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Research review

Glutamate. Its applications in food and contribution to health

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ABSTRACT

This article reviews application of glutamate in food and its benefits and role as one of the common food ingredients used. Monosodium glutamate is one of the most abundant naturally occurring amino acids which frequently added as a flavor enhancer. It produced a unique taste that cannot be provided by other basic taste (saltiness, sourness, sweetness and bitterness), referred to as a fifth taste (umami). Glutamate serves some functions in the body as well, serving as an energy source for certain tissues and as a substrate for glutathione synthesis. Glutamate has the potential to enhance food intake in older individuals and dietary free glutamate evoked a visceral sensation from the stomach, intestine and portal vein. Small quantities of glutamate used in combination with a reduced amount of table salt during food preparation allow for far less salt to be used during and after cooking. Because glutamate is one of the most intensely studied food ingredients in the food supply and has been found safe, the Joint Expert Committee on Food Additives of the United Nations Food and Agriculture Organization and World Health Organization placed it in the safest category for food additives. Despite a widespread belief that glutamate can elicit asthma, migraine headache and Chinese Restaurant Syndrome (CRS), there are no consistent clinical data to support this claim. In addition, findings from the literature indicate that there is no consistent evidence to suggest that individuals may be uniquely sensitive to glutamate.

Contents

Introduction

For many years, food additives have been used for flavoring, coloring and extension of the useful shelf-life of food, as well as the promotion of food safety (Rangan & Barceloux, 2009). Flavoring systems are very important in savory food manufacturing. Flavorings can play an important nutritional role, particularly in foods that are not very flavorful, by providing the needed appeal (Löliger, 2000). Foods and ingredients high in free amino acids or made up of protein hydrolysates have been used in cooking for many centuries, in many cultures, in order to enhance the sensory qualities of various foods (Bellisle, 1999). Umami taste helps improve flavor in foods, by giving meaty and savory flavors. The most closely studied flavor enhancer is monosodium glutamate, the sodium salt of glutamic acid. Glutamate is a frequently used flavor enhancer in foods, enhances the savory flavors imparted by glutamic acid, which occurs naturally in proteinaceous foods e.g. meats, seafood, stews, soups, sauces (Rangan & Barceloux, 2009). There is no precise definition for basic tastes; however they are defined by prototypical stimuli. The four traditional basic tastes are sweet, sour, salty, and bitter, and the fifth widely accepted basic taste is umami.

The natural occurring glutamate is in the form of L-glutamic acid, firstly discovered in 1866 by Karl Ritthausen, a German

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scientist, who isolated it from the acid hydrolysate of wheat gluten (Ritthausen, 1913). Salts of glutamic acid were first discovered in 1908 when Professor Kikunae Ikeda, a Japanese scientist identified the unique taste of umami attributed by glutamic acid; he identified umami as fifth basic taste after sweet, sour, salty and bitter in the tongue, where umami receptor taste located. Professor Ikeda, also has extracted and identified glutamic acid from soup stock prepared from konbu seaweed as the source of the umami taste, which from then, umami is described as savory, or meat or broth-like taste means delicious in Japanese (Ikeda, 1909; Ninomiya, 2001). In 1913, Kodama, isolated 5′-inosinic acid from dried skipjack as another key component of the konbu seaweed stock. In 1957, Kinoshita explored a bacterial strain *Micrococcus glutamicus* (later changed to *Corynebacterium glutamicus*) which could produce and accumulate large amounts of L-glutamic acid (Kinoshita, Udaka, & Shimeno, 1957). In 1960, Kuninaka isolated 5′-guanylate and recognized its role as key component of umami taste in the broth of dried shiitake mushroom (Kuninaka, 1960).

There have been numerous studies on umami taste and glutamate and their relation to food palatability and flavor acceptance (Baryłko-Pikielna & Kostyra, 2007; Bellisle, 1999; Bellisle, 2008; Fuke & Shimizu, 1993; Gould, Mobini, Prescott, & Yeomans, 2008; Yeomans, Gould, Mobini, & Prescott, 2008), nutritional considerations (Bellisle, 1999), presence in foodstuffs (Daniels, Joe, & Diachenko, 1995; Khairunnisak, Azizah, Jinap, & Nurul Izzah, 2009; Mau, 2005; Nicholas & Jones, 1991; Populin, Moret, Truant, & Conte, 2007; Skurray & Pucar, 1988), sensing in the oral cavity and gut (Burrin, Janeczko, & Stoll, 2008; Kurihara & Kashiwayanagi, 2000), physiological role in the food digestion (Uneyama, Gabriel, Kawai, Tomoe, & Torii, 2008), safety (Mallick, 2007; Simon, 2000; Walker & Lupien, 2000), and adverse effects (Diniz et al., 2005; Freeman, 2006; Ortiz et al., 2006). This review focuses on applications of glutamate as a food additive in food and its contribution to health.

Glutamate natural occurrence

Glutamate, one of the most common amino acids found in nature, is present in many proteins and peptides and most tissues. Glutamate is also produced in the body and binds with other amino acids to form a structural protein (Filer & Stegink, 1994). When glutamate bounds to protein molecule, it is tasteless and does not provide umami taste to food. However, protein hydrolysis during fermentation, aging, ripening and heat cooking process will liberate free glutamate (Yoshida, 1998). Glutamate is a crucial component of the taste of cheese, seafoods, meat broths, and other foods (Ninomiya, 1998). Ninomiya (1998) reported measured free glutamic acid, which present naturally in different foods, such as meat, poultry, seafood and vegetables (Table 1). Seaweed, cheese, fish sauce, soy sauce, fermented beans (locust beans and soy beans) and tomato showed high levels of free glutamic acid.

Konosu, Hayashi, and Yamaguchi (1987) showed that the characteristic tastes of many natural foods are reproduced by mixing amino acids, umami taste substances and salts in appropriate ratios. In nature, there are three umami taste substances; glutamate, disodium gluanylate (GMP) and disodium inosinate (IMP). Although these umami taste substances were discovered as important taste components in Japan, same substances have been found naturally in the stocks or bouillons of Europe, beef tea and Worcestershire sauce in the UK, the pizzas and tomato sauces of Italy, the 'tan' broth of China and the fish sauces of Southeast Asia (Fuke & Shimizu, 1993). The umami taste substances are contained abundantly in various foods, including vegetables (e.g., tomato, potato, Chinese cabbage, mushroom, carrot, soybean and green tea), seafood (e.g., fish, kelp, seaweed, oyster, prawn, crab, sea urchin, clam and scallop), meat (e.g., beef, pork and chicken) and cheese, and contribute greatly to the characteristic tastes of these foods (Kurihara, 2009; Ninomiya & Funakoshi, 1989). For example, the characteristic taste of snow crab meat is reproduced by mixing glycine, alanine, arginine, glutamate, IMP and salts in a particular. When the umami constituents were eliminated, the characteristic taste of the crab meat disappeared (Konosu et al., 1987). Thus, umami taste

Table 1
Free glutamic acid in foods.

Food items	Free glutamic acid (mg/100 g)
Meat and poultry	
Beef	10
Pork	9
Chicken	22
Seafood	
Scallop	140
Snow crab	19
Blue crab	43
Alaska king crab	72
White shrimp	20
Seaweed	
Dried lever	1378
Kelp	1608
Wakame	9
Vegetables	
Cabbage	50
Spinach	48
Tomato	246
Green asparagus	49
Corn	106
Green peas	106
Onion	51
Potato	10
Mushroom	42
Shiitake mushroom (fresh)	71
Soy sauce	
China	926
Japan	782
Korea	1264
Philippine	412
Fruits	
Avocado	18
Apple	4
Grape	5
Kiwi	5
Cheese	
Emmenthaler	308
Parmegiano	1680
Chedar cheese	182
Milk	
Cow	1
Goat	4
Human breast milk	19
Fish sauce	
China	828
Japan	1383
Indonesia	727
Malaysia	621
Myanmar	948
Philippine	988
Thailand	950
Vietnam	1370
Fermented beans	
Natto/soy beans (Japan)	136
Daw dawa/soy beans (West Africa)	965
Soumnara/locust beans (West Africa)	1700
Douche/soy beans (China)	476
Processed food	

Source: Ninomiya (1998).

substances are essential for producing the unique taste of many natural foods ratio. The predominant flavor of mushrooms is the umamitaste, also called the palatable taste or the perception of satisfaction, which is related to an overall flavor perception induced or enhanced by glutamate, and 5′-nucleotides (Bellisle, 1999; Yamaguchi, 1987).

The increase of free amino acids, sugars and organic acids during the ripening of vegetables, such as tomato contribute to the increase in flavor. For example, flavor maturation in ripening tomatoes has been related to the increase in their natural contents of free amino acids (e.g., glutamate; Inaba, Yamamoto Ito, & Nakamura, 1980; Kader, Stevens, Albright, & Morris, 1977; Stevens, Kader, & Albright-Holton, 1977; Stevens, Kader, & Albright-Holton, 1977). Okumura, Eguchi, Ogawa, and Suzuki (1968) indicated that the taste of the synthetic tomato extract is affected greatly by the ratio of glutamate to aspartate. The ratio and the coexistence of both amino acids were the most important factors in reproducing tomato taste. When no glutamate was added to the extract, the taste was similar to green tomato or citrus. During the ripening of cheese, proteins are broken down progressively into smaller polypeptides and individual amino acids (Weaver & Kroger, 1978). Increases in these amino acids are generally recognized to be a reliable indicator of cheese ripening (Puchades et al., 1989; Weaver & Kroger, 1978), and contribute to the taste and texture of the cheese (Ramos, Caceres, Polo, Alonso, & Juarez, 1987). Large increase in free amino acid content also occur during the curing of ham, and glutamate is the most abundant free amino acid found in the final product (Cordoba, Rojas, Gonzalez, & Barroso, 1994).

Glutamate as a food additive

Although glutamate is naturally occurring in many foods, it is frequently added as a flavor enhancer. Foods containing large amounts of free glutamate, such as tomatoes, mushrooms and cheese are traditionally used to obtain savory dishes (Giacometti, 1979; Yamaguchi & Ninomiya, 2000). When glutamate is added to foods, it provides a flavoring function similar to naturally occurring free glutamate (Yamaguchi & Ninomiya, 2000). Therefore, it is used to enhance the natural flavors of meats, poultry, seafood, snacks, soups and stews (Fuke & Shimizu, 1993). Food additives which provide umami taste are categorized as a flavor enhancer, which are salt of glutamate, namely monosodium glutamate, monoammonium glutamate, monopotasium glutamate, and ribonucleotides compounds, namely disodium 5′-monoinosinate (IMP) and disodium 5′-monoguanylate (GMP) (Ninomiya, 2001). Only the free form of glutamate, in its L-configuration presents flavor enhancing properties, and, for this reason, it is widely used as a flavor enhancer in the food industry (Bellisle, 1999; Populin et al., 2007).

Codex Alimentarius categorized glutamate and its salts, monosodium glutamate, monopotassium glutamate, calcium diglutamate, monoammonium glutamate and magnesium diglutamate, as flavor enhancer (Codex, 1989). The glutamate concentration in convenience foods adds up to 0.1–0.8% of weight which is similar to the concentration of native free glutamate in tomatoes or parmesan (Beyreuther et al., 2007). However, along with some other food additives, glutamate (E620) and its sodium (E621), potassium (E622), calcium (E623), ammonium (E624) and magnesium (E625) salt are not allowed to be added to milk, emulsified fat and oil, pasta, cocoa/chocolate products and fruit juice by the European Union (EU).

Glutamate is present in foods not only as flavor enhancer, but also as a by-product of hydrolyzed vegetable proteins (HVP), which are widely used as seasonings and flavoring agents in canned foods, dry mixes, sauces, and other manufactured products (Bellisle, 1999). Glutamate is frequently added to processed foods and shaken onto foods during preparation, particularly in Asian cuisine (He et al., 2008). Based on psychometric studies on flavor of monosodium glutamate by Yamaguchi and Kimizuki (1979), pure glutamate added has no effect on aroma of food. It can be added pure or as a hidden ingredient of yeast extracts or hydrolyzed proteins, both containing high percentages of glutamate (Hegenbart, 1998; Nagodawithana, 1992). Asian consumers learn to discriminate and appreciate its taste, from early childhood, whereas in the Western world, consumers have only recently learned to discriminate the umami taste, although they have enjoyed its contribution to the palatability of several traditional dishes and foods for centuries (Bellisle, 2008).

The flavor enhancing properties of glutamate have been scientifically investigated in many contexts (Baryłko-Pikielna & Kostyra, 2007; Bellisle, 1999; Bellisle, 2008; Fuke & Shimizu, 1993; Gould et al., 2008; Yeomans et al., 2008). For each food, there is an optimum glutamate concentration. Some foods, however, are not improved by the addition of glutamate, i.e., sweet foods in particular and perhaps some particularly bitter foods (Heyer, Taylor-Burds, Mitzelfelt, & Delay, 2004). As for sweetness and saltiness, the optimal concentration of umami taste varies widely between individual consumers (Yeomans et al., 2008). Some consumers like it, again at varying concentrations, whereas some consumers seem indifferent to it, and some even dislike it. Nevertheless, as the results of many studies clearly showed that most people are sensitive to its flavor-enhancing properties (Yeomans et al., 2008). Studies carried out among Europeans suggest that the optimal concentrations (0.6–1.2%) tend to be somewhat higher than those reported by Asian consumers (Bellisle, 2008); this may be due to the relative deficit in awareness of the distinctive umami taste in Western consumers, or else to the fact that oral sensation varies with genetics and gene-environment interactions. Individual sensory differences are large within the European population and sensory panels in scientific studies of the taste and properties of umami taste substances were often have to be trained to recognize the specific taste.

The use of excess amount of glutamate does not make the food taste better, but it actually worsens the taste. Generally, glutamate will work very well with salty or sour food. The optimum amount of added glutamate to enhance the taste of food is at 0.1–0.8% by weight. For instance, food of 500 g needs 0.5–4.0 g of glutamate to bring a good taste (IFT, 1987), which is the same as that of glutamate naturally found in general food. For example, protein from meat contains 11–22% of glutamate, whereas plant protein shows 40% (IFT, 1987). The addition of glutamate at this amount can reduce the amount of added sodium chloride. It brings out the best natural flavors in food, working well in reduced-sodium and reduced-fat dishes and can reduce total sodium by 30–40% without influencing palatability (Yamaguchi & Takahashi, 1984).

In Western societies, there is a general trend to an increased consumption of flavored convenience food. Theoretically, this change in behavior might lead to an increased glutamate intake, which is used in these products as flavor enhancer. However, the food industry steadily increases the number of glutamate-free products due to an enhanced reservation of the consumer against food additives. Consequently, overall intake of added glutamate might not be significantly altered (Dillon, 1993). Based on survey on measured added glutamate content in food items obtained from the grocery, the daily dose of glutamate in UK was about 12 mg/kg/day for whole population (Rhodes et al., 1991). This is comparable to U.S. which estimates of roughly 0.55 g/day of the average consumer (NAS, 1979). In Asia, especially in Japan and Korea, glutamate and other glutamate salts are used more intensively than in Europe. In these countries the intake of added glutamate is estimated to 1.2–1.7 g/day (Biesalski et al., 1997). A recent study in Malaysia showed lower content of free glutamic acid in local

processed foods and prepared dishes, 0.24–8.16 mg/g. However, the content of free glutamic acid was found to be higher in condiments at 0.28 mg/g in mayonnaise to 170.90 mg/g in chicken stock powder (Khairunnisak et al., 2009). In a highly seasoned restaurant meal, however, intake may reach to as high as 5000 mg or more (Yang, Drouin, Herbert, Mao, & Karsh, 1997). In Taiwan, per capita consumption figures are much lower, averaging 3 g/day (Giacometti, 1979). These amounts are considerably high compared to those consumed in western countries.

Metabolism in human body

Glutamate and disodium 5′-monoisinate (IMP) are the two amino acids that have received attention as oral stimulators of appetite and metabolism. Study by Lenjeune and Smeets (2007) showed that the addition of glutamate and IMP to a high-protein diet has a significant effect on desire to eat and no effect on energy metabolism. Adding glutamate to foods increases their umami taste quality, their acceptability and their consumption (Prescott, 2004). Study on novel savory flavors with glutamate has shown to condition flavor liking (Gould et al., 2008). Both the pleasantness and savory character of a novel soup were enhanced by glutamate and pleasantness of the soup increased. Participants also consumed more soup, and showed a larger increase in hunger on tasting the soup.

The human body metabolizes added glutamate in the same manner it metabolizes glutamate found naturally in many foods. Once glutamate is ingested, our bodies make no distinction between the origins of the glutamate (Daniels et al., 1995; FASEB, 1995). The body does not distinguish between glutamate from foods like tomatoes, or glutamate added to a tomato sauce. In fact, research showed that glutamate from food or glutamate is important for normal functioning of the digestive tract and digestion (Reeds, Burrin, Stoll, & Jahoor, 2000). Glutamate liberated from food protein is quantitatively absorbed from the lumen. Absorption kinetics is influenced by the retention time in the stomach and the surrounding matrix in the gut (Beyreuther et al., 2007). Study of Reeds et al. (2000) also showed that glutamate is the most important oxidative substrate for the intestinal mucosa. Furthermore, glutamate appears to be a specific precursor for the amino acids arginine and proline as well as for the tripeptide glutathione by the small intestinal mucosa. Glutathione clearly plays an important role in the protection of the mucosa from peroxide damage and from dietary toxins (Beyreuther et al., 2007). Glutamate taken up by cells may be used for metabolic purposes (protein synthesis, energy metabolism, ammonia fixation) or be reused as transmitter.

L-Glutamate has multiplicity effects in gastrointestinal tract. Zolotarev, Khropycheva, Uneyama, and Torii (2009) reported that intragastric glutamate application with nutrients enhanced gastric exocrine secretion, and it played an important role in gastric phase digestion. Luminal glutamate induced mucus secretion in the duodenum to protect intestinal wall against gastric acid attack (Akiba, Watanabe, Mizumori, & Kaunitz, 2009). Intragastric administration of glutamate activated the brain nuclei related to appetite, thermoregulation, memory and gut function via vagus afferent pathway (Tsurugizawa et al., 2009). In clinical evidence, Zai et al. (2008) reported that glutamate supplementation to high liquid protein diet accelerated gastric emptying to heal post-ingestive gastrointestinal unpleasantness such as heavy stomach. Furthermore, several studies have reported potential usefulness of glutamate in promoting better nutrition in the elderly and in patients with poor nutrition (Schiffman, 1998; Tomoe et al., 2008; Yamamoto, Tomoe, Toyama, Kawai, & Uneyama, 2009). Glutamate has promising effects on salivary volume and IgA secretion and on stomach function. However, such studies are still preliminary and future researches are needed to provide clarity on the possible digestive and nutritional benefits of supplemental dietary glutamate for the elderly.

Glutamate is a dietary essential amino acid, but recent studies suggest that its level in the diet can affect the oxidation of some essential amino acids, such as leucine. It is a key excitatory amino acid, and metabolism and neural sensing of dietary glutamate in the developing gastric mucosa, which is poorly developed in premature infants, may play a functional role in gastric emptying (Burrin & Stoll, 2009). Glutamate is transported into synaptic vesicles by a vesicular glutamate transporter and subsequently released by exocytosis (Augustine, Burns, DeBello, Pettit, & Schweizer, 1996; Cousin & Robinson, 1999). In astrocytes, glutamate taken up from the extra-cellular fluid may be converted to glutamine which is released to the extra-cellular fluid, taken up by neurons and reconverted to glutamate inside neurons. This trafficking of glutamate and glutamine between astrocytes and neurons has been proposed to be a major pathway by which transmitter glutamate is recycled (Danbolt, 2001). Uneyama, Niijima, Gabrei, and Torii (2006) reported that, among 20 amino acids, only glutamate can induce afferent reactions of gastric *vagal rami* and thereby influence digestion/absorption and activation of metabolism after absorption of nutrients through stimulation of the brain via gastric glutamate sensors (Uneyama et al., 2006). There is a possibility that glutamate may facilitate preparation for digestion/absorption of nutrients on the tongue through stimulation from taste receptors to the brain. It may play a role in the gastric phase to activate digestion/absorption and metabolism of nutrients by stimulation via gastric vagal rami from gastric glutamate sensors (Uneyama et al., 2008). Studies also showed that glutamate is a major oxidative fuel for the gut and therefore, dietary glutamate is extensively metabolized in first pass by the intestine. It also is an important precursor for bioactive molecules, including glutathione, and functions as a key neurotransmitter. The main role of glutamate as an oxidative fuel is its therapeutic potential for improving function of the infant gut, which exhibits a high rate of epithelial cell turnover (Burrin & Stoll, 2009).

Studies in humans and animal have shown that the meal's content of metabolizable carbohydrate had a major effect upon the plasma glutamate response (Daabees, Andersen, Zike, Filer, & Stegink, 1984; Stegink, Filer, & Baker, 1983a). While it has been proposed that there would be an extensive increase in plasma glutamate concentrations after consumption of meals containing glutamate, other studies have shown that glutamate level in plasma is not elevated after glutamate ingestion with consommé (Stegink, Filer, & Baker, 1985a), starch (Stegink, Filer, & Baker, 1985b) and liquid diet (Stegink, Filer, & Baker, 1983b).

Nutritional aspects

L-glutamate is a multifunctional amino acid involved in taste perception, intermediary metabolism, and excitatory neurotransmission (Kondoh, Mallick, & Torii, 2009). The oral stimulation by glutamate solution (umami taste) increases secretion of saliva and promotes mastication, and activation of the efferent pathways of the gastric and pancreatic *vagal rami* to facilitate gastric and pancreatic functions and to increase gastric endocrine and pancreatic exocrine and endocrine secretions (pancreatic digestive enzymes, insulin, etc.) (Horio & Kawamura, 1989; Lidemann, 2001).

Studies suggest that glutamate can be used for dietetic purposes, to stimulate appropriate food choices in certain populations (Bellisle, 2008; Bellisle et al., 1996). The advice of nutrition experts on moderate or low dietary fat intake is not widely followed because low-fat foods are generally less palatable than full fat ones (Bellisle, 2008). Glutamate, as does with salt

could also be used to maintain the palatability of fat-reduced foods (Bellisle, Monneuse, Chabert, Lanteaume, & Louis-Sylvestre, 1991; Prescott, 2004; Roininen, Lahteenmaki, & Tuorila, 1996). The study by Bellisle (2008) confirmed that reducing the participant-specific optimal fat content of the foods by 30% represented a significant decrease in energy and fat intake for pasta and mashed potatoes. It also affected palatability. The addition of participant-specific optimal glutamate amounts to the fat reduced foods reinstated some of the palatability, while maintaining the decrease in ingested fat and energy. It is likely that an interaction of several factors (gender, type of food, optimal fat content, and optimal glutamate content) would affect the ultimate intake behavior and consequently the dietary benefit of such a strategy (Bellisle, 2008).

Medical evidence indicates that reducing sodium intake improves certain disease states (e.g., hypertension) (Yamaguchi & Ninomiya, 2000). Umami taste substances in combination with salt (sodium chloride) which improve the acceptance of many foods can be a solution to the problem of less palatable foods with reduced salt content. Consequently, umami taste substances might be of value in maintaining the palatability of foods in which the salt content must be reduced. As an illustration of this concept, Yamaguchi and Takahashi (1984), using a Japanese clear soup model, reported that palatability could be maintained when reducing NaCl content by the addition of glutamate. Similar results were obtained using chicken broth (Chi & Chen, 1992). Yamaguchi (1987) also showed that the addition of umami taste substances can significantly increase taste quality and decrease the desire for saltiness. Since glutamate contains less sodium than NaCl, the addition of glutamate to foods could allow consumers to use less salt and decrease their sodium intake while enjoying a palatable diet. In clear soup tasted by Japanese panelists, the optimal levels of glutamate and NaCl were estimated as 0.38% and 0.81%, respectively; for maximal palatability, more glutamate was necessary when the NaCl concentration was less and vice versa (Yamaguchi & Takahashi, 1984). Corresponding values were found in American subjects to be around $0.33 \pm 0.38\%$ glutamate and $0.83 \pm 0.87\%$ NaCl (Chi & Chen, 1992). A 40% reduction in the sodium content of soups could be made without affecting palatability provided that $0.6 \pm 0.8\%$ glutamate were added (Altug & Demirag, 1993).

Research has shown that losses in taste and smell are the major contributors to poor nutritional status among older persons, sometimes even leading to anorexia. Dietary research pointed to potential of glutamate to enhance food intake in older individuals (Bellisle et al., 1991; Imai & Hasegawa, 1994; Shiffman & Warwic, 1993). Studies found that moderate levels of added glutamate in certain foods, such as mushroom soup and mashed potatoes, can increase food intake in an institutionalized older population, thus increasing intake of necessary vitamins, minerals and protein from food (Schiffman, 1999; Shiffman & Warwic, 1993). The fortification of an appropriate amount of GLUTAMATE to foods for the elderly is expected to exert effects improving the status of decreased taste stimulation, improving nutritional status via stimulation of gastric glutamate sensors, and thereby improving quality of life (Toyama, Tomoe, Inoue, Sanbe, & Yamamoto, 2008). Murphy (1987) studied elderly subjects (mean age 79.9 years) and compared them to younger controls (mean age 23.7 years) and found that the elderly persons prefer higher glutamate concentrations in soup, as compared to younger controls. The preference for higher concentrations of glutamate in the elderly could be due either to the age-dependent decrease in sensory acuity, while in less adequately nourished subjects, it could be due to an increase in sensory thresholds and/or an increase in the biological drive for protein substrates (Essed et al., 2009). However, Murphy (1987) reported that regardless of age, subjects with relatively poorer biochemical status preferred higher glutamate concentrations. Decrease in food intake due to numerous sensory, metabolic and pharmacologic factors and lower rates of nutrient absorption and utilization are observed (Yearick, Wang, & Pisias, 1980). Hence, the power of post-absorptive factors to reinforce preferences diminishes.

Niijima (1991) reported that dietary free glutamate evoked a visceral sensation from the stomach, intestine and portal vein. His research strongly indicated that glutamate has regulatory effects on the food digestive processes through the gut nutrient-sensing system. It plays physiological and nutritional roles and initiates digestion in the stomach as well as anticipates subsequent processes in the small intestine and the liver. Histochemical analysis also revealed the existence of a glutamate signaling system (metabotrophic glutamate receptors) in the gastrointestinal tract (Uneyama et al., 2008).

One of the most recent studies on activation of the gut-brain axis by dietary glutamate revealed new roles for L-glutamate in gut-brain axis activation and energy homeostasis (Kondoh et al., 2009). Receptors for L-glutamate and their cellular transduction molecules have been identified in gut epithelial cells. Stimulation of such L-glutamate receptors by luminal L-glutamate activates vagal afferent nerve fibers and then parts of the brain that are targeted directly or indirectly by these vagal inputs. Three areas of the brain, namely the medial preoptic area, the hypothalamic dorsomedial nucleus, and the habenular nucleus are activated by intragastric L-glutamate but not by glucose or sodium chloride. These findings indicate that L-glutamate signaling via taste and gut L-glutamate receptors may influence multiple physiologic functions, such as thermoregulation and energy homeostasis (Kondoh et al., 2009).

There are two different pathways involved in monitoring of protein and amino acid, including glutamate, in the brain which are the indirect neural (mainly vagus-mediated) and the direct humoral pathways. The neural pathways transfer preabsorptive and visceral information through the vagus nerve that innervates part of the orosensory zone (stomach, duodenum, and liver). The nucleus of the solitary tract which is localized in the brainstem is the main projection site of the vagus nerve and integrates sensory information of oropharyngeal, intestinal, and visceral origins. Ingestion of protein also activates satiety pathways in the arcuate nucleus, which is characterized by an up-regulation of the melanocortin pathway (α-melanocyte-stimulating, hormone-containing neurons) and a down-regulation of the neuropeptide Y pathway (Tomé, Schwarz, Darcel, & Fromentin, 2009).

Safety evaluation and regulations

In 1958 the U.S. Food and Drug Administration (FDA) designated glutamate as a Generally Recognized As Safe (GRAS) ingredient, along with many other common food ingredients such as salt, vinegar and baking powder (USDHHS, 1958). There was general consensus in the scientific community, based on numerous biochemical, toxicological and medical studies conducted over four decades, that glutamate is safe for the general population, including pregnant and lactating women, and children (IFIC, 2003). The safety evaluation of monosodium glutamate was first evaluated by JECFA at the fourteenth and seventeenth meetings in 1971 and 1974, respectively (FAO/WHO, 1971, 1974). At that time, an Acceptable Daily Intake (ADI) of 0–120 mg/kg body weight was allocated, encompassing the L-glutamic acid equivalents of the salts; this was considered additional to the intake from all non-additive dietary sources. Since there was no human infant data at that time, and considering the observation that neonatal rodents appeared to be more sensitive than adults to the neurologic effects of high blood levels of glutamate, it was stated that the ADI did not apply to infants of 12 week of age. A more comprehensive safety

evaluation was conducted in 1987 (JECFA, 1988). The JECFA reviewed the available data on metabolism and pharmacokinetics of glutamate, together with relevant experimental toxicologic data and results of studies in humans. The review showed that glutamate has a very low acute toxicity under normal circumstances; the oral dose that is lethal to 50% of subjects (LD50) in rats and mice was 15,000–18,000 mg/kg body weight, respectively. Sub-chronic and chronic toxicity studies of up to 2-year duration in mice and rats, including a reproductive phase, did not reveal any specific adverse effects at dietary levels of up to 4%. A 2-year study in dogs at dietary levels of 10% also did not reveal any effects on weight gain, organ weights, clinical indices, mortality or general behavior. The overall safety evaluation directed the JECFA to conclude that the total dietary intake of glutamates arising from their use at levels necessary to achieve the desired technological effect and from their acceptable background in food do not represent a hazard to health. Therefore, the establishment of an ADI expressed in numerical form was not considered necessary and an "ADI not specified" was allocated to L-glutamic acid and the monosodium, potassium, calcium and ammonium salts. The JECFA also noted the evidence that it was not necessary to treat pregnant women and infants as special cases; however, they retained the previously expressed position that food additives, in general (glutamate included), should not be used in infant foods to be consumed before 12 weeks of age.

The Scientific Committee for Food of the Commission of the European Communities (SCF) (1991) conducted a safety evaluation similar to that of the JECFA and reached the same conclusion that glutamate could be allocated an "ADI not specified," and this is the current situation in the European Union. Later, the Federation of American Societies for Experimental Biology (FASEB), based on his review of reported adverse reactions to glutamate and reported in 1995, concluded that although there was no scientifically verifiable evidence of adverse effects in most individuals exposed to high levels of glutamate, there is sufficient documentation to indicate that there is a subgroup of presumably healthy individuals that responds, generally within 1 h of exposure, with manifestations of the glutamate symptom complex when exposed to an oral dose of glutamate of 3 g in the absence of food (FASEB, 1995). Even though the FDA appears to have accepted this conclusion of the existence of the glutamate symptom complex (Hattan, 1996), it was pointed out that the key data relate to single-dose challenges in capsules or simple solutions are limited in their ability to predict adverse reactions resulting from the use of glutamate in food. Their report also concluded that there is no evidence to support a role for dietary glutamate or other forms of free glutamate in causing or exacerbating serious, long-term medical problems resulting from degenerative nerve cell damage. The FDA also interpreted the findings of the FASEB report to be generally consistent with the safety assessments of other authoritative organizations (including the JECFA and SCF) that have affirmed the safety of glutamate at levels normally consumed by the general population, and concurred with the conclusion that there is no evidence linking current glutamate food use to any serious, long-term medical problems in the general population. However, in 1995, a directive of the European Commission (95/2/CE) on food additives fixed a limit of 10 g/kg for the sum of L-glutamate and salts present in food products, except for unprocessed foods, baby foods (for which Glu and salts use are not allowed) and "seasoning and spices" (for which no maximum level is specified).

Manufacturers are acutely aware that many consumers would prefer not to have glutamate in their food. Some manufacturers have responded by using "clean labels," i.e., labels that contain only ingredient names they think consumers will not recognize as containing glutamate – names such as "hydrolyzed soy protein." Others advertise "No MSG," "No MSG Added," or "No Added MSG," even though their products contain glutamate.

A part from all those regulations, the FDA requires that when glutamate is added to a food, it must be included in the ingredient list by its common or usual name, "monosodium glutamate" (IFIC, 2003). However, many food manufacturers have increasingly adopted a strategy of placing additional prominent messages regarding glutamate on food labels. As a result, food labels advertising "No MSG," "No MSG Added," or "No Added MSG" have become ordinary (Dillon, 1993). A possible outcome of such labels is that they generate and reinforce beliefs that glutamate is harmful or an unsafe ingredient (Prescott & Young, 2002). However, placing "No MSG," "No MSG Added," or "No Added MSG" on food labels has been deemed by the FDA to be false and misleading (section (403)(a)(1) of the Federal Food, Drug and Cosmetic Act), when the label also lists any hydrolyzed protein as an ingredient since it contains glutamate (FDA, 1995). Clearly, it is false and misleading to claim "No MSG" or "No MSG Added" on a product label when glutamate is present, even if it is present as a constituent of an ingredient.

Research on the effects of different types of label information showed that these messages may also influence the acceptability of products containing added glutamate (Johansson, Haglund, Berglund, Lea, & Risvik, 1999). However, a more recent study by Prescott and Young (2002) on the impact of information about glutamate content in foods on consumer rating of soups revealed different results. Their data suggested that sensory properties are weighted more than information when products are evaluated during tasting, even when the information is highly relevant to beliefs and attitudes.

Safety concern

Worldwide glutamate consumption has increased dramatically in recent decades (He et al., 2008; Hermanussen et al., 2006). There was a safety concern of glutamate with respect to epidemic overweight or obesity. While there are not much published studies on glutamate intake in relation to obesity or overweight in human, a single study by He et al. (2008) from China provided human data that glutamate intake may be associated with increased risk of overweight independent of physical activity and total energy intake. However, Ebert (2010) has objected this paper with some scientific key facts and supports from other publications. He referred to long-term animal feeding (Anantharaman, 1972; Heywood & Worden, 1972) and human studies (Essed, van Staveren, Kok, & de Graaf, 2007; O'Kane, Martínez-López, DeJoseph, Viña, & Hawkins, 1999; Stoll et al., 1998; Takasaki, 1978), which have shown that glutamate did not increase food intake or induce obesity. The author also referred to recent studies, which showed that glutamate was associated with suppression in body weight gain, fat deposition, and plasma leptin levels (Kondoh & Torii, 2008). Nevertheless, such data cannot be so accurate due to difficulties in quantifying glutamate intake, particularly in countries where it is widely added in commercial food processing.

In 2000, a combined research team from Boston University, Harvard University, Northwestern University and the University of California at Los Angeles conducted the largest study to date of glutamate and its potential side effects. This study, by Geha et al. (2000), specifically included subjects who reported a history of glutamate sensitivity. The study was organized to test subjects for any reaction to glutamate, followed by subsequent re-challenges of those subjects who demonstrated a response. Their tests were double-blind, placebo-controlled, and randomized with the goals of identification of subjects with two or more symptoms of glutamate sensitivity on multiple occasions with no demonstrable response to the placebo. Out of 130 subjects tested, only two

maintained consistent responses to glutamate. The research concluded that there were no reproducible responses. Despite claims that glutamate might cause headache or other symptoms, their study failed to produce any reproducible symptoms. Furthermore, all of the subjects in this study claimed to have a history of glutamate hypersensitivity.

Furthermore, several studies have explored the possibility that glutamate can serve as a trigger for asthma exacerbations (Freeman, 2006; Spergel & Fiedler, 2005). Allen, Delohery, and Baker (1987) conducted a single-blind study with 32 subjects, 14 of who reported a history of asthmatic symptoms after eating Chinese food. In order to minimize confounders, subjects were required to follow a glutamate-restricted diet and certain asthma medications were withheld. Thirteen of the subjects experienced a reduction of 20% or greater in their peak expiratory flow. Despite these alarming results, the study has been criticized for its inadequate measurement of baseline data. Furthermore, subjects who withheld regular asthma medications may have merely been experiencing reduced peak flow because of medication withdrawal. However, Allen et al. (1987) findings were not replicated in a similar study by Moneret-Vautrin (1987) in the same year. Only 2 of 30 asthmatic subjects experienced reduced pulmonary function test results 12 h after a placebo controlled challenge of 2.5 g of glutamate. Like Allen et al. (1987) study, the procedure was not double blind and the issue of subjective effort in pulmonary function tests also may have confounded the results. Studies by Schwartzstein, Kelleher, Weinberger, Weiss, and Drazen (1987) and Germano, Cohen, Hahn, and Metcalfe (1991) followed similar protocols. None of the subjects in Schwartzstein et al. (1987) study had a positive response (i.e. reduction in pulmonary function test results). Altman, Fitzgerald, and Chiaramonte (1994) found that 11 of the 26 subjects in the trial experienced reduction in pulmonary function test results. But in two cases, subjects had a positive result with 3 g of glutamate but not with 6 g, thereby negating any suspicion of a dose–response relationship between glutamate and asthma symptoms. Woods, Weiner, Thien, Abramson, and Walters (1998) found no change in forced expiratory volume in 1 s (FEV1) after 1 and 5 g glutamate challenges. Woessner, Simon, and Stevenson (1999) had one subject experience a 20% drop in FEV1 after a glutamate challenge, but this finding was not replicated. Although some epidemiological studies demonstrated correlations between glutamate and adverse responses in severely asthmatic patients, a single-blind, placebo-controlled challenge study did not detect symptoms of wheezing or reduction in forced expiratory volume. Long-term health effects also did not occur (Woessner et al., 1999). From these studies, it is evident that there is no consistent evidence that glutamate can trigger an asthma exacerbation.

However, a recent review by Williams and Woessner (2009) prevents a critical review of the available literature related to the possible role of glutamate in eliciting asthmatic bronchospasm, urticaria, angio-oedema, and rhinitis. Despite concerns raised by early reports, decades of research have failed to demonstrate a clear and consistent relationship between glutamate ingestion and the development of these conditions. The case for glutamate as a clear cause of asthma, urticaria, angio-oedema, or rhinitis is much less convincing. In the case of asthma in particular, critical analysis of the methods and experimental design of virtually all the studies purporting to demonstrate that MSG causes asthmatic bronchospasm shows a number of limitations that preclude concluding that such a link exists.

Glutamate has also been described as a trigger for migraine headache exacerbations (Woods, Weiner, Abramson, Thien, & Walters, 2006). Radnitz (1990) suggested that glutamate causes a generalized vasomotor reaction, which causes throbbing pain at the temples and a throbbing sensation across the forehead. His claim derived not from a clinical trial but from an advice from the Diamond Headache Clinic. She also argued that those who experience migraine headaches are more susceptible to headache triggered by glutamate; however, this suggestion is not substantiated by any clinical data. Leira and Rodríguez (1995) postulated that glutamate can trigger a migraine headache because of interference with acetylcholine synthesis. However, in the absence of clinical data, it is premature to make any conclusions about glutamate as a potential trigger for migraine headaches. With no consistent data to suggest that glutamate causes any type of headache, much more extensive clinical research would be required to establish a link between glutamate and migraine headaches.

Conclusions

The main goal of this article was to review the benefits and role of glutamate as one of the common food ingredients used all over the world. Glutamate is one of the most common amino acids and present in many proteins and peptides and most tissues. It is a crucial component of the taste of umami or savory which contained abundantly in various foods, including vegetables, seafood, meat and cheese, and contributes greatly to the characteristic tastes of these foods. Although glutamate is naturally occurring in many foods, it is frequently added as a flavor enhancer. When it is added to foods, provides a flavoring function similar to naturally occurring free glutamate. It is also present in foods as a by-product of hydrolyzed vegetable proteins, which are widely used as seasonings and flavoring agents in canned foods, dry mixes, sauces, and other manufactured products. There is an optimum glutamate concentration for each type of food. Some foods, such as sweet and bitter foods, are not improved by the addition of glutamate. The use of excess amount of glutamate does not make the food taste better, but it actually worsens the taste. Glutamate is a dietary essential amino acid and its level in the diet can affect the oxidation of some essential amino acids, such as leucine. The human body metabolizes added glutamate in the same manner it metabolizes glutamate found naturally in many foods. Glutamate is a multifunctional amino acid involved in taste perception, intermediary metabolism, and excitatory neurotransmission. Studies suggest that glutamate can be used, for dietetic purposes, to stimulate appropriate food choices in certain populations. The addition of participant-specific optimal amounts of glutamate to the fat reduced foods reinstated some of the palatability, while maintaining the decrease in ingested fat and energy.

Because glutamate is one of the most intensely studied food ingredients in the food supply and has been found safe, the Joint Expert Committee on Food Additives of the United Nations Food and Agriculture Organization and World Health Organization placed it in the safest category for food additives. European Community's Scientific Committee for Food also confirmed the safety of this ingredient. Based on the extensive scientific data, and in view of large normal dietary intake of glutamates, the committee determined that specification of an Acceptable Daily Intake (ADI) level was unnecessary.

It is apparent that there is enough research conducted on glutamate and its potential health effects. So far there was no strong scientific information reporting negative effects of glutamate on human health in the general population. Studies on Chinese restaurant syndrome were plagued with problems and there were no consistent responses to glutamate were found. Despite claims that glutamate might cause headache or other symptoms, recent studies failed to produce any reproducible symptoms. Early, poorly controlled studies suggested that glutamate might induce, as well as exacerbate, asthma. However,

follow-up double-blind challenges have not replicated those results. The studies explored the possibility that glutamate can serve as a trigger for asthma exacerbations, have suffered from small size and questionable study design. In the absence of clinical data, we cannot make any conclusions about glutamate as a potential trigger for migraine headaches. Therefore, with no consistent data to suggest that glutamate causes any type of headache, much more extensive clinical research would be required to establish a link between glutamate and migraine headaches.

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