Chapter 2
Umami and MSG

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2.1 Historical Context of Umami and MSG

2.1.1 Discovery of Umami Taste by Kikunae Ikeda

The sense of taste, which is elicited by chemical compounds in the oral cavity, plays a critical role for food intake. When we consume sugar, table salt, vinegar, or coffee, we clearly feel a sweet, salty, sour, or bitter taste, respectively. In addition to these four basic tastes, umami is now considered the fifth basic taste. Umami taste was first described about 110 years ago (Ikeda, 1908, 1909, 2002; Lindemann et al., 2002) by Kikunae Ikeda (1864–1936; see Fig. 2.1). Ikeda, a chemistry professor at the Imperial University of Tokyo, had studied in Germany for 2 years in the laboratory of Friedrich Wilhelm Ostwald at the University of Leipzig. At that time, four tastes (sweet, sour, salty, and bitter) were considered "pure" tastes, whereas others, such as hot, metallic, alkaline, and astringent tastes, were not considered "pure" tastes, because chemical compounds eliciting these sensations were detected, at least in part, by the somatosensory system rather than by the taste system.

Ikeda had been interested in the taste of the Japanese seaweed broth dashi because he believed that dashi clearly contained another (pure) taste, which was different from sweet, salty, sour, and bitter tastes and was also recognized in meat and fish dishes. He intended to isolate the principal taste substance from the seaweed *Laminaria japonica*, the main ingredient for dashi. After conducting many procedures, such as aqueous extraction, removal of large-scale contaminants

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Fig. 2.1 Dr. Kikunae Ikeda (photo taken in 1923). (Image from the Umami Information Center website, https://www.umamiinfo.jp/what/whatisumami/)

(mannitol, sodium, and potassium chloride), and lead precipitation, he finally obtained pure crystals of a single substance that he identified as glutamic acid. He proposed to call the taste of glutamic acid *umami*, a word derived from the Japanese adjective *umai* (delicious). Indeed, he noted that the taste of glutamic acid crystals was perceived as umami taste after its sour taste had faded and that the salts of glutamic acid (sodium, barium, calcium, and potassium) had strong umami taste. The term *umami* as a taste was first mentioned in his original Japanese paper, but in later publications, he used the English phrase *glutamic taste* as a scientific term representing the peculiar taste of glutamate (glutamic acid) that is different from all other well-defined taste qualities (Ikeda, 1912).

Ikeda described several aspects of the taste intensity of glutamate (Ikeda, 1909, 2002). He reported that the taste recognition threshold for monosodium L-glutamate (MSG) was about 1/3000 (1.6 mM), which is lower than that of sucrose (1/200, 15 mM) and NaCl (1/400, 43 mM). Although the taste intensity of glutamate increased as its concentration increased, changes in the taste intensity of increasing concentrations of glutamate were likely to be smaller than those of sweet, salty, sour, and bitter tastes—umami taste did not become extremely strong even at high glutamate concentrations. Ikeda also described the taste of mixtures. For example,

the taste of glutamate was substantially decreased by addition of acids. This may be due to the addition of hydrogen ions to the glutamate solution, yielding a no dissociated form of glutamate (hydrogen glutamate), leading to decreased concentrations of the glutamic acid anion, the taste stimulus for umami taste. Mixing salt (NaCl) with a glutamate solution increased the palatability of ionic glutamic acid, although a weak salty taste did not enhance the intensity of the glutamate taste. The sweetness of sugars was not affected by the taste of ionic glutamic acids, but the taste of ionic glutamic acid was decreased by strong sweetness. In addition, the taste of sweet stimuli and the taste of ionic glutamic acid had some similarities: some people perceived the taste of ionic glutamic acid as sweet at a concentration close to the threshold.

Ikeda also addressed the stereochemical structure of the amino acid associated with umami taste (Ikeda, 1909, 2002), but at that time it was difficult to explain the relationship between molecular structure and taste. He further considered umami taste from the viewpoint of its nutritional value. Because meat extract contains a certain amount of glutamic acid, along with other amino acids, he reasoned that the taste of glutamate could be an indicator of the presence of nutritive foods, particularly of protein. Therefore, a preference for umami taste may have evolved to encourage intake of such protein-rich foods. Although Ikeda discussed preference for umami taste, he noted in a later publication that umami taste (glutamic taste) by itself was not palatable or delicious (Ikeda, 1912), and this has also been noted by others (Yamaguchi, 1991; Halpern, 2002). When MSG is added to the appropriate foods, it increases the palatability of those foods (Halpern, 2000). Therefore, in Europe and America, umami tastants have often been regarded as flavor enhancers or potentiators. In summary, the basic logic and characteristics of umami taste were described in the first paper on the taste of glutamate by Ikeda (1909). His work formed the foundation of studies on umami taste.

It was subsequently noted that some nucleotides have taste characteristics similar to glutamate (umami). Shintaro Kodama, a pupil of Ikeda, isolated 5′-inosinic acids from another ingredient of dashi, *katsuobushi* (dried skipjack, bonito flakes), as a constituent having a taste similar to that of glutamate (Kodama, 1913). About a half century after Ikeda's work, Akira Kuninaka found 5′-guanylic acid from dried black mushrooms (shiitake, *Lentinus edodes*) as another umami tastant. He also found that the taste intensity of umami was greatly enhanced by mixing of MSG and 5′-ribonucleotides, the phenomenon known as umami synergism (Kuninaka, 1960). Synergism between glutamate and nucleotides, discussed in more detail below, is a hallmark of umami taste and is widely used in cooking to enhance the palatability of foods. Such synergism has been reported in physiological and psychological studies. For example, gustatory nerve responses to MSG were greatly enhanced by adding inosine 5′-monophosphate (IMP) or guanosine 5′-monophosphate (GMP) in mice (Ninomiya & Funakoshi, 1987, 1989a), dogs (Kumazawa & Kurihara, 1990), and rats (Yamamoto et al., 1991). The first biochemical data indicating synergistic effects of glutamate and nucleotides were demonstrated in bovine taste papillae (Torii & Cagan, 1980). More recently, the molecular mechanism underlying umami synergism has been elucidated (Zhang et al., 2008).

2.1.2 First Symposium on MSG by the US Army

MSG had been used in food industries, restaurants, and some home consumers to improve palatability in the United States since the 1930s. From the 1920s, the Japanese Imperial Army had tackled methods to improve the quality of army rations, including the use of MSG to improve the taste of rations such as canned foods. During World War II, the US Army employed MSG to improve the quality of foods for troops. After the war, in 1948 and 1955, the US Army Quartermaster Food and Container Institute held two symposia on MSG flavor and acceptability. At these symposia, scientists and manufacturers discussed and debated various aspects of MSG, including its production, its use as a flavoring agent, and its sensory properties (Quartermaster Food and Container Institute, 1948; Research and Development Associates 1955; Yamaguchi & Ninomiya, 1998; Beauchamp, 2009).

The usefulness of MSG in recipes of the US Army's master menu was thoroughly explored. In one study, preference tests of 50 foods and recipes were conducted with ~2150 individuals for 18 months (Girardot & Peryam, 1954). Among the 50 foods and recipes, addition of MSG clearly improved the palatability of 25 foods and recipes and weakly enhanced that of 3 foods and recipes. In contrast, 4 foods and recipes were worsened and 18 were not affected by adding MSG. Overall, the palatability of meat, fish, and vegetable dishes tended to be greatly improved by the addition of MSG, whereas that of cereals, milk products, and sweet dishes was not. Thus, MSG has the potential to enhance the palatability of some but not all foods.

Regarding sensory properties of MSG, neither the concept of umami nor the synergistic effect of MSG and nucleotides had been established at that time. Therefore, how its taste was represented by sensory specialists is worth noting to understand the history of umami taste. From Yamaguchi and Ninomiya (1998), some descriptions for MSG taste at that time were as follows (italics indicate the points by the authors):

- Taste of MSG had a *tingling feeling* factor, and *persistency* of taste sensation presented in *the whole of the mouth region*, including the roof of the mouth and the throat. It was hard to describe the sensation other than to call it a *feeling of satisfaction*. These suggest that MSG stimulated nerve endings lying within the buccal cavity and stimulated the sense of feeling as well as that of taste (Crocker, 1948).
- 0.1–0.3% of MSG had a *sweet saline taste* accompanied by *some astringency*. It stimulated all surfaces of the tongue and oral cavity, producing a slight sensation of *furriness* on the tongue and a mild but lasting *aftertaste* (Cairncross, 1948).
- When a small amount of MSG was placed on the tongue, *salivary secretion* was increased and lasted for approximately half an hour. It produced a slight sensation of *furriness* on the tongue and *mild stimulation in the throat and the back part of mouth*. There was a *sensation of bloom*, i.e., the taste seemed to spread rapidly inside of mouth and had an after effect on the tongue (Cairncross & Sjöström, 1948).

- MSG had an *effect of aroma*, without contributing any noticeable odor itself. The principal effect on food flavor was regarded as balancing, blending, and rounding out the total flavor without contributing any noticeable odor or taste, except that it was very noticeable in certain fruits and dairy products. MSG enhanced *mouthfullness* and *satisfaction* (Cairncross, 1948).
- Glutamic taste was not unique and could be *duplicated by a mixture of the four tastes* (Crocker & Henderson, 1932).

Compared to four basic taste qualities (sweet, salty, sour, and bitter), such representations of taste of MSG were complicated and diverse and elicited disagreement. The apparent taste of glutamate was likely to include tactile, olfactory, visceral, and other sensations. At that time (and to some degree even now), the "taste" of glutamate elicited controversy, but the effects of glutamate on oral sensations, such as "tingling," "persistency," "satisfaction," "mouthfullness," and "aftertaste," were noted, suggesting that glutamate may stimulate something other than or in addition to taste in the oral cavity (see Sect. 2.4). In some cases, sweet and salty tastes were mentioned as the taste of MSG. This may be attributed, at least in part, to the sodium component of MSG, since low concentrations of NaCl were recognized as sweet when subjects were adapted to water (Bartoshuk, 1974).

2.1.3 Chinese Restaurant Syndrome and MSG Safety

From the 1930s to the 1960s, production and consumption of MSG became prevalent worldwide. Then, in 1968, a letter to the editor titled "Chinese-Restaurant Syndrome" by Robert Ho Man Kwok, MD, was published in the *New England Journal of Medicine* (Kwok, 1968). He reported that he had experienced a strange syndrome after he had eaten foods in a Chinese restaurant, with symptoms of numbness, general weakness, and palpitations. One of the causes of these symptoms, he speculated, was the high sodium content of the Chinese foods, which may produce hypernatremia, leading to intracellular hypokalemia, causing such symptoms. Because MSG seasoning contains the sodium ion and was used to a great extent in Chinese dishes, he hypothesized that MSG may be a cause of such symptoms. This letter in the *New England Journal of Medicine* elicited a large reaction (Schaumburg, 1968; McCaghren, 1968; Menken, 1968; Rose, 1968; Rath, 1968; Beron, 1968; Kandall, 1968; Gordon, 1968, Davies, 1968).

This original letter, as well as many comments about it often supporting the symptoms listed, led investigators to experimentally test MSG as the culprit. Schaumburg et al. (1969) reported that intake of MSG produced such typical symptoms as burning sensations, facial pressure, and chest pain in all but one test subject. Morselli and Garattini (1970) carried out a study on 24 healthy volunteers using a double-blind technique and showed no significant differences in symptoms between intake of MSG and placebo. But Himms-Hagen (1970) criticized their results as they did not use susceptible subjects. At that time, Olney (1969) reported that subcutaneous injections of MSG (0.5–4 mg/g body weight) in 2- to 9-day-old mice

caused extensive damage to neurons in the hypothalamus and other areas of the brain. A similar result was obtained in one infant rhesus monkey (*Macaca mulatta*) (Olney & Sharpe, 1969). Olney and Ho (1970) also reported that orally administrated MSG (and aspartate and cystatin) induced hypothalamic damage in infant mice.

Such reports had great impact on the general public, and "Chinese restaurant syndrome" (or MSG toxicity) became widely known. However, many following studies showed little or no relationship between MSG intake and the typical symptoms described for Chinese restaurant syndrome (Freeman, 2006; Greisingera et al., 2016). Kenny and Tidball (1972) explored the human reactions to oral MSG and confirmed the results of Morselli and Garattini (1970). Kerr et al. (1977, 1979) investigated aversive symptoms associated with foods and found no respondent who met the criteria for all three aversive symptoms for MSG (tightness and burning sensation in the head and chest, numbness). In 1986 the FDA's Advisory Committee on Hypersensitivity to Food Constituents concluded that MSG posed no threat to the general public, and in 1987 the Food and Agriculture Organization of the United Nations (FAO)-World Health Organization (WHO) Joint Expert Committee on Food Additives placed MSG in the safest category of food ingredient (Tracy, 2016). Figure 2.2 gives a timeline of umami discovery, use, and research.

Indeed, ingested glutamate (and glutamate produced by degradation of proteins in the intestine) in ordinary foods is used for oxidative fuel and as a precursor for other amino acids, glutathione, and N-acetyl glutamate (Blachier et al., 2009; Burrin & Stall, 2009). In healthy human volunteers, jejunal and ileal L-glutamate content is greatly increased at 3 hours after the ingestion of a test meal, but the concentration of glutamate in venous blood plasma was only slightly increased at 1 h after the ingestion of a test meal (Adibi & Mercer, 1973). In addition, MSG ingestion with a meal in healthy human subjects did not result in any significant increase in plasma glutamate level 15–360 min after ingestion (Ghezzi et al., 1985). Experiments in the piglet using a newly developed labeled tracer demonstrated that >95% of enteral glutamate but only 5% of the enteral glucose was utilized by the mucosa (Reed et al., 2000). Although experimental conditions were different, these studies suggest that only a small amount of glutamate is taken into the blood through the intestine and that most glutamate, when taken with food, is used as fuel and as resources for bioactive substances in the gastrointestinal tract after absorption of glutamate in the intestine.

Regarding effects of MSG intake on the brain, administered MSG in animals did not significantly affect brain glutamate levels in infant or adult animals (Airoldi et al., 1979; Garattini, 1979, 2000). Furthermore, extracellular glutamate in the hypothalamus or striatum of rats was not increased when MSG was administrated as a component of food (Bogdanov & Wurtman 1994; Monno et al., 1995). These data suggest that brain glutamate levels are not greatly increased when MSG is ingested along with meals. Although neurotoxic effects of glutamate are well known (Lau & Tymianski, 2010), the conclusion was that normal intake of MSG (with foods) does not damage the brain. However, the impression of MSG as a food additive and also the impression of glutamic taste became worse in the 1960s and 1970s; such an impression still remains in some people today (Yeung, 2020).

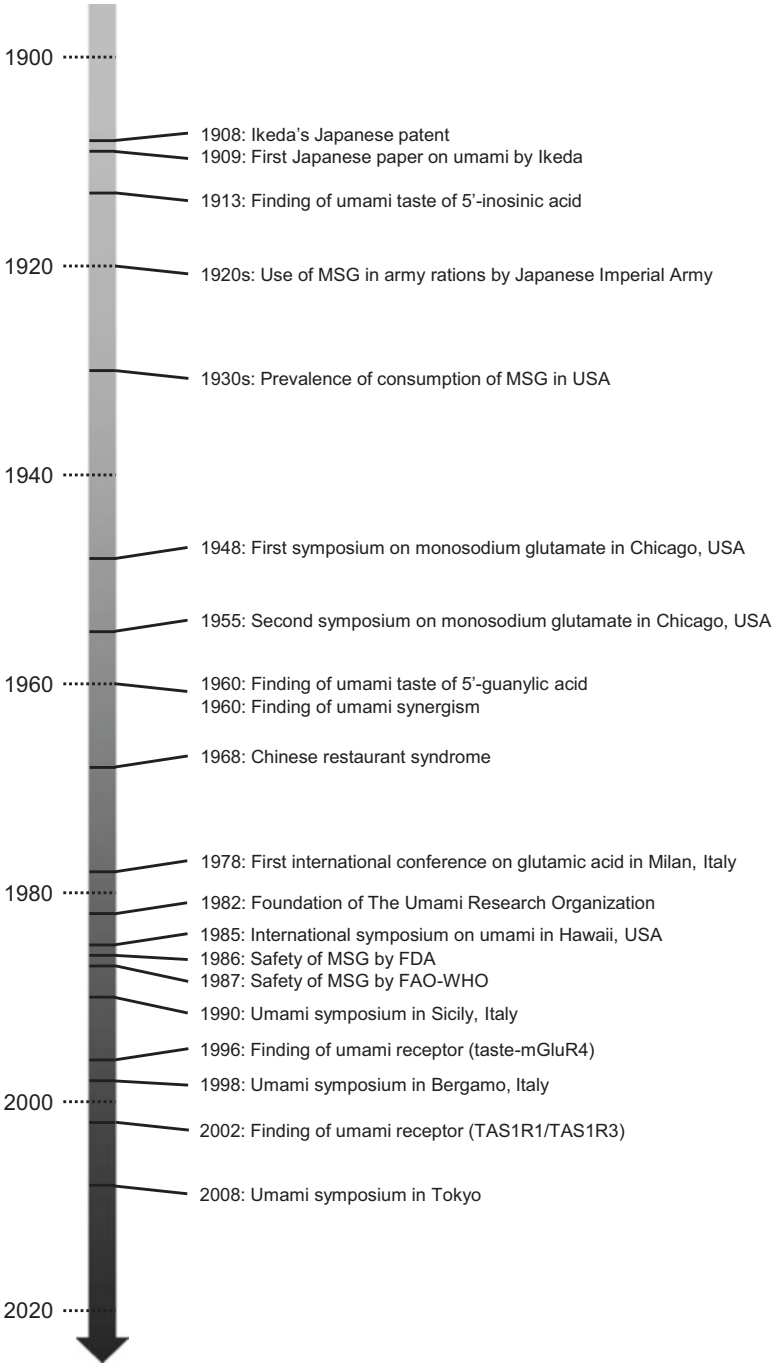

Fig. 2.2 The chronology of umami taste and monosodium L-glutamate

2.1.4 Umami as a Basic Taste

In 1978, the first international conference on glutamic acid ("The International Symposium on Biochemistry and Physiology of Glutamic Acid") was held in Milan, Italy (see Fig. 2.2). This symposium focused on such topics as the sensory and dietary aspects of glutamate, metabolism of glutamate, roles of glutamate in the central nervous system, and evaluation of the safety of glutamate (Filer Jr. et al., 1979). These researchers did not describe glutamate as umami or list its taste as one of the basic tastes, but the term *umami* began to spread among international scientists during this period. In 1982, researchers in fields of physiology, biochemistry, nutrition, and food science established the Umami Research Organization study group to promote research on umami. This organization held the first international symposium on umami in Hawaii (1985). The purpose of this symposium was to explore physiological aspects of the effects of umami substances on flavor evaluation of foods and beverages and to present research findings on the physiological mechanisms of umami taste perception (Kawamura & Kare, 1987). The proceedings of this symposium, "Umami: A Basic Taste," provided a comprehensive view of umami studies, including general concepts, developmental aspects, receptor mechanisms, psychometric analyses, physiology and behavior, brain mechanisms, and nutrition and behavior, as all of these topics relate to umami taste (Fig. 2.3). This symposium drew international participants and contributors, including investigators from Japan, the United States, England, France, Switzerland, Israel, and Mexico. This symposium established the term *umami* internationally. Now we use *umami* as a scientific term representing taste of glutamate (and also nucleotides). Subsequently, this organization held umami symposia in Sicily (1990), Bergamo (1998), and Tokyo (2008) and held sessions on umami taste in International Symposium on Olfaction and Taste (ISOT) meetings in Sapporo (1993), San Diego (1997), Kyoto (2004), San Francisco (2008), Stockholm (2012), Yokohama (2016), and Portland (2020).

When searching the keyword "umami" in PubMed, we find a few articles from the 1980s. The number of articles per year in the 1980s and 1990s was less than 10, except for 1991 (21 reports, containing the proceedings of second international umami symposium in Sicily, held in 1990) and 1999 (12 reports). After that, the number of articles per year rapidly increased, reaching 176 in 2020. During this period, the most pivotal study on umami taste was the identification of umami taste receptors (Lindemann et al., 2002). The first report demonstrating the receptor for glutamate in peripheral taste tissue was published in 1996 (Chaudhari et al., 1996). This study demonstrated that a taste-specific variant of metabotropic glutamate receptor 4 (taste-mGluR4), lacking most of the N-terminal extracellular domain, was expressed in taste buds of rats. In 2002, another G-protein-coupled receptor, the TAS1R1 + TAS1R3 heterodimer, was reported to function as an umami (amino acid) receptor (Li et al., 2002, Nelson et al., 2002). Furthermore, the variant of metabotropic glutamate receptor 1 was reported to be expressed in taste tissue and may function as an umami taste receptor (San Gabriel et al., 2005). The findings of

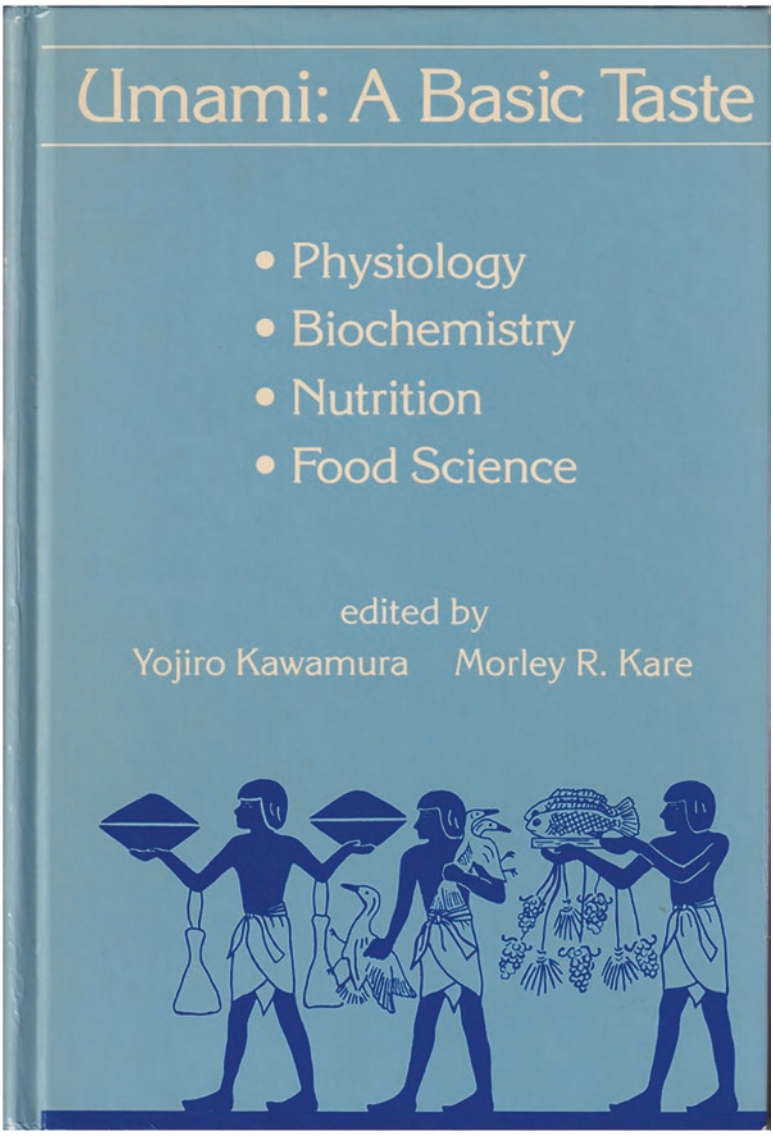

Fig. 2.3 Cover of the proceedings for the 1987 symposium "Umami: A Basic Taste"

specific receptors for glutamate (and other amino acids) in taste cells emphasized that umami taste is different from sweet, salty, sour, and bitter taste. Besides previous evidence of physiological and psychological studies on umami taste (described in Sect. 2.2), these molecular studies supported the concept that umami is one of the basic tastes. More than a century after the discovery of umami by Ikeda, umami has become well accepted internationally in the scientific field of taste perception.

2.2 Umami and Other Basic Tastes

From ancient times, sensations of taste were classified, divided, or categorized into qualities (elements). In ancient Greece, Aristotle proposed seven elements of taste (flavor): sweet, bitter, salty, sour, pungent, astringent, and rough. In Ikeda's first report on umami, he noted as follows:

> In the past it was said that there are five taste qualities: sour, sweet, salty, bitter, and hot. A hot sensation is just a skin mechanical sensation; therefore, today's scientists do not regard this sensation as taste. Furthermore, such qualities of metallic, alkaline and astringent are not considered to be tastes, because they cannot be separated from the sensation accompanied by tissue damage. Therefore, physiologists and psychologists recognize only the four tastes sour, sweet, salty and bitter. (Ikeda, 1909, 2002)

Thus, for thousands of years in writings by Chinese and Indian scholars, as well as in traditional medicinal practices around the world, sour, sweet, salty, and bitter have been accepted as distinct, primary, or basic taste qualities (Beauchamp, 2019). Each of these tastes is considered to provide an organism with specific information about energy sources (sweet), minerals (salty), acids (sour), and poisonous compounds (bitter) in foods and drinks. Typical taste compounds used in taste researches are sucrose (sweet), NaCl (salty), citric acid (sour), and quinine (bitter). To consider whether umami is a basic taste or not, some definitions of a *basic taste* are required. There have been many attempts to identify appropriate criteria for defining a basic taste (Beauchamp, 2019). One of the most widely accepted set of criteria was proposed by Kurihara in the proceedings of symposium "Umami: A Basic Taste." He proposed that a basic taste could be defined as follows (Kurihara, 1987, 2015):

1. A basic taste should be found universally in many foods.
2. A basic taste should not be produced by any combination of other basic tastes.
3. A basic taste should be independent of other basic tastes as proven by psychophysical and electrophysiological studies.
4. A specific receptor for a basic taste should exist.

Since umami taste fulfills these definitions, umami can be considered a fifth basic taste.

2.2.1 Umami Substances in Foods

Compounds eliciting sweet, bitter, sour, and salty tastes are found naturally in many foods at detectable concentrations. Do umami compounds also exist naturally in many foods? Indeed, glutamate and umami ribonucleotides are widely distributed in natural foods (Ninomiya, 1998a, 2002; Yoshida, 1998). Glutamic acid is a prominent component in such foods as meats, fishes, and vegetables (Table 2.1). Some vegetables and seafood contain considerable amounts of free glutamate (Table 2.2). It is noteworthy that human milk contains a considerable amount of free glutamate

Table 2.1 Amino acid composition of selected foods

	Amount (mg/100 g)							
Amino acid	Beef	Chicken	Tuna	Oyster	Tomato	Potato	Cow's milk	Human milk
Ala	840	1600	1400	360	19	45	100	36
Arg	900	1700	1400	340	19	74	100	32
Asp	1300	2200	2400	570	71	320	250	86
Cys	160	250	256	81	8.9	20	29	24
Glu	2100	3400	3500	840	240	260	620	170
Gly	730	2100	1100	360	18	44	59	22
His	500	910	2400	130	12	26	88	26
Ile	630	980	1200	220	15	50	170	51
Leu	1100	1700	2000	370	25	78	310	99
Lys	1200	1900	2300	400	25	82	260	66
Met	360	600	760	140	6.3	24	83	15
Phe	570	900	970	220	18	59	150	42
Pro	610	1400	850	290	17	56	300	92
Ser	540	950	950	250	22	54	150	41
Thr	620	1000	1100	260	17	54	130	43
Trp	160	240	300	58	5	17	41	15
Tyr	480	750	860	180	14	36	120	40
Val	700	1100	1300	250	17	79	210	56

Data extracted from *Standard Tables of Food Composition in Japan* (MEXT, 2015)

Table 2.2 Free glutamate in selected foods

Food product	Free glutamate (mg/100 g)
Beef	0.56–19.1
Pork	6.0–18.5
Chicken	7.1–13.0
Tuna	3–5
Salmon	6.2–25.4
Oyster	123–207
Sea urchin	67–219
Tomato	93.6
Potato	90.6
Cow's milk	3
Human milk	18.3
Cheese	41.2–453
Soy sauce	782
Cured ham	636

Data extracted from Database for Free Amino Acid Compositions of Foods (Japan Society of Nutrition and Food Science, 2013)

(18.3 mg/100 g). It is possible that exposure to glutamate during nursing could influence later acceptance and liking (Mennella et al., 2009).

The amount of free glutamate is increased in fermented and processed foods such as cheese, soy sauce, and cured ham. In general, content of free glutamate in foods is increased by storage, maturation, ripening, cooking, and other processing. In the case of meats, free glutamate increases during storage. Free glutamate in tomato increases as the fruit matures: fully ripe tomatoes contain ten times the concentration of free glutamate as green tomatoes. The content of free glutamate in cheeses and cured ham also increases during their ripening. Thus, glutamate can be a natural stimulant (tastant) when we eat various food stuffs. Nucleotides such as IMP and GMP are also abundant in some foods (Table 2.3). Dried skipjack (bonito) contains a large amount of IMP, while dried black mushroom contains a large amount of GMP. Both of these materials have been used to isolate umami compounds (Kodama, 1913; Kuninaka, 1960). Therefore, nucleotides also are natural tastants in many foods. Taken together, the umami compounds glutamate and nucleotides are abundant in many foods and act as stimulants to taste organs, fulfilling one of criteria for a basic taste.

Although some foods contain glutamate abundantly, the contribution of glutamate (and also other substances) to the taste of foods needs to be investigated. To do this, omission tests have been conducted (Fuke & Konosu, 1991). In these tests, first the chemical composition of a food is analyzed and determined. Then, the mixture of pure chemicals representing chemical compounds of the food is made, and the taste is tested to determine whether the synthetic mixture has a taste similar to the

Table 2.3 5′-Ribonucleotides in foods

	Amount (mg/100 g)		
Food product	5′-Inosinic acid	5′-Guanylic acid	5′-Adenylic acid
Beef	70.7	3.7	7.5
Pork	200.2	2.2	8.6
Chicken	201.3	5.3	13.1
Tuna	286	—	5.9
Snow club	5.0	4.0	32.0
Prawn	—	/	86.8
Scallop	—	—	172.0
Sea urchin	—	—	28.0
Dried skipjack	474	/	52
Asparagus	—	—	4.0
Tomato	—	—	20.8
Potato (raw)	—	—	/
Potato (boiled)	—	2.3	3.8
Black mushroom (raw)	—	—	/
Black mushroom (dried)	—	150	/

Data from Ninomiya (1998a)
— not detected, / not analyzed

Table 2.4 Extractive components in the leg meat of snow crab

Component	mg/100 g
Ala	187
Arg	579
Asp	10
Glu	19
Gly	623
His	8
Ile	29
Leu	30
Lys	25
Met	19
Phe	17
Pro	327
Ser	14
Thr	14
Trp	10

Component	mg/100 g
Tyr	19
Val	30
Adenine	1
Adenosine	26
Betaine	357
Cytosine	1
Guanine	1
Homarine	63
Hypoxanthine	7
Inosine	13
Ornithine	1
Sarcosine	77
Taurine	243
τ-Methylhistidine	3
α-Aminobutyric acid	2

Component	mg/100 g
Trimethylamine oxide	338
Glucose	17
Ribose	4
Lactic acid	100
Succinic acid	9
ADP	7
AMP	32
CMP	6
GMP	4
IMP	5
Cl^-	336
K^+	197
Na^+	191
PO_4^{3-}	217

Data from Fuke and Konosu (1991)
Abbreviations: *ADP* adenosine 5′-diphosphate, *AMP* adenosine 5′-monophosphate (5′-adenylic acid), *CMP* cytidine 5′-monophosphate, *GMP* guanosine 5′-monophosphate, *IMP* inosine 5′-monophosphate. Compounds whose omission changed the taste of crab leg in omission tests are shaded

original food. After that, one or more of the compounds are omitted from the synthetic mixture, and the taste of the mixture is tested to determine whether the omitted mixture still tastes similar to the original food. If the omission of a certain compound changes the taste, that compound may be essential for the taste of the original food.

Using this procedure, essential taste compounds for boiled snow crab meat were analyzed. The extracts from the leg meat of boiled snow crab contained many compounds, including glutamic acid (Table 2.4). Among these compounds, omission of glutamate, glycine, arginine, adenosine 5′-monophosphate (AMP), GMP, and sodium and chloride ions changed the taste of crab meat. Glutamate and 5′-ribonucleotides were particularly important in increasing the overall identity and preference. Similar to the crab meat, the taste of other seafood such as abalone, sea urchin, scallop, short-necked clam, dried skipjack, and salted salmon eggs was unfavorably altered by omission of glutamate or 5′-ribonucleotides. Thus, umami compounds are essential components for the taste of many types of seafood.

2.2.2 Interaction Between Umami and Other Tastes

Do umami substances such as glutamate and nucleotides affect other basic tastes and vice versa? As indicated earlier (see Sect. 2.1), Ikeda first noted that (a) the taste of glutamate was substantially decreased by the addition of acids, (b) a weak salty taste did not enhance the intensity of glutamate taste, and (c) the sweetness of sugars was not affected by the taste of ionic glutamic acids, whereas strong sweetness weakened the taste of ionic glutamic acid (Ikeda, 1909, 2002). To reveal the interaction between umami and other basic tastes, many psychophysical studies have since

been carried out, with somewhat inconsistent results. For example, Lockhart and Gainer (1950) reported that MSG did not affect the thresholds of sugar and salt solutions. Mosel and Kantrowitz (1952) reported that administration of MSG reduced the threshold of sour and bitter tastes but not of sweet and salty tastes. Van Cott et al. (1954) demonstrated that MSG at a concentration 0.75 times threshold reduced the threshold of sweet and salty tastes but not of bitter and sour tastes. To clarify the effect of umami substances on the taste of sweet, salty, sour, and bitter, Yamaguchi and Kimizuka (1979) measured the thresholds of four basic tastants (sucrose, NaCl, tartaric acid, quinine) with or without 5 mM MSG or IMP. The detection threshold for quinine sulfate was slightly increased by addition of IMP but not MSG. The threshold of tartaric acid was considerably raised by adding MSG or IMP, but those of sucrose and NaCl were not affected by addition of MSG or IMP. The effect of IMP on bitter thresholds may be explained by a masking effect by the slight bitter side taste of IMP, and that of MSG and IMP on sour taste may be caused by changes in pH.

Conversely, effects of other tastants on the detection threshold of MSG were investigated (Yamaguchi, 1987). In this case, the threshold of MSG was not greatly increased by addition of other tastants, even at high concentrations, except for higher concentrations of sucrose. From these results, there may be some interactions between umami and other tastes, but these interactions may be explained by physicochemical properties or side tastes of umami substances. Thus, umami taste is likely to be independent from other basic tastes.

2.2.3 Psychophysical and Multidimensional Studies of Umami Independence

Although Ikeda described umami (glutamic taste) as distinct from sweet, salty, sour, and bitter tastes, many US researchers believed that it could be duplicated by a mixture of the four basic tastes. For example, Crocker and Henderson (1932) reported that the taste of MSG could be duplicated by mixing sucrose, NaCl, tartaric acid, and caffeine. The taste of glutamate is generally weak, and the addition of MSG to an appropriate food increases the flavor, pleasantness, and acceptability of the food (Halpern, 2000). Therefore, glutamate has been often considered to be a flavor enhancer rather than a taste substance itself.

In 1916, the German psychologist Hans Henning proposed the concept of the taste tetrahedron (Henning, 1916, 1984). If each of basic tastes is arranged at one of the apices of a tetrahedron, the taste of a certain compound will be represented as a point within that tetrahedron. This idea is essentially that taste perception of any compound or mixture of compounds could be duplicated by mixtures of four primary tastes (sweet, salty, sour, and bitter). This implies that if a certain taste could not be depicted within the taste tetrahedron, that taste should be categorized as a specific, primary, or basic taste.

This concept has been adopted to show the independence or distinctiveness of umami taste. By mathematical analysis of psychological and physiological data using a method called multidimensional scaling (MDS), tastes of many substances can be represented within three-dimensional space. MDS can thus provide a visual representation of the pattern of proximities among a set of objects. Using MDS of human psychophysical data, the similarity of the tastes of amino acids, including MSG, was analyzed (Yoshida & Saito, 1969). This report included an MDS three-dimensional representation of taste of amino acids, NaCl, and MSG, at 12 times the concentration of their thresholds. The taste tetrahedron had apices of salty (NaCl), bitter (tryptophan, etc.), sour (glutamic acid, aspartic acid), and sweet (alanine, glycine); MSG was found to be positioned outside of the tetrahedron. However, this report did not demonstrate a clear segregation of the taste of MSG.

Schiffman et al. (1980) used MDS to show the similarity of the taste of sodium salts, including MSG, in humans. They used 13 sodium salts, as well as sucrose (sweet), citric acid (sour), and quinine (bitter). In their MDS representation, the taste tetrahedron has four vertices (sucrose, citric acid, quinine, and NaCl), and the position of MSG was separate from these tastes, outside of the taste tetrahedron. Furthermore, Yamaguchi (1987) used MDS to examine similarities of 21 taste stimuli of single and mixture solutions of sucrose (sweet), NaCl (salty), tartaric acid (sour), quinine sulfate (bitter), and MSG. In the three-dimensional representation of the results, the four basic tastes were located at the four vertices of the tetrahedron (Fig. 2.4, dashed lines). All mixtures of four basic tastes were located on the edges, the faces, the inside, or the vicinity of the tetrahedron. In contrast, MSG was clearly positioned at a distance from the tetrahedron. These mathematical analyses of human psychological data on taste similarity suggest that the taste of MSG is not composed of the four basic tastes and has characteristics different from those of the four basic tastes, fulfilling one of the criteria for a basic taste. However, it should be noted that this could be caused by the presence of other, nontaste sensory properties of MSG, such as tactile sensations.

MDS was also used to analyze taste response properties in experimental animals. Ninomiya and Funakoshi (1987, 1989a) investigated responses in mice of gustatory nerve fibers in the chorda tympani nerve (innervating the anterior part of the tongue) and the glossopharyngeal nerve (innervating posterior part of the tongue). They found multiple fibers showing responses to MSG and also synergism between MSG and GMP. In the glossopharyngeal nerve, they identified MSG-best fibers that did not show responses to sweet, salty, sour, or bitter tastants. This provided strong evidence for the existence of a neural pathway that specifically sends umami information to the brain. The MDS of these responses demonstrated that umami compounds (MSG, GMP, IMP, MSG+GMP) formed a cluster present outside of the tetrahedron circumscribed by salty (NaCl), sour (HCl), bitter (quinine), and sweet (sucrose, fructose, maltose, glucose, saccharin) tastes, especially when using the data of glossopharyngeal nerve fibers or of all of tested fibers.

Ninomiya and Funakoshi (1987, 1989b) also investigated taste similarity of 16 test stimuli in mice by using a conditioned taste aversion paradigm. If mice were conditioned to avoid either MSG, monosodium L-aspartate (MSA), disodium

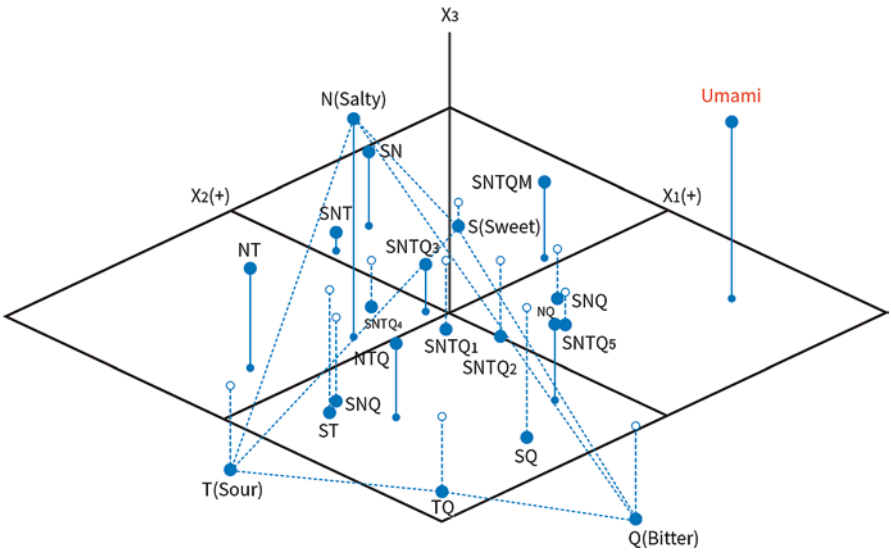

Fig. 2.4 Multidimensional scaling produced this three-dimensional representation of taste similarities among 21 taste stimuli (individually and as mixtures): S, sucrose, sweet; N, NaCl, salty; T, tartaric acid, sour; Q, quinine, bitter; and M, monosodium L-glutamate, umami. $SNTQ_{1–5}$ consist of different concentrations of S, N, T, and Q. X_1 (X_2, X_3), dimension 1 (2, 3); (+), positive value. The dashed lines outline the classic taste tetrahedron with salty, sweet, sour, and bitter at the vertices. (Image from the Umami Information Center website, https://www.umamiinfo.jp/what/attraction/taste, modified from Yamaguchi (1987))

5′-inosinate (IMP), or disodium 5′-guanylate (GMP) alone, they also avoided the other three compounds as well. This phenomenon is called *generalization*. Such data indicate taste similarity among MSG, MSA, IMP, and GMP in mice. The MDS of these data demonstrated that a cluster of umami compounds (MSG, MSA, IMP, GMP, MSG+GMP) was outside of the taste tetrahedron apices composed of salty (NaCl), bitter (quinine), sour (HCl), and sweet (sucrose, saccharin, glucose, fructose, glycine, L-glutamine). Thus, in mice the taste of glutamate may be perceived as different from the other basic tastes. In investigations of the gustatory nerve fibers of chimpanzees, similar MDS showed a separateness of umami taste from other basic tastes (Hellekant et al., 1997a). In a hierarchical cluster analysis, they found an M-subcluster of gustatory fibers that responded robustly to umami substances (MSG, GMP, MSG+GMP). Using MDS, the positions of MSG, GMP, and MSG+GMP were apart from all other tastants, suggesting that umami taste is distinct from other basic tastes in the chimpanzee at the level of the peripheral gustatory nerve fibers.

Taste responses have also been investigated in the higher-order neurons and analyzed by MDS. Baylis and Rolls (1991) investigated taste responses of neurons in the taste cortex of macaques to understand the neural encoding of glutamate taste in a primate. Using five tastants (glucose, NaCl, HCl, quinine, and MSG), they

recorded 190 neurons and found single neurons tuned to respond best to MSG. MDS of these data showed that MSG was located apart from the tetrahedron composed of the other four basic tastes. In addition, Rolls et al. (1996) examined responses to the glutamate ion and IMP in neurons of the taste cortex. MSG-best neurons responded well to glutamic acid, and the response to glutamic acid correlated well with that to MSG but not to glucose, NaCl, HCl, or quinine. The response to IMP also correlated well with that to MSG. In MDS, glutamic acid was located near MSG, which was distant from the tetrahedron composed of sweet, sour, salty, and bitter tastants. Therefore, in the taste cortex of macaques, umami taste (MSG, IMP, and glutamic acid) may be encoded differently from the other basic tastes. In summary, the MDS of taste data in humans and some experimental animals strongly emphasizes the different characteristics of umami taste compared with the other four basic tastes.

2.2.4 Umami Receptors

Marked additional evidence showing that umami is a basic taste comes from molecular studies of taste receptors. The first biochemical evidence for an umami taste receptor was demonstrated by using bovine taste papillae (Torii & Cagan, 1980). In this study, binding of L-[^{3}H]glutamate to bovine circumvallate papillae was measured, showing that the addition of nucleotides substantially enhanced binding of glutamate to a preparation of bovine taste papillae, providing molecular evidence for umami synergism. Beginning around 2000, molecular studies have led to the identification of several receptors for the basic tastes. In 2000, G-protein-coupled receptors named taste 2 receptors (TAS2Rs) were identified as bitter taste receptors (Chandrashekar et al., 2000; Matsunami et al., 2000). In 2001, TAS1R3 was identified as the gene product of the *Sac* locus and was shown to function as a sweet receptor together with TAS1R2 (Bachmanov et al., 2001; Kitagawa et al., 2001; Max et al., 2001; Montmayeur et al., 2001; Nelson et al., 2001; Sainz et al., 2001). Regarding umami taste receptors, a taste-specific variant of mGluR4 (taste-mGluR4) was first identified as a candidate receptor for umami taste expressed in taste tissue of rats (Chaudhari et al., 1996, 2000). Thereafter, the dimer TAS1R1 + TAS1R3 was identified as another candidate receptor for umami (amino acid) taste (Li et al., 2002, Nelson et al., 2002). Furthermore, taste-mGluR1 was also reported to be a candidate receptor for umami (San Gabriel et al., 2005). Together with the salt taste receptor ENaC (epithelial sodium channel; Chandracheker et al., 2010) and sour taste receptor OTOP1 (otopetrin 1; Teng et al., 2019; Zhang et al., 2019), one or more taste receptors have been identified for each of the five basic tastes. These molecular studies suggest that umami receptors are different from receptors for other basic tastes, providing additional evidence that umami is a distinct basic taste. It is noteworthy that TAS1R3 is a common component both for sweet and for umami receptors; such sharing is not found for the other classes of receptors for bitter, salty, and sour.

2.2.5 Neural Pathways for Umami Taste

Based on the abovementioned studies, umami taste fulfills all conditions for the definition of a basic taste as listed by Kurihara (1987, 2015): (1) found universally in many foods, (2) not produced by any combination of other basic tastes, (3) independent of other basic tastes by psychophysical and electrophysiological studies, and (4) has a specific receptor. A fundamental question is how umami taste is coded in the neural system. Is there any specific neural pathway for umami taste? As mentioned earlier, the existence of a specific neural pathway for umami taste was demonstrated in single-fiber recordings in mice (Ninomiya & Funakoshi, 1987). In addition, more recent studies have demonstrated the existence of umami-best (or umami-specific) gustatory nerve fibers (Yasumatsu et al., 2012) and neurons in the geniculate ganglion (Barretto et al., 2015; Wu et al., 2015), which contains cell bodies of gustatory nerve fibers in mice. At the taste cell level, MSG-best taste cells were found in mice in both circumvallate papillae (Maruyama et al., 2006) and fungiform papillae (Niki et al., 2011). These taste cells may transmit their information to MSG-best gustatory nerve fibers, forming a peripheral neural pathway conducting information of umami taste to higher-order neurons.

In the brain, how basic taste qualities are represented in the primary taste cortex of mice was examined by using an in vivo two-photon calcium imaging technique (Chen et al., 2011). They found that each taste quality is represented in its own separate cortical field, forming a "gustotopic" map in the insula. The umami cortical field, which is apart from sweet, bitter, and NaCl cortical fields, was specifically tuned to umami stimuli and contained fewer neurons responding to the other four taste qualities. Thus, umami may be coded in such an umami cortical field in the insula. Given that umami-best (or umami-specific) cells exist in the taste buds, the taste ganglions, and the taste cortex, it would not be surprising if a dedicated neural pathway coding umami taste from the peripheral to the central nervous system is present in mice.

2.3 Differences in Umami Taste

2.3.1 Species Differences

Many animal species have been studied for their taste sensitivity to umami substances. As mentioned above, mice have some specific neural lines for umami taste (Ninomiya & Funakoshi, 1987, 1989a). At the behavioral level, mice can discriminate the taste of MSG from that of sweet (sucrose, saccharin, fructose, glucose, and maltose), bitter (quinine), sour (HCl), and salty (NaCl) (Ninomiya & Funakoshi, 1987, 1989b). Thus, mice have the ability to sense MSG as a taste different from others. However, some differences in umami sensitivity might exist among mouse strains. Many inbred mouse strains have been developed and used in various

studies. Among them, B6 strains have higher avidity for sweeteners than do 129 strains (Lush, 1989). Regarding umami taste, umami synergism between MSG and GMP varies across strains, in the order of C3H > B6 > BALB strains, at the gustatory nerve level (Ninomiya et al., 1992). B6 mice consumed more MSG than did 129 mice in behavioral tests, but gustatory nerve responses to MSG did not differ between B6 and 129 strains (Bachmanov et al., 2001). Nonetheless, mice can sense the taste of glutamate.

In hamsters, Yamamoto et al. (1988) examined electrophysiological and behavioral responses to umami substances. Single-fiber recording of chorda tympani nerve fibers demonstrated that some fibers responded to MSG, IMP, and/or MSG+IMP. These responses to umami substances were highly correlated with NaCl responses but poorly with other taste stimuli, suggesting no or little specific neural line for umami taste in the chorda tympani nerve of hamsters. In whole-nerve recordings of the glossopharyngeal nerve, no response was observed for 0.3 M MSG, 0.3 M IMP, or 0.3 M NaCl. In addition, synergistic enhancement between MSG and IMP was not observed in whole-nerve recordings of the chorda tympani nerve. At the behavioral level, hamsters conditioned to MSG showed avoidance to NaCl and vice versa. Thus, hamsters may not discriminate the taste of MSG and NaCl and also may not sense synergism between glutamate and nucleotides.

In rats, single chorda tympani nerve responses to umami substances demonstrated that some fibers responded to MSG, GMP, and MSG+GMP (Sato et al., 1970). Among these fibers, synergism between MSG and GMP was found in sucrose-sensitive fibers. In whole-nerve recordings, the chorda tympani nerve showed clear synergism between MSG and IMP (Yamamoto et al., 1991). Chorda tympani nerve responses to MSG and IMP were mostly inhibited by amiloride, an epithelial sodium channel blocker, whereas those to MSG+IMP and monopotassium L-glutamate (MPG) + IMP were suppressed by *Gymnema sylvestre* extract, a sweet taste inhibitor. In behavioral experiments, rats conditioned to avoid umami substances showed avoidance to sucrose but not to NaCl, HCl, or quinine. If rats were conditioned to avoid sucrose, they also avoided umami substances (Yamamoto et al., 1991). Such a link between sweet and umami substances has been reported in other studies (Chaudhari et al., 1996; Stapleton et al., 2002; Heyer et al., 2003, 2004). These neural and behavioral data indicate that rats may have difficulty distinguishing between umami and sweet taste.

Umami responses have been investigated in animals other than rodents. In the dog, neural responses to umami substances from the chorda tympani nerve showed a large synergism between MSG and GMP or IMP in most mongrel dogs and between MSG and GMP, IMP, or AMP in beagles (Kumazawa & Kurihara 1990). Addition of nucleotides did not enhance responses to NaCl, sucrose, HCl, or quinine, suggesting canines have an umami receptor that shows a synergistic effect between glutamate and nucleotides. In the pig, gustatory nerve fiber responses in the chorda tympani and glossopharyngeal nerve showed the existence of M-type fibers with large responses to MSG (Danilova et al., 1999). M-type fibers in the glossopharyngeal nerve showed high specificity to umami stimuli compared to those in the chorda tympani nerve, suggesting that the umami information derived from the

glossopharyngeal nerve is more important than that from the chorda tympani nerve for discriminating umami stimuli from other stimuli. In the calf, single-fiber responses of the chorda tympani nerve demonstrated that some fibers responded to MSG but most also showed responses to NaCl, LiCl, and urea (Hellekant et al., 2010). In case of the calf, taste fibers dominantly responding to MSG may not exist in the chorda tympani nerve. However, it is possible that these fibers exist in the glossopharyngeal nerve, as is the case for pigs and mice. Because biochemical evidence for a synergistic effect between glutamate and nucleotide was demonstrated using bovine circumvallate papillae (Torii & Cagan, 1980), a receptor system underlying umami synergism should exist in taste cells of the posterior part of the bovine tongue. In primates, as mentioned previously, an M-subcluster of gustatory fibers was found in the chorda tympani nerve of chimpanzees (Hellekant et al., 1997a). Single cortical neurons tuned to respond best to MSG were found in the taste cortex of macaques (Baylis & Rolls, 1991). In addition, MSG-best fibers were found in the glossopharyngeal nerve of rhesus monkeys (Hellekant et al., 1997b).

Taken together, many species of animals are sensitive to umami substances, but species do differ in sensitivity and neural representation of umami signals. More details on species differences of umami taste from the view of receptors are described in Chap. 3 of this volume. In brief, genes for umami receptor components, *TAS1R1* and/or *TAS1R3*, are pseudogenized (inactive) in some species, including the sea lion, the bottlenose dolphin, and the giant panda (Li et al., 2010; Jiang et al., 2012). These animals lack functional TAS1R1 + TAS1R3 receptors and thus may not taste umami substances.

2.3.2 Tongue Regional Differences

Sensitivity of the tongue differs by region. In experimental animals, these regional differences are inferred by finding differences between tongue areas innervated by different nerves. In the case of mice, regional differences of sensitivity to amiloride were reported (Ninomiya et al., 1991, Ninomiya, 1998b). Amiloride selectively suppressed NaCl responses of the chorda tympani nerve innervating the anterior part of the tongue by about 50% of control but did not inhibit those of the glossopharyngeal nerve innervating the posterior part of the tongue. Similarly, gurmarin, a sweet receptor blocker for mouse and rat isolated from the plant *Gymnema sylvestre*, selectively suppressed sweet responses of the chorda tympani nerve but not of the glossopharyngeal nerve (Ninomiya et al., 1997). Umami substances such as MSG, IMP, and MSG+IMP contain the sodium ion. Therefore, responses of the chorda tympani nerve to these substances are partly suppressed by amiloride. In the chorda tympani nerve, fibers showing large responses to MSG and synergism between MSG and IMP predominantly responded to sucrose (S-best fibers). Gurmarin almost completely suppressed responses of this type of fiber not only to sucrose but also to MSG+IMP. However, chorda tympani nerve fibers predominantly sensitive to umami substances (M-type fibers) did not exhibit such suppression of responses to

umami substances by gurmarin (Ninomiya et al., 2000; Yasumatsu et al., 2006). In contrast, the glossopharyngeal nerve of mice contains a much greater number of M-type fibers and showed greater responses to umami substances (Ninomiya et al., 2000). In line with these data, at the behavioral level, transection (cutting) of the glossopharyngeal nerves affected licking behavior of mice in a conditioned taste aversion paradigm (Ninomiya & Funakoshi, 1989b). Mice conditioned to avoid MSG showed no avoidance to sucrose, NaCl, HCl, or quinine (no generalization to other taste stimuli), but these mice did show avoidance to NaCl (generalization to NaCl) if the glossopharyngeal nerves but not the chorda tympani nerves were bilaterally transected. Thus, the glossopharyngeal nerve likely sends taste information for umami, which can be discriminated from that of the other basic tastes in mice. The presence of M-type fibers in the glossopharyngeal nerve was also demonstrated in rhesus monkeys (Hellekant et al., 1997b).

Although there are no data on gustatory nerve responses to umami substances in humans, psychophysical experiments have been done using a filter-paper test, in which a small piece of filter paper soaked with the taste solution is applied directly to the area of interest on the tongue. These studies demonstrated that umami sensitivities stimulated with MSG, IMP, and MSG+IMP were higher on the posterior than on the anterior part of the tongue (Yamaguchi & Ninomiya, 2000; see Fig. 2.5).

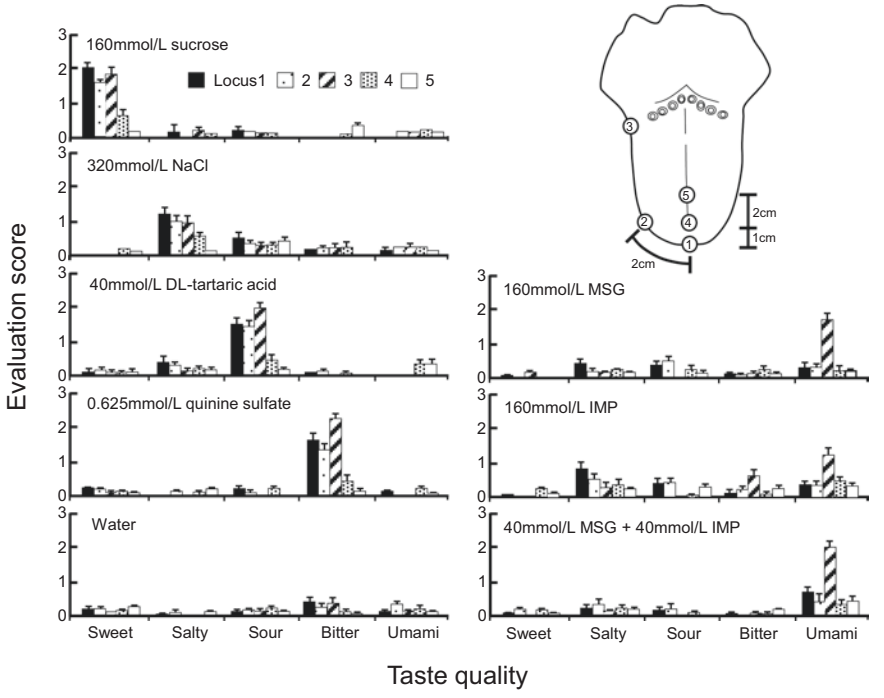

Fig. 2.5 Evaluation scores as mean certainty ratings (0 = none or uncertain, 1 = likely, 2 = fairly, 3 = absolutely) for each taste quality perceived for each taste stimulus at five loci of the tongue. Stimuli were taste solutions on a filter paper disk ($n = 30$). MSG, monosodium L-glutamate; IMP, inosine 5′-monophosphate. (Modified from Yamaguchi and Ninomiya (2000))

Similar results were reported by other researchers (Feeney & Hayes, 2014). Based on this research, it is suggested that the posterior part of the tongue may play the major role in detection and discrimination of umami-specific (or umami-dominant) information.

2.4 Distinctive Phenomena of Umami Taste

Although Ikeda laid the foundation for umami taste more than 100 years ago, subsequent evidence on the taste of glutamate has solidified the concept of a unique umami taste. However, several puzzling phenomena about umami taste remain to be elucidated. In Western countries, the taste of glutamate has been described as "savory," "mouthfullness," or "brothlike" (Ninomiya, 2002). As mentioned by sensory specialists from the 1948 symposium on MSG flavor and acceptability (described in Sect. 2.1 above), the "taste" or flavor of glutamate was described as "tingling," "persistent," and "satisfying" (Beauchamp, 2009). In addition, "long-lasting," "aftertaste," and "stimulation in the throat" were keywords representing taste of glutamate in that symposium (Yamaguchi & Ninomiya, 1998). Of course, glutamate in the oral cavity stimulates taste receptor cells on the tongue. However, from these descriptions of its taste, glutamate may engage sensory pathways other than those detected by the sense of taste, such as tactile (touch) sensations. For example, the oral sensation of acids may consist of sour taste and nociceptive or painful sensations. Although wild-type mice avoided drinking acid solutions such as citric acid, genetic ablation of sour taste receptor OTOP1 did not affect avoidance of acid solutions (Zhang et al., 2019). Similarly, ablation of trigeminal neurons expressing TRPV1 (transient receptor potential member V1) did not eliminate avoidance of acid solutions. In contrast, mice lacking both the *Otop1* gene and TRPV1-expressing trigeminal neurons showed reduced avoidance of an acid solution, suggesting both taste and nociceptive components are required for perception and avoidance of acid stimuli. Further studies are required to elucidate whether oral glutamate stimulates sensations other than taste.

2.4.1 Intensity of Umami Taste

As mentioned by Ikeda, one of its characteristics that distinguishes umami from other tastes is that umami does not become extremely strong even at high concentrations of glutamate. At the suprathreshold level, the relationship between the subjective taste intensity and the concentration of tastants can be expressed by the following equations (Yamaguchi, 1998):

MSG: $S = 9.69 \log_2(x/0.0195)$
Sucrose: $S = 14.98 \log_2(x/0.873)$
NaCl: $S = 15.50 \log_2(x/0.0943)$

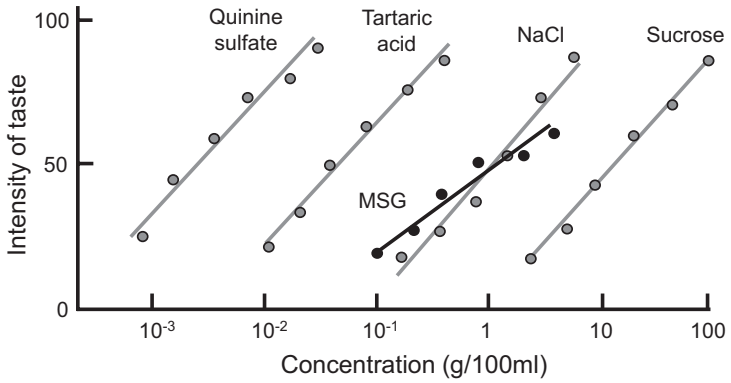

Fig. 2.6 Relationship between taste intensity and concentration. (Modified from Yamaguchi (1987))

Tartaric acid: $S = 14.45 \log_2(x/0.00296)$
Quinine sulfate: $S = 14.16 \log_2(x/0.000169)$

Here, x is the concentration of each taste stimulus (g/dl) and S is the subjective taste intensity (the taste intensity of saturated sucrose solution is represented as $S = 100$). Although the subjective taste intensity of MSG, like that of the other four basic tastants, follows Fechner's law, where the subjective sensation is proportional to the logarithm of the stimulus intensity, the slope of MSG's concentration-intensity function is less steep than that of others (Fig. 2.6). Ikeda used an analogy to express this characteristic: it is like the color of yellow, which does not appear to intensify when the concentration is increased; in contrast, sweet taste is like the color red, which does intensify as the concentration increases. The mechanisms underlying this unique taste characteristic of umami are still unknown, but this characteristic may prevent us from noticing umami taste in many foods—umami is much less salient in foods than are sweet, sour, salty, and bitter.

2.4.2 Synergism

Umami synergism was first reported by Kuninaka (1960). He noticed that the umami taste of MSG solutions was greatly increased if ribonucleotides such as GMP and IMP were mixed with MSG. Synergism between MSG and ribonucleotides was extensively investigated by Yamaguchi (1967). She demonstrated that the relationship between the proportion of IMP in a mixture of MSG+IMP and its perceived intensity was bell-shaped (Fig. 2.7). The synergistic effect between MSG and IMP can be expressed by the following formula:

$$y \quad u \quad v,$$

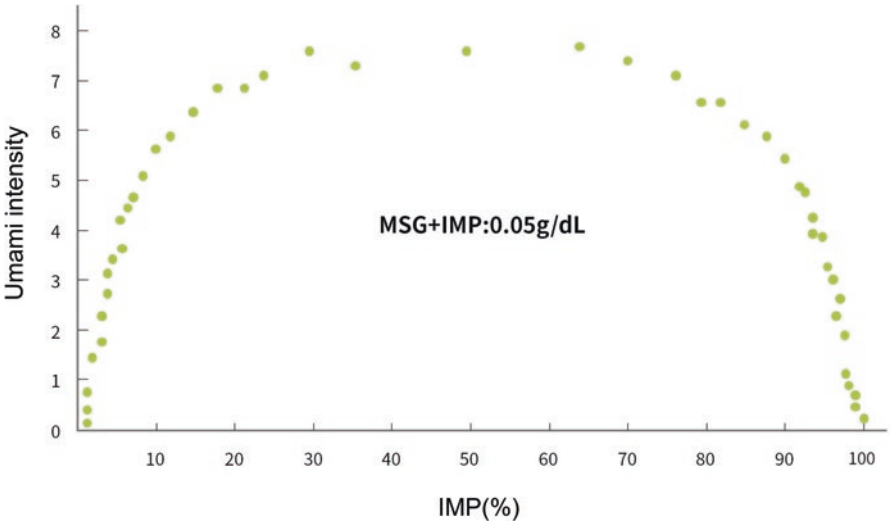

Fig. 2.7 Relationship between umami intensity and proportion of inosine 5′-monophosphate (IMP) in a mixture of monosodium L-glutamate (MSG) and IMP. (Image from Umami Information Center website, https://www.umamiinfo.jp/what/attraction/discovery/, modified from Yamaguchi (1967))

where u and v are the concentrations (g/dl) of MSG (u) and IMP (v) in the mixture, γ is a constant (1218), and y is the equi-umami concentration of MSG alone.

In humans, umami synergism may contribute to sensitivity to ribonucleotides, because human saliva contains a small amount of glutamate. To test this hypothesis, the detection threshold of IMP was investigated in the presence of MSG at various concentrations, and it was estimated that 0.63 ppm MSG, which is lower than salivary glutamate, was required to affect the detection threshold of the IMP anion (Yamaguchi, 1991). Thus, salivary glutamate might affect sensitivity to ribonucleotides, which may be based on the synergism between these substances. Synergism between MSG and ribonucleotides has been observed in various animal species (see Sect. 2.3). More recently, a molecular mechanism for umami synergism has been elucidated: the TAS1R1 + TAS1R3 umami receptor is the site responsible for synergism (Zhang et al., 2008; see Chap. 1).

2.4.3 Long-Lasting

One of the unique characteristics of umami taste is that it is long-lasting, which may be characterized as “persistency” or “aftertaste.” Time-dependent perception of taste intensity was investigated in healthy subjects (Yamaguchi, 1998), who were asked to keep a taste solution in their mouth for 20 s and then expectorate it. Taste intensity was evaluated up to 100 s thereafter. When subjects sipped and

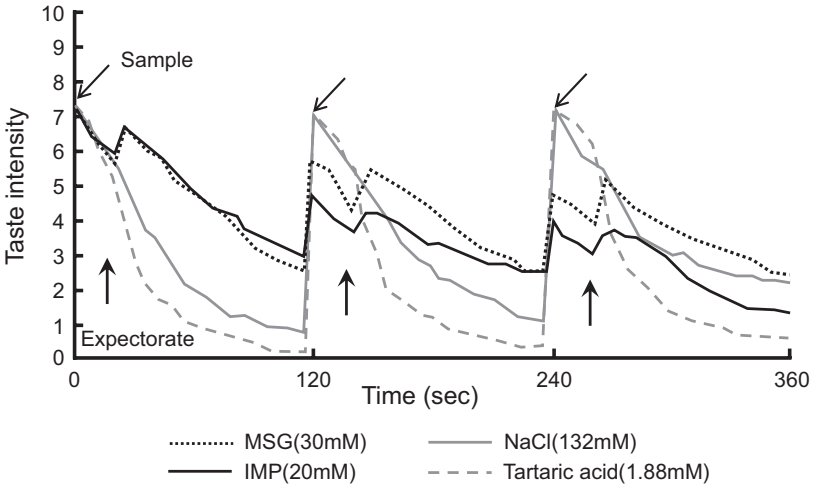

Fig. 2.8 Successive time-intensity curves in response to the umami taste of monosodium L-glutamate (MSG) and inosine 5′-monophosphate (IMP), the salty taste of NaCl, and the sour taste of tartaric acid. (Modified from Yamaguchi (1998))

expectorated salty (NaCl) or sour (tartaric acid) solutions, the taste intensity of these solutions rapidly decreased (Fig. 2.8). In contrast, a decrease in the taste intensity of umami solutions (MSG and IMP) after expectorating was considerably slower. This long-lasting effect of umami taste is concentration dependent: when the concentration of umami substances was increased, the duration of aftertaste became longer (Kawasaki et al., 2016). This long-lasting aftertaste may explain why umami taste has been described as persistent. Such long-lasting effects of umami taste may be explained in part by umami signals from the larynx and the pharynx region, that is, "stimulation in the throat."

In mice, whole-nerve recordings from the superior laryngeal nerve innervating the larynx demonstrated that the superior laryngeal nerve showed large responses to MSG in a concentration-dependent manner (Arai et al., 2010). Because NaCl stimulation caused a concentration-dependent decrease in responses of the superior laryngeal nerve, responses to MSG must be elicited by the glutamate ion, not the sodium ion. The pharynx is innervated by the pharynx branch of the glossopharyngeal nerve. Whole-nerve recordings from the pharynx branch of the glossopharyngeal nerve in mice showed that umami substances such as MSG, IMP, and MSG+IMP elicited greater responses than water stimulation, which also induced large responses of the pharynx branch of the glossopharyngeal nerve (Kitagawa et al., 2007). In the same manner as for the superior laryngeal nerve, NaCl stimulation elicited weaker responses in the pharynx branch of the glossopharyngeal nerve. Therefore, responses to MSG, IMP, and MSG+IMP were likely elicited by the glutamate and/or inosinate ion, not the sodium ion. Interestingly, responses to MSG+IMP were almost the same as the sum of responses to MSG and IMP, suggesting that there is no umami

synergism in the pharynx region. Thus, detection mechanisms for umami compounds may be different in the oral cavity than in the pharynx.

Imamura and Matsushima (2013) identified substances in soy sauce that suppress this umami aftertaste. They found that polysaccharides with molecular weight between 44,900 and 49,700 suppressed umami aftertaste. Although the mechanism for this suppression was not elucidated, these data may indicate the existence of receptor(s) for umami aftertaste other than TAS1R1 + TAS1R3. In summary, umami signals from the larynx and pharynx region may contribute to the aftertaste of umami, but this possibility should be verified with further studies.

2.4.4 Saliva Secretion

Oral taste stimulation induces saliva secretion. The volume of saliva secretion differs according to taste quality. Similar to other tastants, umami substances also induce saliva secretion. Horio and Kawamura (1989) examined saliva secretion from the parotid gland in response to taste stimuli in humans. Among the taste stimuli used, tartaric acid (0.01 M) induced the largest saliva secretion; saliva secretion by umami tastants such as MSG (0.1 M), IMP (0.1 M), and GMP (0.1 M) was similar to that induced by other tastants, including NaCl (0.1 M), sucrose (1 M), and quinine (0.0005 M). They also examined regional differences between the anterior and posterior part of the tongue and reported that umami stimulation of the posterior part of the tongue tended to be more effective than that of the anterior tongue, although there was no statistically significant difference.

Other researchers have investigated saliva secretion by umami stimuli. Hodson and Linden (2006) examined parotid saliva flow induced by taste stimuli in humans. They demonstrated that the parotid saliva flow induced by MSG showed a dose-dependent response and that the overall order of relative saliva flow induced by taste stimuli was sour (citric acid) > umami (MSG) > salty (NaCl) > sweet (sucrose) ≥ bitter (magnesium sulfate). Sato-Kuriwada et al. (2018) demonstrated a similar result by examining taste-induced saliva secretion from the labial minor salivary gland; umami and sour tastes evoked greater saliva secretion than did the other tastes. They also showed greater saliva secretion by MSG+IMP than by MSG or IMP alone. These studies suggest that oral umami stimulation causes greater saliva secretion than do sweet, salty, and bitter stimulation.

Saliva secretion induced by umami stimuli may correlate with umami sensitivity in humans. Pushpass et al. (2019) investigated the effect of older age on subjective (perception) and objective (stimulated saliva response) measures of stimulants for transient receptor potential channels (capsaicin, menthol), odors (menthol odor), and basic tastants (caffeine, MSG). In this study, both perceived intensity of umami stimulation and saliva secretion induced by umami stimulation were lower in older subjects (>60 years) than in young subjects (18–30 years). These data indicate that higher umami sensitivity may lead to greater saliva secretion by umami stimuli.

However, other reasons associated with human aging may underlie these results. In addition, saliva secretion induced by umami stimuli may be long-lasting just as umami taste perception is. Uneyama et al. (2009) demonstrated the time course of saliva secretion after taste stimulation in healthy adult subjects. In the case of sour stimulation (3.8 mM citric acid), saliva secretion returned to the basal level about 3 min after taste stimulation. In contrast, saliva secretion induced by umami stimulation (100 mM MSG) was long-lasting, continuing for more than 10 min. Therefore, the total amount of saliva secretion within 10 min after umami stimulation was significantly greater than that after sour stimulation. Such an effect of umami taste on salivation might be helpful in maintaining the oral mucosal integrity in patients with dry mouth.

2.4.5 Mouthfullness

As described earlier in this chapter, characteristic descriptions of umami taste often include such words as *mouthfullness* and *persistency*. These same words are elicited by the addition of some flavor compounds named *kokumi*, a Japanese word literally meaning "rich taste." *Kokumi* is characterized by thickness, continuity, and mouthfullness in the flavors and textures (Ueda et al., 1990). By adding a water extract of garlic to umami solutions, *kokumi* flavors were clearly recognized by panelists (Ueda et al., 1990). By chromatographic separation of garlic extracts, the key compounds were determined to be sulfur-containing components, such as alliin.

Many compounds are thought to impart *kokumi* flavor. One of the recognized compounds found in foods that elicit *kokumi* flavor is glutathione (Ueda et al., 1997). Yamamoto et al. (2009) tested the effect of glutathione on taste responses in mice. In short-term and long-term behavioral experiments, mice showed greater preference to IMP or MPG + IMP when glutathione was added to these solutions. In a conditioned taste aversion paradigm, mice conditioned to avoid MPG generalized this response moderately to glutathione, whereas glutathione aversion did not generalize to MPG. Gustatory nerve recordings showed synergism between IMP and glutathione but not between MPG and glutathione. Thus, glutathione increased preference for umami solutions containing IMP in mice. In humans, the taste intensity of MSG+IMP+NaCl solution was significantly increased by the addition of glutathione. *Kokumi* qualities (thickness, continuity, and mouthfullness) were also increased by addition of glutathione added to salty, sweet, or umami solutions (Ueda et al., 1997; Ohsu et al., 2010). Furthermore, sensory identification of MSG+NaCl as meaty and long-lasting was increased by addition of glutathione, and an increase in central nervous system activation attributed to MSG+NaCl+glutathione compared with MSG+NaCl alone was observed in the left ventral insula in functional MRI experiments (Goto et al., 2016). These data indicate an interaction between umami (also sweet and salty) and *kokumi*.

The receptor for *kokumi* is believed to be the calcium-sensing receptor CaSR, since agonist activities for CaSR correlated well with *kokumi* intensity (Ohsu et al.,

2010). CaSR was found in a subset of taste cells that did not express the umami and sweet taste receptor component TAS1R3, and these cells were activated by agonists for CaSR, including glutathione (San Gabriel et al., 2009; Maruyama et al., 2012). Thus, umami and *kokumi* appear to be detected by a different subset of taste receptor cells. The interaction site for umami and *kokumi* still has not been elucidated, but further studies should reveal the mechanisms for such interactions.

2.4.6 Satisfaction

Another description often used for MSG flavor is "satisfaction." This feeling not only may depend on oral sensation but may also include information from the throat and the gastrointestinal tract. As mentioned above, some neural information for glutamate arises from the pharynx and larynx region, which contains taste buds (taste cells). Furthermore, a characteristic type of cell called the solitary chemosensory cell (SCC) exists in the throat (and nasal epithelium and trachea). These cells can detect chemical substances in a manner similar to taste receptor cells (Tizzano et al., 2011). They express the umami taste receptor TAS1R1 + TAS1R3, although the chemosensitivity of the umami receptor in SCCs has not been elucidated. It was reported that activation of SCCs leads to the release of acetylcholine, which stimulates trigeminal nerve fibers that innervate the SCCs (Saunders et al., 2014). Therefore, glutamate may interact with somatosensory fibers, which may contribute to the sensations of "persistence" and "satisfaction." After ingestion, glutamate could enter the gut and activate umami receptors in the gastrointestinal tract.

Supporting this idea, MSG infusion into the mouth, stomach, and duodenum of rats increased afferent activity in the vagal gastric and celiac nerves (Niijima, 2000), suggesting transmission of neural information about MSG from the stomach and the gut. In the gut, the umami receptor component TAS1R3 was reported to be expressed in ghrelin-positive endocrine cells (Vancleef et al., 2018). The ghrelin receptor is reported to be expressed in dopaminergic neurons in the ventral tegmental area, which is involved in brain reward circuits (Zigman et al., 2006). Therefore, activation of such reward systems in the brain by ghrelin could contribute to the sensation of "satisfaction" induced by glutamate intake. Further, glutamate may stimulate umami receptors in the intestine. The umami receptor TAS1R1 + TAS1R3 and cholecystokinin (CCK) are coexpressed in the same endocrine cells of mouse proximal intestine (Daly et al., 2012). They also found that stimulation of L-amino acids, including glutamate, induced CCK release from an STC-1 enteroendocrine cell line. CCK acts as a satiety hormone, suppressing food intake. Thus, CCK-mediated humoral and neural signals induced by glutamate stimulation in the intestine could also be involved in the sensation of "satisfaction" induced by glutamate ingestion.

2.5 Conclusion and Perspective

The first paper on umami, published by Kikunae Ikeda over 100 years ago, described many basic properties of umami taste. Subsequent studies conducted by many researchers around the world supported and expanded Ikeda's original observations. However, the establishment of the scientific concept of umami taste was not achieved until the first international symposium on umami in Hawaii in 1985. Now, umami taste is recognized worldwide, and studies on MSG and umami taste continue to increase. But there are still many questions on umami taste that we need to tackle, some of which were also raised at the 100th anniversary symposium of umami discovery (Beauchamp, 2009). Many of these questions, and avenues to pursue them, are discussed in the following chapters in this volume.

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