salty taste (NaCl solution) and sweet taste (glycine solution) rather than the umami taste (monosodium glutamate solution). However, as protein content in the diet increases, the taste preference to these solutions gradually changes. Interestingly, at a 20% protein diet, rats favor umami solution rather than NaCl solution or glycine solution [4,8,9].

The central topic of this review is why perceived palatability and appetite for the umami taste changes during high protein loading. Palatability of food changes when we need to adjust for the excess or deficiency of a particular nutrient to satisfy adequate nutritional requirements for health, or when we need specific nutrients to effectively control the absorption and utilization of dietary foods within our body. It is thought that the mechanism enabling the body nutrient homeostasis is complementing the essential nutrients through integration of taste and visceral nutrient information within brain. In this review, we try to explain the reason why free glutamate derived umami taste has been thought to be a marker of protein intake.

Chemical Perception for Nutrients in the Gut: The Hypothesis of Gut Taste Perception

We can find taste active proteins such as monelin and Talin (sweet proteins) [10], but major macronutrients (starch, fat and vegetable proteins) with high molecular weight indispensable to life are usually tasteless, because their high molecular weight nutrients are unable to interact with taste receptors on the tongue. In fact, we cannot distinguish the taste of dextrin, vegetable oil and casein after purification. We can recognize each food by tasting low molecular substances that co-exist with those macronutrients (i.e., carbohydrates; sugars, fats; fatty acids, proteins; amino acids). For example, we can recognize the taste of crab meat when glycine, alanine, arginine and glutamic acid (and inosinic acid, salt, potassium phosphate) are added to purified protein such as casein protein [11]. In recent years, development of the molecular biology of taste receptors have been identified in a series of candidate taste receptors which interact with these low molecular tastants on the tongue [12]. Interestingly, there have been many reports that these taste receptors are also expressed on the mucosal epithelium in the digestive tract, such as the stomach and intestine, and that the receptors mediate chemical perception for dietary nutrients in the gut.

Famous physiologists have presented basic theories explaining the mechanisms involved in the gut nutrient-sensing. In the early 19th century, I. Pavlov presented the "antenna nerve theory" that luminal nutrients were sensed by the afferent sensory nerve endings exposed to the intestinal mucosa [13]. Bayliss and Starling then proposed the "tissue hormone theory" that luminal nutrients were caught by the gastrointestinal mucosa and released to tissue hormone to the bloodstream [14]. The American physiologist M. Grossman presented a new theory combining those previous two hypotheses that recognition of gut nutrients was made by afferent sensory nerve endings on the intestinal mucosa and the intestinal endocrine cells released secretory granules (hormones) through the stimulation of the nerve reflex [15]. After that, Drs. Fujita and Kobayashi at Niigata University in Japan proposed the famous "gut sensor cell hypothesis" with electron microscopy and physiological techniques [16]. The gut sensor cell hypothesis claims that luminal chemical and physicochemical information (nutrient information such as amino acids, glucose and fat, pH and osmolarity) is perceived by "open-type" intestinal endocrine cells, and the endocrine cell itself releases secretory granules into the blood, regulating gastrointestinal motility and exocrine in a paracrine or humoral manner. This hypothesis changed the basic concept of the gut nutrient-sensing from the ancient abstract to the modern molecular-based concept as stimulus/secretory coupling via nutrient molecule-receptor interaction.

The molecular mechanism of the gut nutrient perception was not known for a long time. The research has rapidly advanced in the view point of the existence of taste-like cells in the gastrointestinal mucosa since the German anatomist Höfer reported that GTP binding protein (α-gustducin) specific for taste cells was expressed on the brush cell in the pyloric antrum and duodenum [17]. A wide variety of taste receptors are now known to be distributed in the gastrointestinal mucosa. For example, the T2Rs responsible for the bitterness on the tongue are expressed on gut enterochromaffin cells [18]. T1Rs and CaSR (calcium-sensing receptor) sensing for amino acids, and fatty acid receptors such as GPR120, have also been shown to be widely distributed in the gastrointestinal epithelium [19-21] Robert Margolskee and colleagues reported that endocrine cells of the intestinal epithelium (L cells) expressed the sweet taste receptor T1R2/T1R3 complexes and released the gut hormone, GLP-1, in response to luminal sugars and regulated body glucose utilization through pancreatic endocrine regulation [19]. Additionally, this researcher is now trying to explain the molecular mechanism involved in the "incretin effect," which has been questioned so far between endocrinologists. On the other hand, we showed in 2007 that glutamate receptors are expressed on gastric mucosa and presented the possibility that the glutamate receptors mediated luminal glutamate-sensing via the vagal afferent pathway in the stomach [22,23]. We are now trying to formulate a systematic explanation for the regulation of perceived palatability and protein digestion/absorption via the gastric glutamate receptors [24-27].

Vagal Afferent Nerve Activation by Luminal Nutrients: Visceral Nutrient Information

How does our brain recognize dietary nutrient composition in the gut during food digestion? Taste information is transmitted from taste buds to the brain stem via taste nerves (chorda tympani and glossopharyngeal nerve). Incontrast, visceral nutrient information in the gastrointestinal tract is carried by the abdominal vagal afferent nerves as well as gut hormone secretions to the brain stem. Abdominal vagal afferents are innervated into digestive routes of dietary foods such as the stomach and small intestine, convey individual nutrient information to the brain, and regulate food digestion and nutrient absorption and utilization through stimulating gastrointestinal motility and secretions during meals. At the same time, the vagus pathway is considered to be an essential route to homeostatic control of feeding behavior such as formation of satisfaction (satiety).

First research mentioning the possibility of nutrient sensing for amino acids by the abdominal vagus goes back half a century. The French physiologist Mei reported that the vagal afferent nerve was activated after intraduodenal administration of amino acid solutions [28]. Since then, many researchers have revealed the existence of chemoreception for many nutrients, since the vagal afferent pathway was also activated by the duodenal application of glucose, peptide and fatty acids [10,29].

Professor Niijima at Niigata University first reported the possibility of the existence of glutamate perception in the stomach in 1991 [30]. We then found very interesting evidence based on the electrophysiological experiments for the responsibility of gastric and celiac vagal afferents to

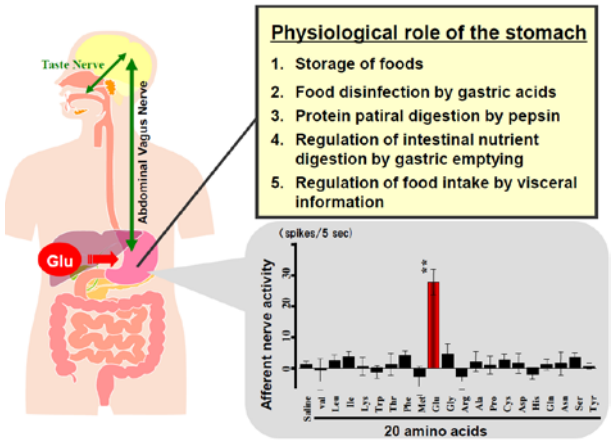

Figure 2: The stomach can taste glutamate through vagal afferents. Effects of 20 amino acids composing dietary proteins. Each amino acid aqueous solution was introduced directly into the stomach at a concentration of 150 mmol/L. Data are modified from Uneyama et al. [23].

20 dietary amino acids. In the small intestine, celiac branch of the vagus nerve activity was inhibited by luminal glycine, and enhanced by the luminal glutamate, aspartate, and tryptophan. All amino acids can be detected by the celiac afferents [23,31]. However, in the stomach, vagal gastric afferents stimulated only glutamate among those 20 amino acids (Figure 2) [23]. This strongly suggests that the intestinal mucosa has a mechanism that can recognize all the individual amino acids formed during protein digestion, but the gastric mucosa has a mechanism that can detect only glutamate contaminated in proteins because the gastric proteolytic enzyme cannot digest protein to each amino acid.

Glutamate is the most abundant dietary protein-bounded amino acid as well as free-form amino acid co-existing with dietary proteins. When considering the digestion of proteins, the denaturing and partial digestion of dietary proteins with gastric acid and the proteolytic enzyme pepsin are the most important processes during gastric digestion. The existence of a specific chemoreception for glutamate in the stomach indicates the possibility that the stomach may act as a taste organ sensing free glutamate contained in dietary protein and that the stomach regulates gastric exocrine functions to accelerate the gastric protein digestion in response to free glutamate. The stomach is not only a simple storehouse for food, but also a highly intelligent functional organ.

Next, we show the nutrient recognition process within the brain after introducing glutamate into the stomach, using rats. MEG, functional NIRS and MRI are well known non-invasive methods for detecting brain functions. We succeeded in performing real-time monitoring of brain functional images after gastric glutamate perception with the functional MRI (4.7T fMRI) technique [32-34]. The result is shown in figure 3. Intra-gastric administration of 1% glutamate aqueous solution activated the brain nuclei, including the Dorsal Vagal Nucleus (DVN) and the Nucleus of the Solitary Tract (NTS), which is the output and input of the vagal nerve, and the insula cortex integrated with taste and visceral information. At the same time, each nucleus of the hypothalamus conveying feeding behavior and body temperature control was activated. Since the brain activation was diminished by cutting the vagus nerve, it was confirmed that most of the brain response induced by luminal glutamate was carried through the vagal afferent pathway (visceral sensation). On the other hand, the intra-gastric application of another nutrient, glucose, brought the activation of some brain nucleus, but the activation was not affected by cutting the vagus nerve [32]. It is assumed that glucose detection by the brain seems to be mediated by humoral factors such as gut-pancreatic hormones. The brain mechanisms for gut-nutrient perception seem to vary depending on nutrients.

Regulation of Gastric Protein Digestion via Visceral Nutrient Information

Pioneer research on gastric glutamate physiology was done by Russian scientists at Moscow University who graduated from the I. Pavlov Institute of Physiology. They reported on their results in a Russian paper entitled "Effect of glutamate and combined with inosine monophosphate on gastric secretion" In 1993 [35]. They used a dog model with a surgically split stomach, known as the Pavlov pouch model, as originally described by Pavlov. The small gastric pouch was prepared from tissues of the fundus and the upper corpus preserving vagal branches. It was fully separated from the main stomach, so that solutions applied to the main stomach did not interact with mucosa of the pouch. With this model, they monitored changes in gastric acid secretion when the dog had meat foods supplemented with and without the umami taste flavor (mixture of 92% monosodium glutamate and 8% inosine monophosphate). They reported that supplementation of the umami taste seasoning increased the amount of gastric secretion at approximately 1.6 times to accelerate gastric protein digestion.

The Pavlov Institute of Physiology is known as the largest physiological research center of the Russian Academy of Sciences, and was named after the Nobel Prize winner in Medicine, Ivan Petrovitch Pavlov (1849-1936). The Pavlov Institute has continued to research Pavlovian sensory physiology focusing on neural control of gastrointestinal functions. There have been long-term ties between glutamate researchers in Japan and the Pavlov Institute. The Japanese physiologist Takashi Hayashi (1897-1969), the first professor of Physiology at the School of Medicine at Keio University, studied at the Pavlov Institute at 1932, and after returning home, discovered that glutamate was a major excitatory neurotransmitter within the brain [36]. Hayashi then enlighten the general public enthusiasm

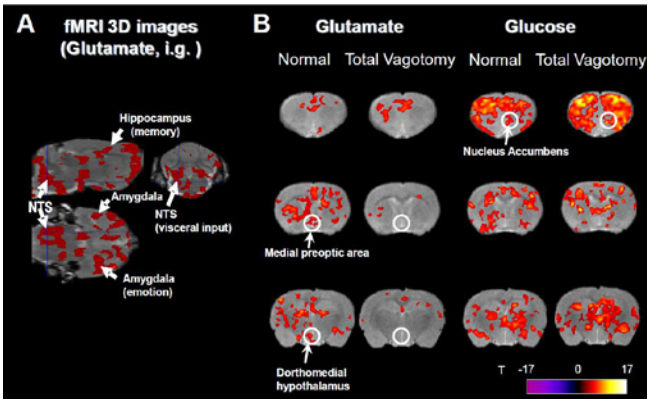

Figure 3: Neural processing of the glutamate information from the stomach. Brain activation was continuously monitored after gastric application of glutamate, using functional MRI technique (4.5T).
A: 3D reconstruction images after gastric loading of 60 mmol/L glutamate solution. Red region means increase of neural activities.
B: fMRI image after intra-gastric administrations of glutamate and glucose. Almost all gastric glutamate-mediated signaling was diminished by the total vagotomy (TVX), but gastric glucose (120 mmol/L) -mediated signaling was not affected by the TVX. Data were referred to Tsurugizawa et al. [32,33].

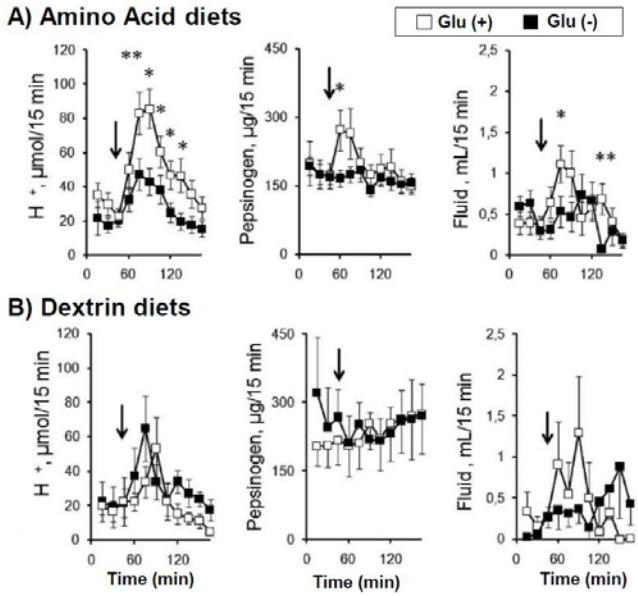

Figure 4: Free glutamate stimulates gastric secretion via vago-vagal reflex. Supplementation with 100 mM monosodium L-glutamate (MSG) enhanced gastric secretion induced by a high-caloric amino acid-rich diet, but did not affect secretion induced by a carbohydrate-rich amino acid-free diet in Pavlov pouch dogs. A) Secretion of acid, pepsinogen and fluid in the small gastric pouch stimulated with an amino acid-rich diet (Elental diet). B) Secretion in the small gastric pouch induced by 100% dextrin, amino acid-free diet. Both diets were infused through a fistula into the main stomach and secretions were measured in the washes from the Pavlov pouch. Data are expressed as mean±SEM. Infusion of each diet are marked with arrows. Paired comparisons were made with Student's t test; * : p_0.05, ** : p_0.01; n=9 in each group. Data are quoted from ref. 28. Data are quoted from Zolotarev et al. [37].

for the neurotransmitter glutamate, and advocated that intake of dietary free glutamate would make up human memory. At that time, Japanese people were eager to obtain free glutamate as an umami taste seasoning. However, subsequent research rejected his hypothesis, with the following findings. 1) Almost all dietary free glutamate with meal is used as an energy source in the intestinal mucosa to transfer only about 5% of glutamate to the bloodstream. 2) Even if the plasma glutamate level is markedly increased, the existence of the blood-brain barrier blocks the penetration of plasma glutamate into brain tissue. 3) Glutamate levels in the brain keeps homeostatic control and glutamate required for neuronal function is synthesized within the brain, not recruited from peripheral blood.

In 2007, about a century after Pavlov's golden age, we began collaborative research to clarify the physiological regulation of dietary free glutamate in gastric protein digestion, under a new hypothesis that the gut glutamate perception controls gastrointestinal functions via brain-gut communication. In this experiment, we examined the effect of free glutamate on gastric acid secretion when injected directly into the main stomach, using Pavlov's pouched dog (Figure 4) [37,38]. We used an enteral liquid diet (Elental™) as a nutrient, which is mainly composed of a mixture of amino acids and final nutrients digested from protein. The composition of Elental™ is 17 amino acids (Ile, Leu, Lys, Met, Phe, Thr, Trp, Val, His, Arg, Ala, Asp, Gln, Gly, Pro, Ser, Tyr), vitamins, carbohydrates and micronutrients, and this amino acid diet completely lacks glutamic acid in its composition. As a result, injection of the amino acid diet (1 Kcal/mL, 20 mL) into the main stomach induced slight gastric secretion. Surprisingly, in the presence of an Elental™ diet, intra-gastric application of free glutamate induced powerful gastric secretion in a dose-dependent manner. The intra-gastric administration of glutamate aqueous solution without Elental™ failed to induce the gastric acid secretion as well [37]. Interestingly, the glutamate effect seemed to appear specifically in the amino acid diet. Figure 4 shows the effects of free glutamate added to Elental and a carbohydrate (100% dextrin) liquid diet on the gastric secretions. Glutamate has an enhancing effect on the gastric secretions in the presence of Elental, but no effect in the presence of amino acid-free dextrin diets. Moreover, the gastric effects of glutamate were markedly decreased by about 80% after cutting the vagus nerve innervations to the stomach [37]. That is, it was revealed in the dog's experiments that glutamate acts directly on the stomach and helps the digestion of dietary protein in the stomach through stimulating vagal nerve-dependent gastric exocrine secretion.

Protection of Gastrointestinal Mucosa by Umami Taste Substances

The stomach wall itself is formed by many cells which consist of proteins and lipids. The fact that dietary free glutamate promotes partial digestion of protein with gastric acid and pepsin indicates that the intake of glutamate poses a risk, as glutamate can attack the gastric and duodenal wall, leading to gastric and duodenal ulcer. To confirm the possibility of this adverse effect, we performed collaborative research on mucosal defense with Dr. Akiba at the CURE/UCLA, an institute founded by M. Grossman (intestinal chemoreception research pioneer in the U.S., above). In this experiment, using a laser microscope, they tested the effect of the luminal application of glutamate to the gastric and duodenal mucosa against the mucus secretions. As a result, the duodenal mucus layer was markedly increased in the presence of luminal glutamate solution, but this effect was found to be mostly lost by the destruction of the submucosal layer of the nerve using capsaicin treatment [39]. The same result has been observed in gastric mucosa as well as in duodenal mucosa [40]. Focusing on this action of glutamate, Takeuchi and colleague at Kyoto pharmaceutical university showed that glutamate fortification to the diets (1% to 5%) attenuated Non-steroid Anti-inflamatory Drugs (NSAIDs)-induced gastroduodenal ulcers in the rats [41,42] . Thus, the dietary free glutamate increases gastric exocrine function as well as acting to protect the gastrointestinal mucosa against gastric acid and pepsin attacks via mucus secretion.

Possible Clinical Application Based on the Physiological Aspects of Umami Taste

We can find several important human studies examining the effect of dietary free glutamate on the digestion and absorption of protein foods. Dr. Kusano and his colleague discovered that the addition of free glutamate to a high protein diet improved delayed gastric emptying and abdominal unpleasantness such as a heavy stomach after eating (Figures 5 and 6) [43]. With a breath test using stable isotope-labeled (^{13}C) sodium acetate, they studied the supplemental effects of free glutamate to a high protein liquid diet (a mixture of 50% casein calcium and 50% dextrin, 1 Kcal/mL, 400 Kcal) and 100% pure dextrin diet (1 Kcal/mL, 400 kcal) on the human gastric emptying rate in 10 healthy adults. The addition of free glutamate (0.5%) to the pure 100% dextrin diet failed to increase the gastric emptying rate, but the supplementation of free glutamate to the high protein diet significantly promoted the delayed gastric emptying. We also conducted a human sensory study to confirm the effect of free glutamate on post-ingestive abdominal discomfort, using the same high-protein liquid diet. Free glutamate had no effects on abdominal discomfort in young adults (between 20-39 years old), but in adults more than 40 years old, heavy stomach and fullness

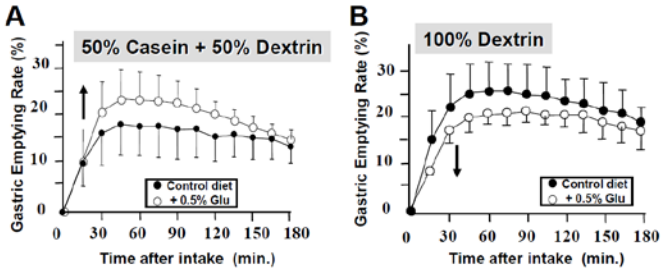

Figure 5: Modulation of human gastric emptying by free glutamate. With a human breath test using a stable isotope, gastric emptying rates were measured after ingestion of a high protein liquid diet (a mixture of 50 % casein calcium and 50 % dextrin) and a high carbohydrate liquid diet (100% dextrin), with or without 0.5% monosodium glutamate. Data were modified from Zai et al. [43].

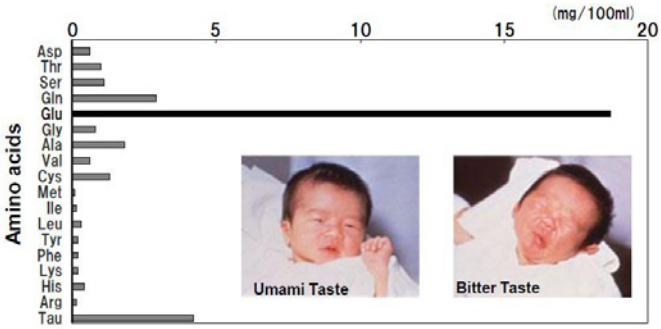

Figure 6: Free glutamate contents in meals in Japanese hospitals. **A**: Example measuring free glutamate contents in hospital meals in the Kyushu area of Japan. **B**: Contents of free glutamate and NaCl in miso soup served in 220 different hospital and nursing homes in Japan. Data were quoted from Toyama et al. [46] and Uneyama et al. [26].

improved after ingestion of the 0.5% glutamate-supplemented protein diet [44]. This result was obtained because the addition of free glutamate to a protein rich diet enhanced gastric secretion, improving gastric protein digestion and accelerating the gastric emptying rate, leading to improvement of post-ingestive abdominal unpleasantness. Another report describing the possible contribution of free glutamate in protein digestion was reported from the Russian Academy of Sciences in 1992 [45]. They studied the free glutamate fortification of hospital meals served to patients with chronic atrophic gastritis. Supplementation of about 2-3 grams of free glutamate per day for a month markedly improved Basal Acid Output (BAO) and Maximal Acid Output (MAO) and appetite in the hospitalized patients.

Hospitalized elderly often have advanced gastric atrophy with a decreased appetite and protein digestion, which cause a low-protein nutritional status below which the plasma albumin level is 3.6 g/dl (Protein Energy Malnutrition: PEM). Based on the results measuring free glutamate contents of typical hospital meals for the elderly, Toyama and Tomoe reported that the free glutamate intake of the hospitalized elderly was about half that of the average glutamate intake of the healthy Japanese elderly [46]. Therefore, to confirm the benefits of free glutamate intake in the hospitalized elderly, they conducted a clinical study of glutamate fortification to hospital meals. They obtained evidence that free glutamate supplementation to the daily main dish (porridge) of about 2.7 g/day improved the elderly QOL such as level of consciousness and some nutritional parameters (numbers of peripheral circulating lymphocytes and plasma albumin levels) [27,46,47]. Moreover, taking advantage of glutamate use for a clinical diet, a clinical physician, Dr. Ohura pointed out many benefits for nutritional management of enteral liquid diets containing 0.5% monosodium glutamate, which can reduce the incidence of diarrhea and gastro-esophageal reflux [48]. In keeping with this report, we showed that 0.5% glutamate supplementation to the protein liquid diet prevented the incidence of diarrhea induced by repetitive injection of the liquid diet through gastric tube feeding in rats, and suggested possible involvement of the gastric glutamate-sensing in the diarrhea prevention [49]. To date, the physiological role of taste substances such as free glutamate (umami taste) contained in natural foods has been ignored, since historically enteral liquid diets have been developed with the first priority of delivering simple purified nutrients to patients. Free glutamate supplementation to enteral liquid diets might improve the nutritional management by recognizing the purified artificial diets as natural foods through the glutamate signaling from the stomach to the brain.

Perspective

As mentioned above, we can explain the physiological significance of dietary free glutamate in protein digestion from the viewpoint of two aspects of sensory physiology [9,24-27]. Every day we consume free glutamate in daily foods. Free glutamate may increase palatability for foods containing proteins via the umami taste perception in the mouth, leading us to consciously feel that a dish is delicious. At the same time, after swallowing the foods, free glutamate is sensed again by the gut glutamate sensors to induce the triggering of gastric digestion such as gastric acids and ploteorytic enzyme via the vago-vagal reflex. Thus, free glutamate has two physiological effects on food digestion during a meal, the induction of taste and visceral nutrient information. At present we do not determine which visceral signaling via luminal glutamate is important in protein digestion from gastric or intestinal mucosa. This point should be clarified in the future. In the beginning of this review, we introduced the experimental result that rats preferred to drink umami taste solution containing free glutamate, depending on the increase of protein ingestion. This phenomenon can be explained by the fact that rats can increase their preference for umami taste as a protein intake marker since the intake of free glutamate is needed to help protein digestion in the stomach.

Why is the umami taste so important for human life? The word protein originates from the Greek ***proteios***, which means the most important material for human living. It is crucial for life survival to produce amino acids as stuffs of proteins within body, or to intake more effectively amino acids from dietary proteins with digestion and absorption. After birth, the first protein food is casein in breast milk. Since babies grow up only depending on breast milk as a protein source, it's the most important matter how babies digest and absorb well the milk protein. Interestingly, human breast milk is known to contain the highest concentration of free glutamate among 20 amino acids [50]. We might have an effective system within our body to maximize the re-use amino acids contained in milk protein. This system may be the free glutamate sensing system in the gastrointestinal tract. The interesting photographs of a newborn baby accepts umami taste as a sweet taste, but rejecting the bitter taste [51]. The facial expression of baby may indicate that umami taste derived from free glutamate is an essential taste sense for baby to grow up and keep health. Furthermore, free glutamate is rich in seasoning stuffs such as tomato (ketchup), cheese and fermentated sauces (soy, fish, oyster sauces) [52]. Human being might use these free glutamate rich materials for cooking to help the digestion of protein-rich foods. Physiological meanings might be under the closing of our food culture.

For human health, it is very important to secure sources of protein and reconstruct the dietary protein to our body protein. In Japan, umami taste derived from free glutamate might have contributed to the improvement of the protein nutritional status of Japanese people through using the umami taste as a seasoning, which makes food delicious via oral umami taste perception and increases the efficacy of protein digestion and absorption via the gut glutamate perception. In the developing world, protein energy malnutrition (PEM) is frequently a result of socioeconomic, political, or environmental factors. In contrast, PEM in the developed world usually occurs in the context of chronic disease and aging [53]. According to a survey by the Japan Ministry of Health, which has achieved high economic growth, over 50% of hospitalized elderly people are under-nutrition in Japan [54]. Research also indicates that the problem is the same in Western countries [55]. Umami taste substances in daily meal might help the improvement of nutritional problems facing the world.

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