Food and Health

Ana San Gabriel
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Gary Beauchamp *Editors*

Umami

Taste for Health

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Food and Health

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The editors dedicate this book to the memory of Dr. Kunio Torii (1946–2023). During an illustrious career, Dr. Torii made major contributions to our understanding of the functions and mechanisms of umami. His professional life was characterized by his passion for rigorous science, support and encouragement of younger colleagues, and dedication to enhancing human health. We will miss his enthusiasm for work, family, and life.

Preface

In October 1985, the first International Symposium on Umami was held in Hawaii. The purpose of that conference was to explore physiological aspects of umami substances (mainly monosodium glutamate [MSG] and 5′-ribonucleotides) and present findings on the physiological mechanisms of umami taste perception. Two years after this symposium, the book *Umami: A Basic Taste* was published, comprising 28 chapters reflecting the presentations at this meeting. It was at this meeting and after publication of its proceedings that the idea of umami as a novel (fifth) taste quality became widely discussed and debated internationally in the sensory and nutrition fields. Since this time there has been a growing scientific interest in umami, as evidenced by several additional symposiums, many scientific publications, and several popular science books.

There has been a substantial amount of progress over the intervening years in understanding of the mechanisms and functions of umami perception and preference. It is not the purpose of this volume to review all of this work. Instead, the current volume specifically focuses on: (1) providing summaries and analyses on current knowledge of the perception, physiology, and molecular biology of umami; (2) focusing on specific health-related aspects of umami; and (3) providing an overview of some of the culinary issues relevant to umami.

Specifically, Chap. 1 briefly discusses some of the current issues surrounding the concept of umami from a perceptual and evolutionary perspective. Chapters 2 and 3 are devoted to basic biology of umami. These two chapters overlap to some degree, but they provide distinctly different approaches and different emphases. This is in part because the authors of Chap. 2 are Japanese, and it was in Japan that umami was first identified. Japanese scientists, including these authors, have played major roles in the scientific understanding of umami. Chapter 3 is authored by US-based researchers who have also significantly advanced our knowledge of umami. Taken together, these two chapters complement each other to provide a comprehensive overview of our current understanding of the basic biology of umami.

Chapters 4–8 directly address important aspects of umami in human nutrition and health. These chapters are authored by scientists who have played significant investigative roles in their topics. Amid concerns about the obesity epidemic, there

is a strong interest in understanding factors controlling satiety and satiation. It is widely believed that umami sensation signals the presence of protein. Based on the widespread conviction that protein is highly satiating, it has been natural to suggest that umami may thus play an important role in satiation. Chapter 4 addresses this issue comprehensively. Chapter 5 describes the early childhood development of sensitivity and preference for umami stimuli. This chapter highlights how very young infants are exposed to different levels of free (unbound) glutamate from a very early age and how this impacts later preferences for similar flavors. Complementing Chap. 4, it also addresses the role of umami stimuli in regulation of infant satiety and growth.

At the other end of the age spectrum, Chap. 6 addresses umami and aging in humans. It focuses on special nutritional challenges among the elderly population and how umami can be used to improve their health. This topic is particularly relevant given the growing proportion of elderly people in many countries around the world. Chapter 7 highlights a particular diet-related health challenge: the necessity to reduce consumption of excess salt (sodium) in virtually every country around the world. Umami and salt are closely allied (both NaCl and MSG contain sodium), and now considerable research indicates that umami stimuli can replace a certain amount of salt in many foods, thereby reducing an individual's overall sodium consumption. Chapter 7 comprehensively reviews the growing literature on this topic. Chapter 8 provides a broader overview of health and umami, presenting umami as a seasoning that can increase the appeal of foods that align with human and planetary health. While there are several barriers to consuming healthful diets, taste is among the most important. Global data analysis has shown that poor diets lead to chronic diseases. Chapter 8 considers how the use of umami, due to its taste and physiological functions, could enhance acceptance of foods that may reduce the risk of chronic diseases and their contributions to premature mortality. To conclude our volume, Chap. 9 reminds us that umami is, after all, a food-related concept and that culinary usage of umami ingredients has a long history in many cuisines worldwide. This chapter also includes practical guidance for umami usage from experts in the field.

A note on the book cover: Green is evocative of health, plants, and growth, and peas are one of many fresh vegetables high in glutamate.

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Chapter 1
Introduction: Umami as a Taste Percept

Gary Beauchamp

Umami is now commonly identified as the fifth "basic" taste quality, joining sweet, salty, sour, and bitter. It must be emphasized that the term *taste quality* refers to human (and perhaps other species) *psychological* representations, not to the ligands that elicit those representations; for example, NaCl elicits a salty taste in humans, but sodium chloride itself is not "salty." The four traditional basic taste qualities have a very long and deep history in human experience. As detailed in a recent review (Beauchamp, 2019), sweet, salty, sour, and bitter, along with pungency and astringency (these last two are tactile qualities, not taste qualities), were identified as the basic building blocks of perceived taste in Chinese, Indian, and Greek writings dating back several thousands of years. Moreover, these four taste qualities, as well as the two tactile qualities, also make up much of what is reported to be the current taste world in many independent, relatively isolated cultures around the world (Beauchamp, 2019).

These four basic taste qualities likely exist to provide vital information on the health and safety of potential foods. Sweet and salty substances are generally highly palatable, signaling vital nutrients: calories and sodium. Bitter compounds, with generally negative hedonic qualities, usually signal danger or poison. However, bitter has also been seen as a signal for medicinal value, both historically and currently, in many cultures around the world (Beauchamp, 2019). Functionally, sour remains a puzzle. Among several hypotheses to account for it, one is that it acts as an inhibitory signal for unripe fruit that could also injure the oral cavity, and another is that it could signal the presence of certain micronutrients (Breslin, 2019; Liman & Kinnamon, 2021). It is significant that, for sweet, salty, and bitter, the perceptual signal is generally identical with the actual function of the signaling molecules. That is, most sweet compounds in nature are calorie-rich, virtually all salty

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substances in nature contain sodium, and most molecules that are bitter act as poisons at least in high concentrations.

At the beginning of the twentieth century, the Japanese chemist Kikunae Ikeda identified the glutamate ion as inducing a novel taste quality that he proposed was a signal for protein, analogous to sweetness being a signal for energy or calories (see Chaps. 2 and 3). He described this novel quality as "the peculiar taste we feel as *umai* [meaning, according to the translators, meaty, brothy, or savory]." He called this taste *umami*. Subsequent studies further identified the ribonucleotides 5′-inosinate and 5′-guanylate as synergistic enhancers of this novel taste, although for humans and some other species, they may not produce a taste on their own. Beginning in the late 1960s and 1970s, additional researchers also proposed umami as a novel fifth basic taste. This idea gained momentum from a scientific meeting held in 1985 and the publication of the proceedings *Umami: A Basic Taste* (Kawamura & Kare, 1987). The evidence used to support the proposal that umami was the fifth basic taste at that time consisted primarily of human sensory studies and animal model studies of behavior and physiology.

The discovery in the 1990s and 2000s of specific taste receptors responsive to amino acids (see Chaps. 2 and 3 in this volume) gave substantial impetus to the idea that umami might be the fifth basic taste. Yet even the proponents of umami as a basic taste acknowledge that it differs significantly from the classic four (e.g., Hartley et al., 2019): it is more subtle, which may account for it not being identified historically or in most traditional cultures, and unlike the other appetitive taste qualities, sweet and salty, relatively pure solutions of monosodium glutamate (MSG) are very rare in nature and are not palatable for human adults or infants (see Chap. 2). Moreover, unlike sweet, salty, and bitter, the perceptual quality of umami for humans does not directly signal the presence of the purported nutrient, proteins (which generally have no taste), or even amino acids. Indeed, many umami-rich foods are not naturally high in protein (Breslin, 2013).

Although much current research on umami focuses on its apparently unique taste to humans, early descriptions of the umami *percept*, or perceptual characteristics, included a strong component that is best described as tactile rather than taste (Beauchamp, 2009). Whether this tactile percept, sometimes called *mouthfeel*, results from a true ability of MSG to engage somatosensory rather than taste pathways, or whether it is mediated by anatomically defined taste pathways, as has recently been argued by Yamamoto and Inui-Yamamoto (2023), remains to be determined. Nevertheless, mouthfeel is an extremely important and salient component of the umami percept, and it merits future research. For example, does this attribute have any causal relationship to the observation that umami sensations are involved in satiety and satiation?

1.1 Species Differences in Umami Perception

Do other species detect umami? Taste qualities are human-derived percepts, so it can be problematic to discuss umami in the context of other species—which of course is also true of the other basic taste qualities. The words *salty*, *sweet*, *bitter*, and *sour* refer to sensory properties that humans perceive. However, for these taste qualities, there are at least two reasons to believe that at least some other animal species perceive something similar to what humans perceive. First, many of the compounds we classify as sweet or salty and as bitter or sour elicit similar behaviors in several other well-studied species. For example, rats and mice tend to avoid bitter compounds and are attracted to many compounds humans describe as sweet—sweet is good and bitter is bad, for the most part. What is more, if a rodent is made ill by exposure to a simple sugar such as glucose (to which a tasteless purgative, e.g., has been associated), it will not only avoid this taste when presented again but also avoid many other simple sugars and even some nonnutritive compounds humans describe as sweet, such as saccharin. This suggests that all these compounds elicit a common percept—a common taste quality.

Is the umami taste similar across species? The apparent answer is no. Umami stimuli for humans are restricted to MSG and, to a lesser extent, aspartate and are synergistically enhanced by some ribonucleotides. However, this specificity is not evident for rodents (Nelson et al., 2002) and perhaps many other species. In some species, MSG appears to be sweet or salty, whereas in others, glutamate may elicit the same percept (neither sweet nor salty) as many other amino acids. That is, the putative receptor for umami in humans (the dimer T1R1/T1R3; see Chaps. 2 and 3) may be quite different in other species, due to molecular changes in its binding affinities and more central projections and thus different in the perceptual characteristics it elicits in many other species. Consequently, it is much more problematic to speak of the "umami receptor" in species other than humans than it is to speak of the "sweet receptor" or the "bitter receptors" in some other species.

1.2 Umami Perception in Humans

Why, from a functional and evolutionary perspective, is human perception of umami elicited almost exclusively by glutamate and, to a lesser degree, by aspartate? Several suggestions have been proposed to explain this—while none are definitive, each may have merit. Following the lead of Ikeda (2002) who was writing in 1909, Breslin (2013, 2019) has suggested that humans developed a preference (and presumably a specific receptor) for glutamate and ribonucleotides as markers for protein. But many high-protein foods do not have a strong umami taste. Breslin's idea

is that the specific umami taste quality is particularly human because it signals easily digested protein as formed during cooking (see Chaps. 5 and 9) and fermentation. He noted that fermented foods also have the nutritional advantage of providing easy access not only to amino acids but also to probiotic bacteria. Thus, he partially attributes specificity of human umami perception and preference for food manipulation by our human ancestors. As Breslin (2019, p. 15) summarizes: "We can presume that this taste, which we call savory or umami, was initially related to fermentation." Although this explanation has merit, it fails to explain why other primate species as well as nonprimate mammals (which do not cook or ferment their foods) also appear to have a receptor system focused on glutamate and/or ribonucleotides.

A second recent approach toward understanding the human specificity of umami has been suggested in a comprehensive evaluation of the T1R1/T1R3 receptor in 17 species of primates (Toda et al., 2021). Each of these primate species has a functional T1R1/T1R3, but this receptor varies in which stimuli engage it most effectively. To evaluate these differences, Toda and colleagues tested the receptor responses to glutamate and to ribonucleotides 5′-inosinate and 5′-guanylate separately in each of these species and attempted to associate relative responsiveness to these compounds to the primate's dietary habits. They concluded that for primates that consume primarily insects, this receptor is specialized for detection of unbound (free) ribonucleotides, which is consistent with the presence of large amounts of these molecules in insects. In contrast, unlike in humans, the T1R1/T1R3 receptor in these species does not respond well to glutamate. They proposed that ribonucleotide sensitivity was the ancestral response of all primates. Subsequently, the T1R1/T1R3 receptor evolved to respond specifically to glutamate in a variety of primate species, including human precursors. These species consume primarily leaves, which are low in free ribonucleotides but are relatively rich in free glutamate. They concluded that glutamate sensitivity could be useful for these species for detecting dietary protein in their plant-based diets. They further speculated that this responsiveness to the free glutamate in plant leaves also functions to mask or inhibit the bitterness of leaf-based secondary metabolites, thereby heightening leaf palatability. Although Toda and colleagues focused on primate analyses, they also investigated glutamate responsiveness in the isolated T1R1/T1R3 receptor in several other species of mammals, including mice, cats, dogs, horses, and pigs. The receptors of all these nonprimate species except pigs were relatively unresponsive to glutamate, but all were highly responsive to the ribonucleotides. This further emphasizes the novel specialized nature of the umami response in humans and closely related primates.

One additional aspect of umami in humans bears mentioning. Human milk is particularly rich in glutamate, as are the milks of several other closely related primates (gorillas, chimpanzees, and even rhesus macaques; Rassin et al., 1978; Davis et al., 1994; Sarwar et al., 1998). These species' T1R1/T1R3 receptors are also highly responsive to glutamate (Toda et al., 2021). Could there be a causative relationship between specificity for glutamate and a high concentration of glutamate in breast milk? Thus, leaf eating may not be the only driving force toward high

receptor specificity for free glutamate and thus for umami as a positive stimulus in primates that are more closely related to humans.

1.3 Conclusion

Although many mysteries about umami taste remain, we nevertheless know much more about this potent sensory percept and its health-related aspects now than we did even 20 years ago. Taste and associated oral sensations such as mouthfeel provide the last chance for an organism to decide whether to ingest or reject a particular food. Taste signals the potential worth and possible danger of foods. Umami perception in the oral cavity is now recognized as a significant force in nutrition and health, as are the associated physiological effects of umami stimulations of T1R1/T1R3 and perhaps other receptors in the oral cavity and elsewhere in the body. The chapters in this book dramatically illustrate this, describing what we know and calling attention to what we still do not know about mysterious umami.

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Chapter 2
Umami and MSG

Ryusuke Yoshida and Yuzo Ninomiya

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).

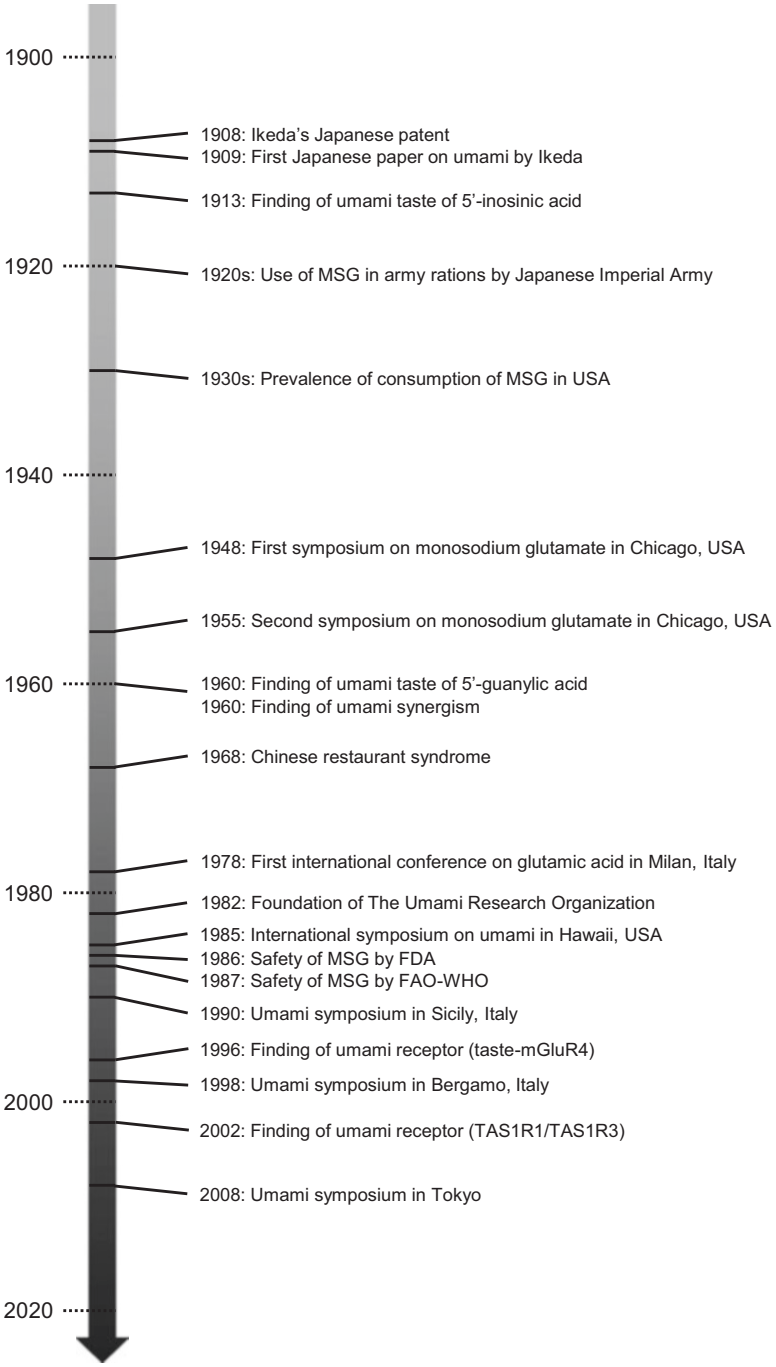

Fig. 2.2 The chronology of umami taste and monosodium L-glutamate

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

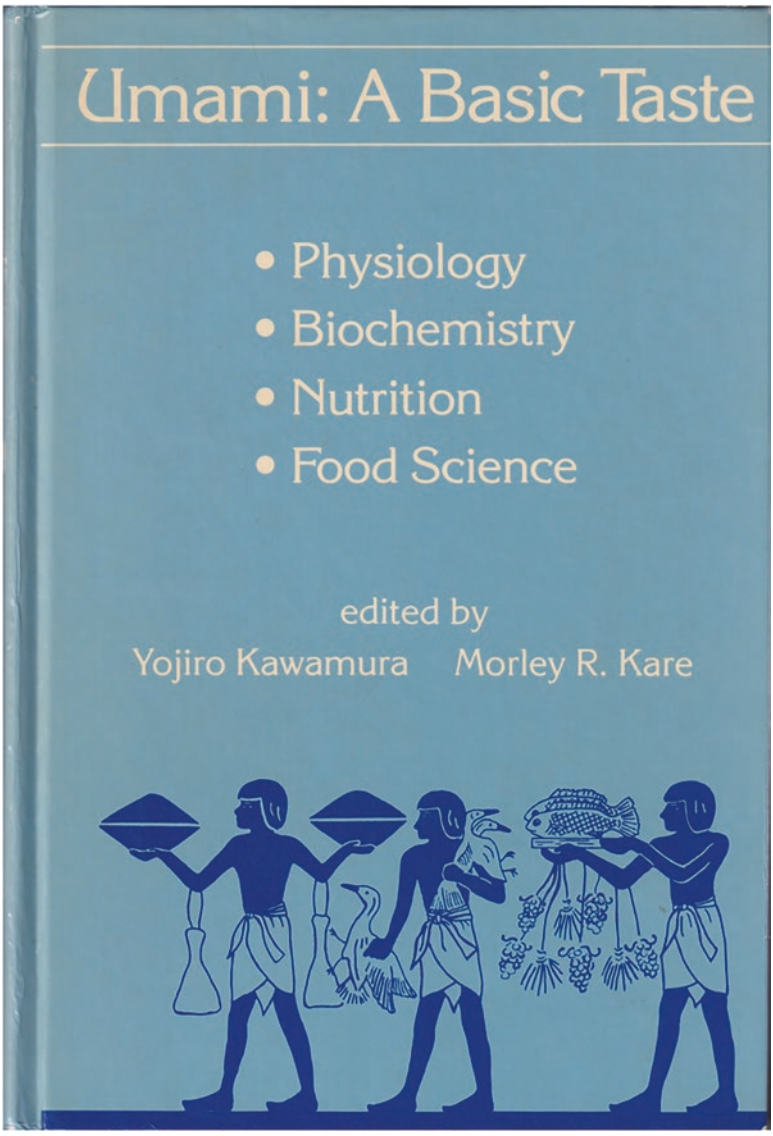

Fig. 2.3 Cover of the proceedings for the 1987 symposium "Umami: A Basic Taste"

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

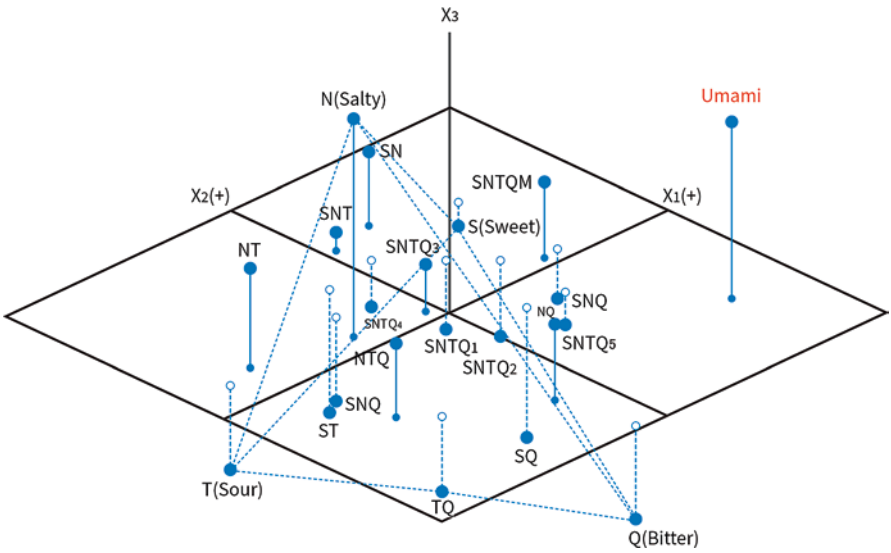

Fig. 2.4 Multidimensional scaling produced this three-dimensional representation of taste similarities among 21 taste stimuli (individually and as mixtures): S, sucrose, sweet; N, NaCl, salty; T, tartaric acid, sour; Q, quinine, bitter; and M, monosodium L-glutamate, umami. $SNTQ_{1–5}$ consist of different 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).

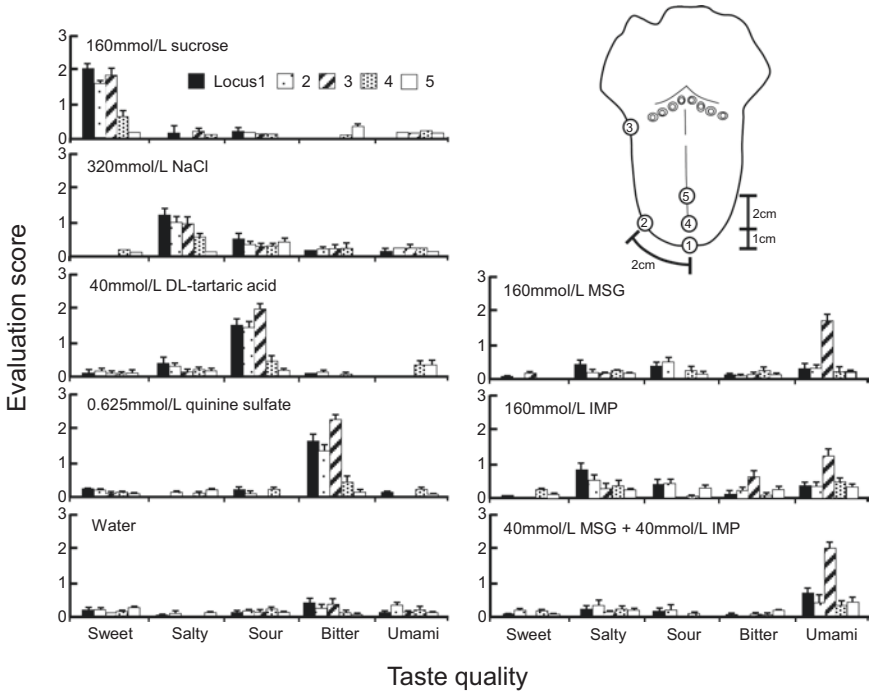

Fig. 2.5 Evaluation scores as mean certainty ratings (0 = none or uncertain, 1 = likely, 2 = fairly, 3 = absolutely) for each taste quality perceived for each taste stimulus at five loci of the tongue. Stimuli were taste solutions on a filter paper disk ($n = 30$). MSG, monosodium L-glutamate; IMP, inosine 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: $S = 15.50 \log_2(x/0.0943)$

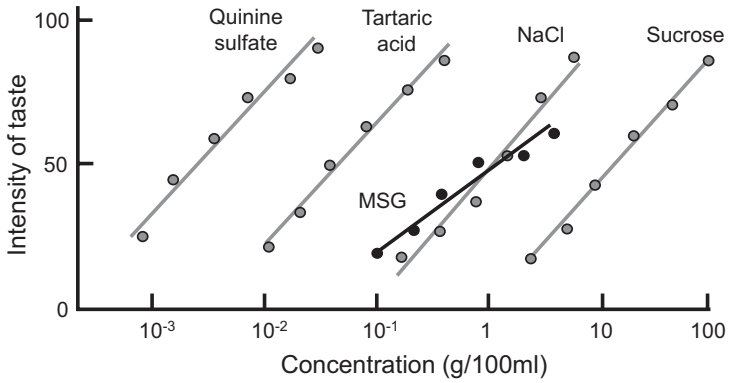

Fig. 2.6 Relationship between taste intensity and concentration. (Modified from Yamaguchi (1987))

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:

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

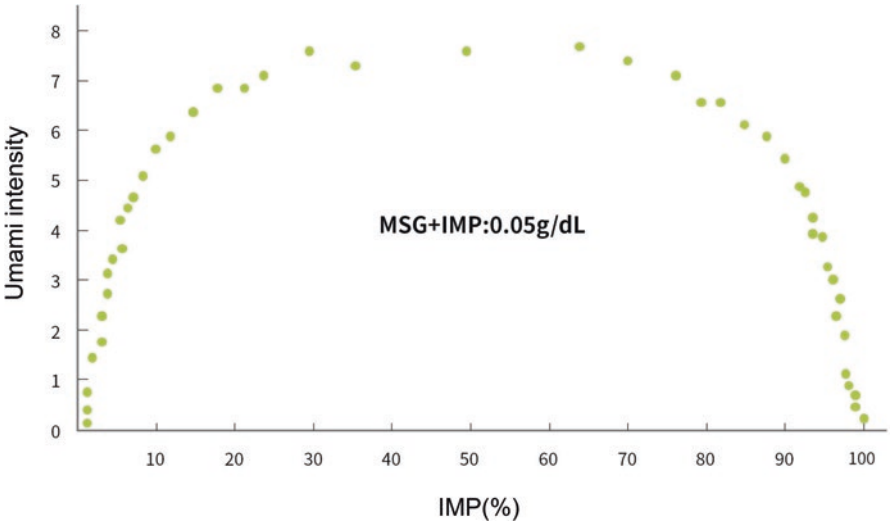

Fig. 2.7 Relationship between umami intensity and proportion of inosine 5′-monophosphate (IMP) in a mixture of monosodium L-glutamate (MSG) and IMP. (Image from Umami Information Center website, https://www.umamiinfo.jp/what/attraction/discovery/, modified from Yamaguchi (1967))

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

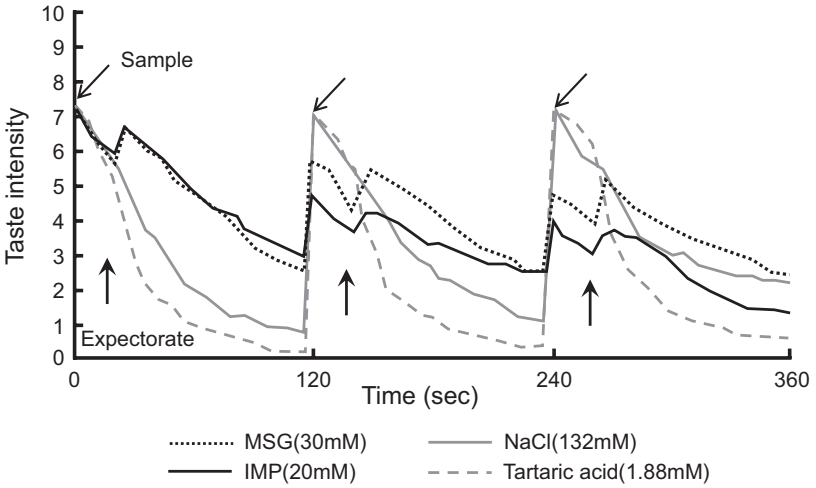

Fig. 2.8 Successive time-intensity curves in response to the umami taste of monosodium L-glutamate (MSG) and inosine 5′-monophosphate (IMP), the salty taste of NaCl, and the sour taste of tartaric acid. (Modified from Yamaguchi (1998))

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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Chapter 3
Umami Taste Signaling from the Taste Bud to Cortex

Eugene R. Delay and Stephen D. Roper

Umami is the meaty or savory taste evoked by certain amino acids present in foods, especially monosodium glutamate (MSG) (Fig. 3.1). It is now recognized as one of five (and possibly more) basic taste qualities that influence nutritional intake in a wide range of animals, including humans (Roper & Chaudhari, 2017). Umami taste is thought to signal the presence of dietary protein. In small quantities, MSG enhances flavor and increases the palatability of food and thus food intake. This effect gives umami a potentially important role in regulating nutritional balance and, consequently, in maintaining health (Bellisle, 1998, 1999). As a taste quality, umami has been recognized for over a century by Eastern cultures but only recently has been studied by Western society. As discussed below, MSG in Western society has had a checkered history as a taste stimulus and still is viewed by many as an unacceptable food additive. This history, however, triggered research that has advanced our understanding of the gustatory system, for example, identifying the first mammalian taste receptor (Chaudhari et al., 1996, 2000) and providing the basis for identifying cortical structures and their functions underlying cognitive systems that regulate food-directed behavior. Consequently, this chapter provides an overview of our understanding of the mechanisms by which umami taste stimuli are detected and subsequent signals are processed. This knowledge can be of fundamental importance to healthcare professions as well as to basic sciences.

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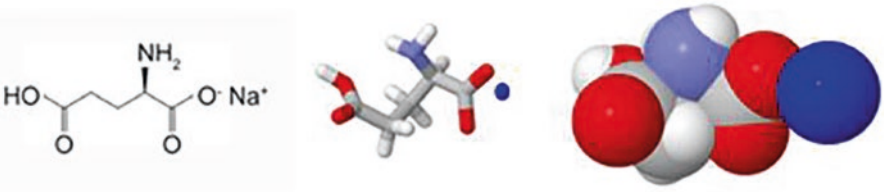

Fig. 3.1 Three different views of monosodium glutamate (MSG), showing a sodium ion (blue) near the bonding carboxylic acid. (Spacing-filling models from BioTopics. http://www.biotopics.co.uk/JmolApplet/gludisplayhalos.html)

3.1 A Brief History of Umami

Until the opening of the twentieth century, the history of umami was in the realm of culinary arts. The name *umami* itself did not yet exist. Kitchen lore included the use of seasonings, broths, mushrooms, meat and fish extracts, and other savory ingredients to enhance the palatability of prepared foods. Kikunae Ikeda, a distinguished food chemist working at Imperial University of Tokyo's College of Science at that time, conjectured that a fundamental taste quality was the basis for the savory or meaty taste sensation in fish, meat, and most notably, broth prepared from bonito or dried seaweed. Ikeda reasoned that this taste quality was distinct from the traditional four basic tastes: sweet, sour, salty, and bitter. He prepared aqueous extracts of dried seaweed, which he selected as the primary material because its protein content could readily be removed. After an extensive series of extractions to remove the unexpectedly high amounts of mannitol (200 g from 1 kg of dried seaweed) and the anticipated sodium chloride and potassium chloride from the seaweed extract, Ikeda was able to crystallize a miniscule amount of the amino acid glutamic acid. When he tasted a sample, it evoked a weak sourness along with a strong savory taste he named *umami* (Ikeda, 1909, 2002).

Glutamic acid (glutamate) was not unknown to food chemists at the time. This amino acid had first been isolated from wheat gluten (hence the name) in 1866 by H. Ritthausen. Previewing its later discovery by K. Ikeda as the prototypic umami stimulus, Ritthausen noted that glutamate elicits a unique "meaty" aftertaste: "…Entfernt an den Nachgeschmack einer geringen Menge von concentrirtem Fleischextract" ("[glutamate has]…somewhat of an aftertaste of a small amount of concentrated meat extract"; Ritthausen, 1866). Other chemists cataloged glutamic acid as having an unpalatable, weakly sour taste (Fischer, 1906). However, Ikeda recognized that the (neutral) sodium, potassium, and calcium salts of glutamic acid have an intense umami taste. In his remarkable 1909 paper, where he outlines his discovery of the savory taste umami, Ikeda commented that the preference for glutamate conceivably evolved with the consumption of meat, which always contains varying amounts of glutamate (Ikeda, 1909, 2002). He compared this with an evolution of sweet taste, which is imparted by sugars in nutritious vegetables and fruits.

According to the historian Jordan Sand (2005), Ikeda, who had been trained in Germany, was strongly influenced by Justus von Liebig, a leader in food chemistry. In 1840 von Liebig had extracted the essence of meat and invented a beef extract that later became the world-famous product Oxo. Sand mentions that von Liebig's beef extract "fed German armies" in the nineteenth century, and Oxo was widely used in military rations in World War I. Half a century later, after Ikeda had discovered, patented, and promoted MSG, this additive was also incorporated into military rations for the Japanese army and, after World War II, for US Armed Forces MREs (meals ready to eat). In 1952 MSG was included in the Marine Corps Recipe Manual (US Marine Corps, 1952) which, for example, listed the additive in a recipe for creamed beef (Fig. 3.2). Perhaps the use and acceptance of MSG in Western cuisine after World War II was influenced by young recruits consuming this flavor enhancer in their meals, though there is no hard evidence for this speculation (see, e.g., Geiling, 2013).

Ikeda was aware of the impact of his discovery of umami and its potential as a food seasoning, like von Liebig's meat extract. Indeed, he patented MSG in Japan, the United States, England, and France and began producing the substance as a seasoning named Ajinomoto (meaning "essence of *aji*" or "taste"). Ajinomoto, a.k.a. MSG, was fairly quickly accepted in Japan, which was undergoing a rapid cultural evolution in the early twentieth century. Initially, due to its cost, only the

RECIPE N0. - K-16
USMC RECIPE MANUAL
NAVMC 1067-SD

YIELD:	5 PORTIONS WEIGHT	5 PORTIONS MEASURE	10 PORTIONS WEIGHT	10 PORTIONS MEASURE	METHOD
INGREDIENTS					
Beef, ground	1-1/4 #		2-1/2 #		1. Cook meat in its own fat until brown, stirring frequently.
Onions, chopped	.8 oz.	3-1/4 Tbsp	1.6 oz.	6-1/2 Tbsp	
Bacon fat	.8 oz.	3-1/4 Tbsp	1.6 oz.	6-1/2 Tbsp	2. Cook onions in bacon fat, add flour and blend thoroughly.
Flour	1-1/4 oz.	4-3/4 Tbsp	2-1/2 oz.	9-1/2 Tbsp	3. Mix milk and beef stock and heat.
Milk, evaporated		1-1/2 Cup		3 Cup	4. Add hot milk mixture to fat and flour mixture. Heat to boiling point; boil 1
Beef stock for milk *		1-1/2 Cup		3 Cup	minute, stirring constantly. Add salt msg and pepper.
Salt	To taste	To taste	To taste	To taste	
Mono-sodium-glutamate		1 tsp		2 tsp	5. Pour sauce over meat, simmer until meat is well done but not overcooked.
Pepper, black	To taste	To taste	To taste	To taste	6. Serve over toast points or biscuits.

Fig. 3.2 Recipe for creamed beef from the *US Marine Corps Recipe Manual* (US Marine Corps, 1952), documenting use of MSG in US Armed Forces mess halls

wealthier segments of society could afford it. However, as the twentieth century progressed, women adopted a new domesticity geared toward scientific inventions and discoveries and were ready to accept Ajinomoto. With continued efforts to make MSG more affordable to the general population, in 1931 Ajinomoto was sold for the first time in containers equivalent to saltshakers that could be placed on a table (Sand, 2005).

Use of MSG was slower to reach the US market. However, ongoing scientific research in an entirely different area, neuroscience, was soon to make a discovery that put an indelible and, as has later been shown, an undeserved stigma on MSG. Researchers studying the effects of a number of agents on hereditary retinal dystrophy in rodents noticed that injecting monosodium glutamate into pregnant female mice resulted in damage to the inner retina (Lucas & Newhouse, 1957), with effects much more pronounced in the newborn mice than in the mothers. Further, parental injections of glutamine, quinine, epinephrine, methanol, and other compounds showed no similar retinal pathology. Because of the similarity between retinal cells and neurons in the central nervous system (CNS), these experiments were soon repeated by other laboratories focused on damage in the brain. A firestorm of claims and counterclaims ensued regarding whether and how MSG injections damaged brain tissue. Then in 1968, a letter appearing in the prestigious *New England Journal of Medicine* claimed that MSG, a seasoning commonly used in Chinese restaurants, seemed to cause "…numbness at the back of the neck, gradually radiating to both arms and the back, general weakness and palpitation" (Kwok, 1968). This became known as the "Chinese restaurant syndrome." Soon after, a pair of letters based on anecdotal experiences—one written by a group of second-year medical students—again in the *New England Journal of Medicine* stated that MSG was at the root of Chinese restaurant syndrome (Ambos et al., 1968; Schaumburg & Byck, 1968).[1] The students even proffered therapies: Atarax (hydroxyzine, an antihistamine), Librium (chlordiazepoxide, an anxiolytic), and atropine (a cholinergic receptor antagonist). A subsequent study by one of these groups published in the leading journal *Science* cited experimental evidence for MSG as the cause of Chinese restaurant syndrome (Schaumburg et al., 1969). This cemented the fate of MSG in the eyes of many, who were convinced that the seasoning was at the root of their bad experiences with oriental food. Subsequently, several organizations have conducted thorough and exhaustive investigations of the dangers of ingesting MSG. In each case, MSG was declared safe for consumption (e.g., Bellisle, 1999; US Food & Drug Administration, 2020). Moreover, the authenticity of the initial claim in the *New England Journal of Medicine* about MSG and the Chinese restaurant syndrome has been disputed (Blanding, 2019; Glass, 2019). Despite all this, and against overwhelming evidence for its safety, the questionable reputation of MSG lingers on in the eyes of many consumers.

[1] Interestingly, regarding Chinese restaurant syndrome, the lead author of one of these publications had only a few weeks previously (and in the same journal) explicitly stated, "I don't think the cause is soy sauce or monosodium glutamate" (Schaumburg, 1968).

What is indisputable, however, is that the sodium salt of L-glutamate (MSG) is found naturally in abundance in many common foods, such as cheeses (especially Parmesan cheese), meats, fish, and vegetables (such as tomatoes, mushrooms, eggplant). Also, it is unassailable that MSG, especially in combination with other foods, is a preferred taste for humans and other animals. Thus, the history of umami is not one of the discoveries of a new taste but the story of how an existing taste has been identified, popularized, scrutinized, and criticized.

3.2 Umami Psychophysics: Humans and Rodents

Research has given us some understanding of the psychophysical properties of umami taste that gives it the ability to influence ingestive behavior and nutritional regulation. Among the most fundamental properties of a sensory system is its sensitivity to stimulus intensity. In taste, *detection thresholds* establish the minimum intensity (concentration) at which the presence of a substance can be sensed. Knowledge of detection thresholds provides important standards for diagnosing chemosensory disorders and studying physiological and molecular mechanisms.

In general, detection thresholds for glutamate appear to average between 0.5 and 2 mM in human adults (Yamaguchi & Kimizula, 1979; Schiffman et al., 1981), which is unaffected by the concentration of sodium (Na^+) (Yamaguchi, 1991). Monopotassium glutamate and monosodium aspartate, which are also umami compounds (Maga, 1983), have similar detection thresholds (Schiffman et al., 1981; Yamaguchi, 1991).

Inosine 5′-monophosphate (IMP) and 5′-guanosine monophosphate (GMP), which are catabolic products of nucleic acids that are often found alongside glutamate in many meats and vegetables, are also flavor enhancers that elicit an umami sensation. The detection threshold for IMP (a disodium salt) is in the same range as that for MSG, but unlike MSG, its value is affected by the presence of Na^+ (Yamaguchi, 1991). Mixtures of MSG plus IMP or GMP are synergistic, that is, are capable of reciprocal increases in sensitivity. Indeed, one of the defining properties of umami taste is a synergy between MSG and IMP or GMP (Yamaguchi & Kimizula, 1979). Either nucleotide can intensify the umami sensation of MSG and other amino acids in a nonlinear manner (Rifkin & Bartoshuk, 1980; Yamaguchi, 1991; Kawai et al., 2002). Subthreshold concentrations of IMP lower the detection threshold for MSG taste by nearly 100-fold, and conversely, the threshold of IMP is lowered by MSG (Yamaguchi, 1991).

Another important property of sensory systems is *recognition threshold*, the minimum intensity at which a stimulus can be identified, not merely detected, and begins to exert motivating influences over behavior (Halpern, 1997). Recognition thresholds typically are higher than detection thresholds. Yamaguchi (1991) found that about 50% of subjects were able to identify the umami taste of MSG at a concentration twice its detection threshold. In contrast, identifying the umami taste of IMP required a concentration four times its detection threshold. In comparison,

recognizing the salty taste of NaCl required concentrations more than ten times its detection threshold. As might be expected, mixing MSG and IMP significantly lowers the recognition threshold for umami (Shigemura et al., 2009). It may be important to note that the concentration of glutamate and IMP in natural products varies widely, from below to well above recognition thresholds (Giacometti, 1979; Ninomiya, 2003). Moreover, either compound might influence taste perception by interacting with yet other food substances at or near recognition thresholds. An important consideration is that genetic variations in umami taste receptors appear to directly affect sensitivity and recognition thresholds for umami compounds in humans and mice (Raliou et al., 2009; Shigemura et al., 2009).

Evidence from a variety of sources supports Ikeda's initial observation that glutamate elicits a unique taste quality (Ikeda, 1909, 2002). For example, human subjects use different verbal qualifiers to describe glutamate taste compared to the other four basic tastes (Yamaguchi, 1991; Hettinger et al., 1996). This effect crosses cultural boundaries (Yamaguchi, 1991; Prescott, 1998). Interestingly, MSG and other umami compounds at concentrations found in food additives are hedonically positive and are typically described as "savory" or "meaty," but high concentrations of MSG alone are not preferred by humans (Schiffman et al., 1981; Okiyama & Beauchamp, 1998).

The perceived taste of glutamate salts is often complex due to the presence of sodium or other cations. The most important attribute of glutamate and other umami compounds in fact may be their ability to enhance the palatability of other food components. When added to solutions containing compounds that elicit a single basic taste (e.g., sucrose/sweet or quinine/bitter), MSG has little effect on the quality or intensity of the taste (Yamaguchi & Kimizula, 1979). However, when MSG is added to soup broth, potatoes, or other food items, subjects find them much more palatable and exhibit eating behaviors consistent with an increase in hedonic value (e.g., increase eating rates or shorter between-bite pauses), especially if paired with a novel flavor or with the odor of a savory vegetable (Bellisle & Le Magnen, 1981; Rogers & Blundell, 1990; Okiyama & Beauchamp, 1998; Prescott & Young, 2002; Prescott, 2004; McCabe & Rolls, 2007).

Studying perceptual experiences of nonhuman animals is a challenging but important endeavor for chemoreception sciences. Much of our understanding of cellular and molecular mechanisms of taste transduction, including umami taste, is based on research with nonhuman species. Direct comparisons with human perceptual experiences are difficult at best, but a number of methods have been used to develop psychophysical profiles of gustatory phenomena (e.g., Spector, 2003). Comparing taste profiles from animal studies with human taste profiles for the same umami substances reveals striking similarities and some important species-specific characteristics. Taste sensitivity of rodents for glutamate and L-aspartate is comparable to that of humans. For example, detection thresholds are between 1 and 4 mM for rats (Stapleton et al., 2002; Taylor-Burds et al., 2004) and between 0.01 and

2.5 mM for mice[2] (Stapleton et al., 2002; Mukherjee & Delay, 2011). Recognition threshold in rats for glutamate taste is between 5 and 10 mM (Yamamoto et al., 1991; Chaudhari et al., 1996; Stapleton et al., 1999; Heyer et al., 2003), whereas mice have slightly higher thresholds. Interestingly, at low, near-threshold concentrations of MSG, rodents can confuse the taste of glutamate with sucrose (Yamamoto et al., 1991; Chaudhari et al., 1996; Stapleton et al., 1999; Heyer et al., 2003). Rats and mice generally show a natural preference (positive valence) for MSG, IMP, and other L-amino acids, even at concentrations that humans find unpleasant (Pritchard & Scott, 1982; Iwasaki et al., 1985; Delay et al., 2000; Ruiz et al., 2003; Wifall et al., 2007), although some of this may be related to postingestive effects (Ackroff & Sclafani, 2016). The perceptual uniqueness of MSG has been demonstrated in mice, which did not generalize a conditioned taste aversion between MSG and the other four basic tastes (Ninomiya & Funakoshi, 1987). Synergy between MSG and IMP in rats has also been reported with brief-access taste tests (Yamamoto et al., 1991; Delay et al., 2000). In addition, it should be noted that detection thresholds for a number of umami stimuli can be influenced by a variety of factors such as temperature, pH, age, diet, and other variables that also are important in food preparation and perception (Barragan et al., 2018; Green et al., 2016; Jeon et al., 2021; Ma et al., 2020; Zhong et al., 2015.

3.3 Overview of Tongue and Gustatory System

Taste sensations are generated in the oral cavity, primarily from taste buds on the tongue, and are transmitted to higher regions in the brain for analysis and interpretation. An overview of the gustatory system is shown in Fig. 3.3. Briefly, taste stimuli are transduced into afferent signals by specialized sensory cells in taste buds embedded in the oral epithelium. These gustatory sensory cells transmit these signals to primary sensory afferent fibers of cranial nerves 7, 9, and 10 (CN7, CN9, CN10, respectively) that project into the hindbrain to the nucleus of the solitary tract (NST). In rodents, afferent signals are then sent to the parabrachial nucleus (PBN) in the pontine area and from there to the ventroposterior medial parvicellular (VPMpc) nucleus of the thalamus or to subcortical structures in the lateral hypothalamus, amygdala, and other structures. Thalamic signals are then transmitted to the insular cortex and other cortical areas. In primates, neurons in the NST project to the thalamus and thalamic neurons project to neurons in the primary gustatory cortex, the frontal operculum/insula (FOI), where the ability to perceive tastes (e.g., sweet and bitter) is thought to occur. Subsequent processing

[2] Specifically, C57BL/J6 mice, a mouse strain often used for genetic manipulations such as gene deletions (knockout) or labeling of proteins involved in taste transduction. Different strains of mice have notoriously different taste thresholds (Bachmanov et al., 2016). Other researchers have reported different threshold estimates (Nakashima et al., 2012; Blonde et al., 2018; Smith & Spector, 2014).

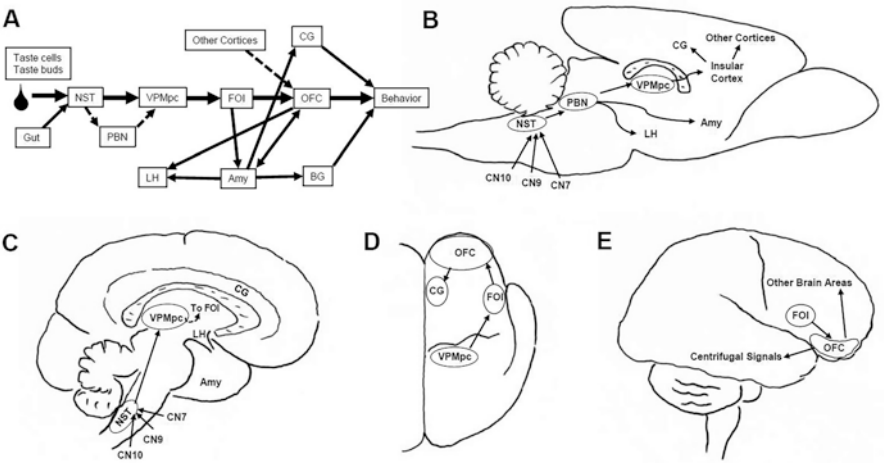

Fig. 3.3 Overview of rodent and human gustatory systems. (**a** and **b**) Schematic diagram of the major structures of the gustatory system (**a**), including sensory input from taste cells and taste buds and from the gut to the nucleus of the solitary tract (NST) and the principle ascending pathways to cortical and subcortical structures that influence taste-directed behavior. In the rodent (**b**), input from the tongue via cranial nerves 7, 9 and 10 (CN7, CN9, CN10) goes to the NST, whose output goes to the parabrachial nucleus (PBN) and then to the ventroposterior medial (parvicellular) (VPMpc) nucleus of the thalamus. Other subcortical structures, such as the lateral hypothalamus (LH) and amygdala (Amy), also receive taste information from the PBN. From the thalamus, taste information is then sent to the insular region of the cortex and to other cortical areas, such as the cingulate gyrus (CG). BG, basal ganglia; FOI, frontal operculum/insular area; OFC, orbitofrontal cortex. (**c**–**e**) Flow of taste signals from the cranial nerves to areas of the cortex that process and subsequently influence taste-directed behavior in humans. (**c**) A view of the medial aspects of the taste system showing the ascending flow of afferent signals through the NST to the VPMpc. (**d**) From a dorsal perspective of the right hemisphere, taste signals go from the VPMpc to the FOI, the primary taste cortex. These signals are then sent to the OFC and other cortical areas, such as the CG, and subcortical structures, such LH, Amy, or BG. (**e**) A lateral view of the right hemisphere with the approximate locations of the FOI and the OFC identified

by association cortices such as the orbitofrontal cortex (OFC) and cingulate gyrus (CG) contributes to higher-order cognitive processes involved in taste-directed behavior. In humans, it appears that umami taste signaling from the tongue to the cortex is predominantly ipsilateral (Iannilli et al., 2012). Below a fuller description of each step in the taste pathway is presented.

3.4 Receptors

The concept that there are specific cell-membrane binding sites for sweet—a glucophore-binding site (Shallenberger & Acree, 1967)—and for salt, a sodium receptor (Beidler, 1954), dominated ideas about a molecular basis of taste reception in the middle of the twentieth century. These ideas were generalized to other qualities such as the "acidophore" (a hydrated proton) receptor for sour (Shallenberger,

1993). Yet these concepts remained theoretical, and the actual identity of membrane surface molecules responsible for interacting with taste compounds was elusive. Only sometime later did researchers begin in earnest to study the molecular basis of umami taste, because of the lack of acceptance of umami as a separate, basic taste. Annick Faurion was an early pioneer in the efforts to identify umami receptors. She surmised that umami taste receptors may be akin to the newly characterized NMDA glutamate synaptic receptors found in the brain (Faurion, 1991). Initial efforts to test this experimentally suggested that there were indeed NMDA-like receptors in membranes isolated from fish lingual tissues rich in taste buds (Brand et al., 1991; Teeter et al., 1992), but pinpointing the results specifically to taste cells was not possible in those experiments.

A major breakthrough occurred when metabotropic synaptic glutamate receptors (G-protein-coupled receptors, GPCRs) were cloned and identified in the brain (Houamed et al., 1991; Masu et al., 1991). There was reason to believe that taste transduction might involve GPCRs because of the early efforts of Naim et al. (1991) showing that in taste tissues, sweet taste generated cAMP, a key second messenger for many GPCRs. Additionally, a taste-specific Gα protein had been cloned and characterized (McLaughlin et al., 1992), reinforcing the notion that taste involved GPCRs. By analogy, it was believed that umami taste might also involve GPCRs. Chaudhari and colleagues identified a novel, truncated metabotropic synaptic glutamate receptor, taste-mGluR4, in rat taste buds and postulated that this molecule might serve as an umami receptor (Chaudhari et al., 1996, 2000). Taste-mGluR4 fit all the requirements for a candidate taste receptor: (a) it was present selectively in a small subset of taste bud cells (Chaudhari & Roper, 1998; Yang et al., 1999), and (b) when expressed in a heterologous cell line (CHO cells), the receptor conferred glutamate sensitivity at taste-appropriate concentrations (Chaudhari et al., 2000). mGluR4 knockout (KO) mice (mutant mice lacking a functional mGluR4 gene) showed abnormal glutamate taste behavior, but the results were enigmatic: they had reduced taste nerve responses to MSG compared to wild-type mice (Yasumatsu et al., 2015) but showed increased, not decreased, preference for umami taste solutions (Chaudhari & Roper, 1998). This taste behavior in mGluR4 KO mice could perhaps be interpreted as due to a decline or muting in umami taste sensations, driving the mutant mice to consume more of the solution to obtain reinforcement. Yet, interpreting the effects of a global knockout (mGluR4 KO mice) is complicated by the fact that this receptor has widespread functions in neural circuitry in the brain; its deletion likely affects many cognitive processes, not merely gustation.

Soon after the discovery of taste-mGluR4, other taste-specific umami receptors were cloned and identified in mouse taste buds. These receptors were also GPCRs and consisted of two different gene products, T1R1 and T1R3, combined into a heterodimer (Nelson et al., 2002; Zhao et al., 2003). The T1R1 + T1R3 heterodimer had similar properties to taste-mGluR4: the molecules were found in a subset of gustatory receptor cells, and expression in heterologous cells conferred sensitivity to glutamate and other amino acids. Importantly, Zhao et al. (2003) reported that mice lacking T1R1, T1R3, or the T1R1 + T1R3 receptor heterodimer were taste blind to MSG. However, these findings have been challenged. T1R3 KO mice had only slightly elevated MSG detection thresholds (Damak et al., 2003; Delay et al.,

2006), challenging the notion that T1R1 + T1R3 receptor heterodimers are the only umami taste receptors and supporting important roles for mGluR4 and other glutamate receptors in umami taste (Yasuo et al., 2008; Delay et al., 2009; Yasumatsu et al., 2009; Kusuhara et al., 2013; Blonde & Spector, 2017; Blonde et al., 2018).

More recently, another candidate umami receptor, a truncated form of the metabotropic glutamate 1 receptor, taste-mGluR1, has emerged (San Gabriel et al., 2005; San Gabriel et al., 2009). Mutant mice lacking mGluR1 have not yet been tested for taste behavior, but the interpretation of these data would be subject to the same reservations as for taste behavior assays in mGluR4 KO mice: mGluR1 is an important synaptic receptor in the brain, and behavioral alterations might be widespread in mGluR1 KO mice, as was described above for mGluR4 global knockout.

In summary, at least four different candidate umami taste receptors have been put forward: NMDA-like, taste-mGluR4, taste-mGluR1, and the T1R1 + T1R3 heterodimer. No strong experimental evidence for NMDA-like umami receptors in taste buds has yet been found, and the bulk of evidence favors the other three receptor candidates.[3] Thus, multiple receptors—T1R1 + T1R3, mGluR1, and mGluR4—may underlie umami taste.

3.5 Structure and Function of Umami Receptors

All the receptors identified to date for umami taste transduction are class C GPCRs. This class of GPCRs is characterized by an extensive extracellular domain, constitutive dimerization, and an unusual N-terminal bilobed ligand-binding region that resembles a Venus flytrap, hence its name: the Venus flytrap (VFT) domain. By analogy with the sweet taste receptor heterodimer, T1R2 + T1R3 (Nelson et al., 2001), T1R umami receptors were shown to be heterodimers of T1R1 + T1R3 (Li et al., 2002; Nelson et al., 2002) (Fig. 3.4). Further, by analogy with synaptic mGluRs, the glutamate binding site for T1R1 + T1R3 was shown to reside in the VFT domain of T1R1 (Zhang et al., 2008; Lopez Cascales et al., 2010; Roura et al., 2011; Toda et al., 2013). IMP interacts with a nearby site to stabilize the closed and active VFT domain occupied by glutamate (Zhang et al., 2008), explaining the ability of IMP to enhance umami taste. Compounds that bind to a transmembrane region of T1R3 also modify umami taste. Examples include lactisole, a sweet taste inhibitor that interferes with umami taste (Xu et al., 2004), and cyclamate, an artificial sweetener that enhances umami responses (Zhang et al., 2008).

[3] Ionotropic glutamate receptors, including NMDA receptors, are expressed on one of the types of taste bud cells (specifically, Type III cells—those that respond to sour taste; Roper & Chaudhari, 2017). However, instead of participating in the initial transduction of glutamate taste, these receptors appear to be involved in signal processing and feedback synaptic circuitry within taste buds (Vandenbeuch et al., 2010; Huang et al., 2012). The presence of these synaptic glutamate receptors may explain early reports claiming the expression of NMDA receptors in taste buds as evidence for umami transduction via these receptors.

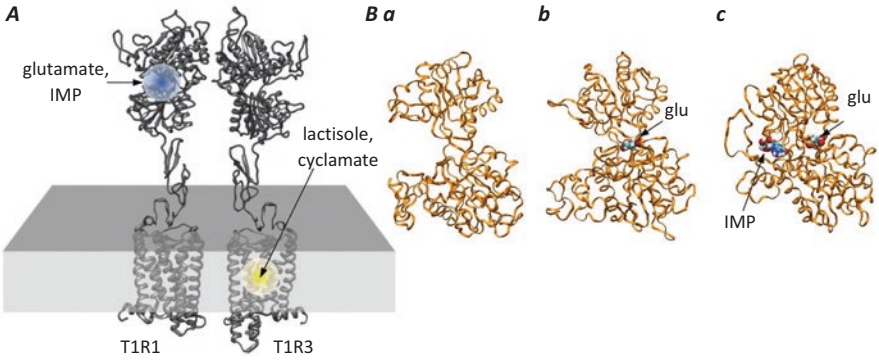

Fig. 3.4 T1R1 + T1R3 heterodimer umami taste receptor. (**a**) Glutamate and IMP bind to the large extracellular Venus flytrap domain of T1R1 in the dimeric umami taste receptor. (Modified from Laffitte, Neiers et al., 2014; Roper, 2020). (**b**) Molecular mechanism of the umami receptor: ribbon-band representation of the Venus flytrap motif on the T1R1 + T1R3 umami receptor in three situations—no bound ligands (*a*), binding of glutamate (glu) (*b*), and binding of both glutamate and GMP (*c*). (Modified from Mouritsen et al. (2013))

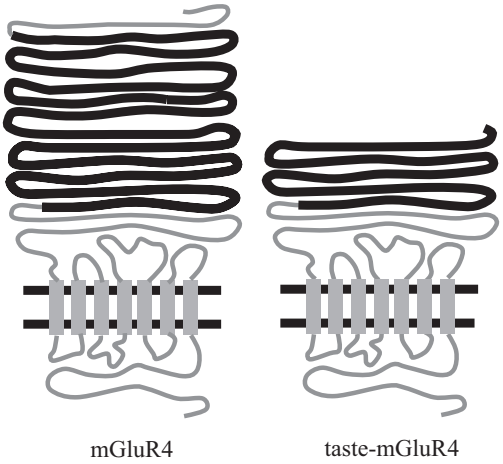

Fig. 3.5 The mGluR umami taste receptor (right) is a truncated splice variant of synaptic mGluR (left). The heavy black line shows the Venus flytrap motif, significantly truncated in taste-mGluR4. (From Chaudhari et al. (2000))

As noted above, the metabotropic umami receptors mGluR1 and mGluR4 found in taste buds are class C GPCRs. These umami taste receptors are distinct from their synaptic glutamate receptor equivalents. Specifically, taste-mGluR1 and taste-mGluR4 umami receptors are N-terminal truncated variants of synaptic mGluR1 and mGluR4 receptors (Fig. 3.5). Interestingly, the truncation eliminates about half the VFT domain, the known glutamate binding region for synaptic mGluRs (O'Hara et al., 1993). Structure-function analyses of glutamate binding domain(s) have not been carried out for taste-mGluR1 or taste-mGluR4. Much less is known about

whether and how MSG activates these mGluR umami receptors. Further, although synaptic mGluRs form dimers (Kunishima et al., 2000), it is not known whether the mGluR1 or mGluR4 umami taste receptor does so.

3.6 Downstream Signaling

Signal transduction downstream of the T1R1 + T1R3 umami receptor follows the canonical GPCR-inositol trisphosphate (IP3)-intracellular Ca^{2+} release pathway, extensively documented in a number of excellent reviews on taste (Kinnamon, 2009; Roper & Chaudhari, 2017; Kinnamon & Finger, 2019; Roper, 2020; Gutierrez & Simon, 2021) (Fig. 3.6). The transduction cascade is initiated by glutamate binding to T1R1 + T1R3 on taste bud umami-sensing cells (specifically, type II taste cells, as distinct from type I glial-like taste cells and type III sour-sensing taste cells; see Roper & Chaudhari, 2017) activating G-proteins, initiating intracellular Ca^{2+} release, which activates TRPM4 and TRPM5 cation channels. The depolarization produced by cation influx through these channels triggers action potentials in the cell, which opens large-pore CALHM 1 and 3 ion channels that allow the release of ATP, the principal type II cell transmitter Finger et al., 2005; Ma et al., 2018).[4]

Early studies also implicated a role for cAMP in the umami transduction pathway. Glutamate stimulation of taste tissue decreases cAMP (Abaffy et al., 2003), and genetically engineered mice lacking Gα gustducin, the G-protein that couples taste GPCRs to cAMP metabolism, have diminished taste responses to glutamate (He et al., 2004). The rather convoluted concept that has evolved (Clapp et al., 2008) (Fig. 3.6, gray arrows) is that cAMP inhibits key steps in the above canonical IP3 pathway and gustducin tonically activates cAMP-dependent phosphodiesterase to maintain cytosolic cAMP at a low level (McLaughlin et al., 1994). In this way, gustducin maintains both phospholipase C β2 (PLCβ2) and inositol 1,4,5-trisphosphate receptor, type 3 (IP3R3), in a primed and ready state (Clapp et al., 2008).

Curiously, little is yet known regarding umami transduction pathways initiated by taste-mGluR1 and taste-mGluR4. This is an area of research that remains to be developed.

3.7 Cranial Nerve Responses to Umami

Study of the afferent pathway gives us some novel insights into the encoding process of umami substances. Taste buds are innervated by three cranial nerves: the facial (CN7), glossopharyngeal (CN9), and vagus (CN10) nerves. Two branches of

[4] Interestingly, unlike synaptic release elsewhere in the nervous system, ATP release in type II cells is nonvesicular and involves only depolarization-activated CaHLM1/3 channels, independent of intracellular Ca^{2+} (Nomura et al., 2020). Indeed, type II taste bud cells lack voltage-gated calcium channels (Clapp et al., 2006).

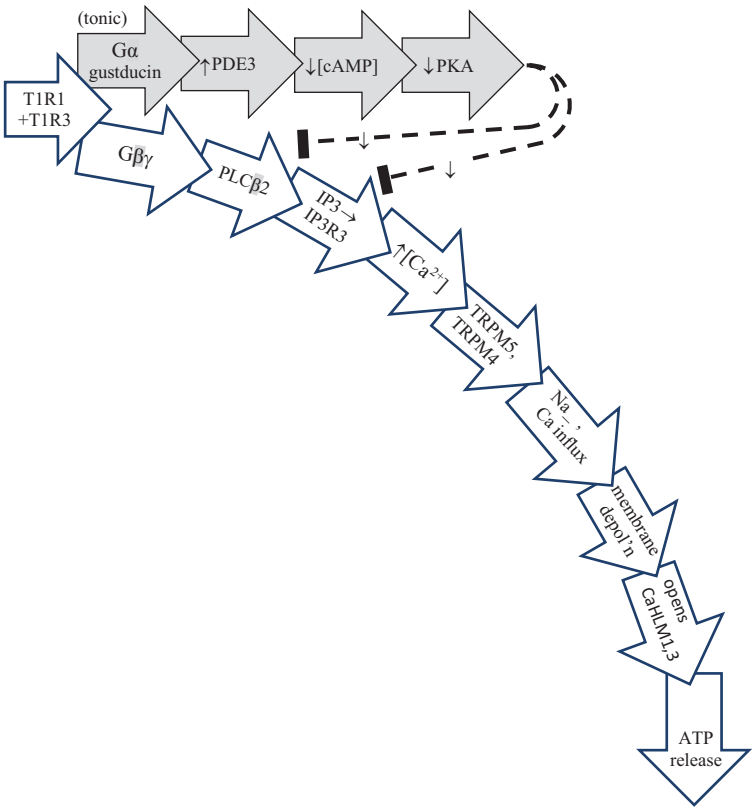

Fig. 3.6 Representation of the canonical G-protein-coupled receptor chemosensory transduction cascade. Open arrows symbolize the pathway for G-protein activation that leads to intracellular Ca^{2+} mobilization, depolarization (depol'n), and neurotransmitter (ATP) release. Gray arrows at the top depict the constitutive (tonically active) Gα gustducin pathway that results in downregulation of protein kinase A (PKA). Tonic activation of this pathway disinhibits key elements of the canonical pathway: phospholipase C β2 (PLCβ2) and inositol 1,4,5-trisphosphate receptor, type 3 (IP3R3). The signal(s) that maintains constitutive Gα gustducin activation is unknown, though taste receptor stimulation is one likely contributor (Clapp et al., 2008). PDE3, phosphodiesterase 3; IP3, inositol trisphosphate; TRPM4 and TRPM5, transient receptor potential cation channel subfamily M, members 4 and 5; CALHM1, 3, calcium homeostasis modulator 1 and 3. (Modified from Roper (2020))

the facial nerve, the chorda tympani and the greater superficial petrosal, innervate taste buds in the anterior portion of the oral cavity. The chorda tympani innervates fungiform papillae on the anterior two-thirds of the tongue and some taste buds in foliate papillae on the lateral tongue. The greater superficial petrosal innervates taste buds in the soft palate. The glossopharyngeal nerve innervates the posterior third of the tongue, including taste buds in the circumvallate papillae and some in the foliate papillae. The vagus nerve innervates taste buds and solitary chemoreceptors in the posterior oral cavity and throat. All of these fibers synapse in the NST, which relays information to other structures of the CNS.

Whole-nerve and single-fiber recordings from gustatory nerves have provided abundant evidence clarifying how umami taste signals are handled by the nervous system. Early investigators demonstrated the synergistic interaction between MSG and a number of 5′-ribonucleotides in rat with whole-nerve (Adachi, 1964) and single-fiber (Sato et al., 1970) recordings of the chorda tympani. More recently, Sako et al. (2000) found that the response to MSG was similar in the greater superficial petrosal nerve and the chorda tympani of rats, including synergistic responding to mixtures of MSG and IMP. In contrast, the glossopharyngeal nerve appears to carry a smaller umami signal, with little or no evidence of MSG-IMP synergy. The greater contribution of the chorda tympani and the greater superficial petrosal nerves for umami signaling were verified by the finding that rats with transections of chorda tympani and superficial petrosal nerves were unable to learn a conditioned taste aversion to MSG mixed with IMP to the same degree of rats with transaction of both the glossopharyngeal and either of the other nerves (Ninomiya & Funakoshi, 1987, 1989). Nonetheless, the importance of this smaller glossopharyngeal signal should not be ignored. If the glossopharyngeal nerve is transected, mice conditioned to avoid MSG cannot distinguish MSG from NaCl (Ninomiya & Funakoshi, 1987, 1989), suggesting that the glossopharyngeal nerve also transmits important qualitative information about glutamate taste.

Early research using whole-nerve recording methods found that MSG and other umami substances elicited strong responses in the chorda tympani, quite similar to responses elicited by sucrose (e.g., Sato et al., 1970) or NaCl (Yamamoto et al., 1991). At this time, the overlap in nerve responses to umami, NaCl, and sucrose raised questions about whether umami was a basic taste or simply a combination of sucrose and NaCl activity. This forced researchers to compare glutamate responses to those elicited by NaCl and sucrose to identify any unique effect attributable only to glutamate. Single-fiber recording studies and the reduction of responses by the sodium inhibitor amiloride and by sweet taste inhibitors have helped researchers parse the components of MSG-evoked whole-nerve responses. Single-fiber recording studies have searched for fibers that respond best to MSG and other umami substances (so-called M-best fibers), but evidence of these fibers has been slow to accumulate because these studies have often encountered fibers that appear to carry signals for MSG as well as for sucrose or NaCl, especially in the chorda tympani. Moreover, the population of M-best fibers appears to be much smaller than that for sweet (S-best fibers) or salt (N-best fibers) stimuli. Nevertheless, there is now evidence of M-best fibers in several species, such as mouse, rat, pig, dog, and chimpanzee (Danilova et al., 1999; Hellekant et al., 1997; Kumazawa et al., 1991; Ninomiya & Funakoshi, 1987, 1989), but not in hamsters (Yamamoto et al., 1988). M-best fibers respond to MSG and do not respond to sucrose. They also often show synergy between MSG (or monopotassium glutamate) and either IMP or GMP.

While evidence of M-best fibers accumulated slowly, evidence that signaling of umami stimuli also involves nerve fibers that respond to sucrose was discovered in early studies (Sato et al., 1970; Ninomiya & Funakoshi, 1987, 1989), which probably explains why rodents often have difficulty discriminating sucrose and glutamate at lower concentrations (Yamamoto et al., 1991; Stapleton et al., 2002; Heyer et al., 2003). Four fiber types in the chorda tympani of mice have been identified

based on their responses to sucrose and monopotassium glutamate and evidence of synergy when IMP is mixed with glutamate (Yasumatsu et al., 2012, 2015): M-best fibers exhibit synergy (M1 fibers) or not (M2 fibers), and sucrose-best fibers exhibit synergy (S1 fibers) or not (S2 fibers) when stimulated with monopotassium glutamate and IMP. Subsequent studies using an array of sweet inhibitors and glutamate agonists and antagonists determined that each fiber type appears to be activated by a specific set of taste receptors: S1 and S2 fibers are activated by T1R receptors, M1 fibers are activated by mGluR1 receptors, and M2 fibers are activated by mGluR4 receptors (Yasumatsu et al., 2012, 2015). Thus, the density of each receptor family along the anterior-posterior dimension of the tongue appears to influence the nature of glutamate responses within each nerve.

Lastly, in mice, recordings from geniculate ganglion neurons that innervate taste buds on the anterior tongue and soft palate reveal a small population of sensory neurons that respond exclusively to MSG, presumably representing the parent neurons of M-best fibers (Barretto et al., 2015; Wu et al., 2015).[5] However, hierarchical clustering of the geniculate ganglion neurons showed a good deal of overlap and no clean separation between clusters of sucrose- and MSG-responding sensory neurons (Wu et al., 2015), reinforcing the similarity between sucrose and umami tastes, at least in rodents, and the involvement of the T1R3 monomer that is common to both sweet and umami taste receptors.

3.8 Nucleus of the Solitary Tract and Parabrachial Nucleus

Far fewer studies have examined the response of CNS neurons to MSG, and most of these studies have been conducted in rats and mice. These have often compared response patterns of neurons to equimolar concentrations of NaCl, sucrose, and MSG. The most illuminating of these studies have used the salt taste inhibitor amiloride to help dissociate the responses of Na^+ and the glutamate anion. Neural responses to umami substances from neurons located in the NST have received some attention. In the rat, neuronal responses to 0.1 M MSG were quite similar to responses elicited by 0.1 M NaCl (Giza & Scott, 1991; Giza et al., 1996, 1997). However, the addition of amiloride reduced the overall response to NaCl and changed neuronal response profiles more for NaCl than for MSG, presumably due to a glutamate anion signal that is unaltered by the presence of amiloride. Interestingly, profiles of neural responses in the NST of rats revealed differences in temporal coding between sucrose and MSG taste stimuli in awake and behaving rats (Roussin et al., 2012). This suggests that brain stem coding and transmission of taste qualities of umami, NaCl, and sucrose may be accomplished by overlapping populations of neurons but qualitatively distinguished by more subtle properties in the train of action potentials.

[5] Neither of these studies attempted to differentiate M1 and M2 responses. These studies used a mixture of IMP with MSG (Wu et al., 2015) or monopotassium glutamate (Barretto et al., 2015).

The gustatory portion of the NST projects to the medial PBN in the rodent (Norgren, 1978). In the rat, neurons in the medial PBN do not exhibit as strong a relationship in their response to NaCl plus MSG or to sucrose plus MSG as do neurons in the NST, suggesting more dissociation in the pathways carrying the afferent signals for these stimuli (Nishijo et al., 1991). In the mouse PBN, sucrose and umami signals appear to be processed more medially, whereas signals for other basic tastes are processed more laterally (Tokita et al., 2012). Even so, evidence of overlapping taste signals for sucrose, umami, and NaCl has been observed. Many of the medially located neurons identified as sucrose-best neurons also show stronger, synergistic responses to mixtures of monopotassium glutamate and IMP, indicating convergence of glutamate taste signals with sucrose within the brain stem (Tokita & Boughter Jr., 2016; Tokita et al., 2012). These investigators, however, did not screen for glutamate-best neurons to determine if a similar convergence of sucrose signaling on umami-best cells also occurs.

Currently, our understanding of neural processing of umami taste stimuli in the NST and PBN in rodents is limited. For example, besides taste perceptual functions, the NST and PBN are involved in post-ingestive effects of umami capable of directing behavior. However, little is known about how these structures contribute to post-ingestive effects or if their perceptual and nonperceptual functions overlap. This analysis may require experimentally distinguishing neural responses to umami, sucrose, and NaCl to determine the presence or absence of glutamate-IMP synergism. In addition, more precise analysis of the specific characteristics of taste-evoked responses in the NST and PBN of awake and behaving animals, such as those described by Roussin, D'Agostino et al. (Roussin et al., 2012), may be needed to better understand how umami taste is distinguished from other taste stimuli in the brain stem.

3.9 Thalamus

A dissociation between signaling of NaCl and MSG was reported for neuronal responses recorded from the ventroposterior medial parvicellular (VPMpc) nucleus of the thalamus when studied using amiloride to reduce the contribution from Na^+ taste (Tokita & Boughter Jr., 2012). The addition of amiloride reduces the similarity in response profiles of these neurons to NaCl and MSG but has no effect on the relatively weak correlations between MSG and other basic tastes such as sweet (Verhagen et al., 2005). Thus, the greater impact of amiloride on NaCl responses than on MSG responses suggests that glutamate signaling may follow a channel separate from that for sodium. Neural fMRI (functional magnetic resonance imaging) data also suggest that umami and salty taste sensations are processed somewhat differently in the thalamus of humans (Iannilli et al., 2012; Han et al., 2018). Whether such differences between sweet and glutamate signaling also exist has not yet been adequately tested.

3.10 Forebrain

Responses of the FOI, the primary gustatory cortex (see Fig. 3.3), to umami stimuli are of particular interest, because generally this is considered where quality-intensity discriminations are made, at least in monkeys and humans. Much of the earlier work on cortical responses to umami was in nonhuman primates, primarily macaque monkeys (Scott et al., 1986; Scott & Plata-Salaman, 1999; Scott et al., 2001). Baylis and Rolls (1991) reported finding neurons in the macaque primary taste cortex and caudolateral OFC (a secondary taste cortex) that responded best to glutamate. These glutamate-best neurons were of approximately the same number and exhibited similar responsiveness to glutamate as neurons tuned to respond to glucose or any of the other basic tastes. Moreover, responses in these glutamate-best cells did not correlate well with responses to NaCl or sucrose. In the macaque caudolateral OFC, cortical cells exhibited response profiles for MSG independent of NaCl or any of the other basic tastes (Baylis & Rolls, 1991; Rolls & Baylis, 1994). Moreover, evaluation of the reward value and pleasantness of umami stimuli appears to occur in the OFC.

In rats and mice, recent studies of gustatory cortex have capitalized on innovative methods to relate neural responding with behavior. A two-photon imaging study detected discrete areas within insula layers 2 and 3 that responded to discrete stimuli, including umami (Chen et al., 2011). Stapleton et al. (2002), using temporal assays of cortical responses to taste stimuli with multielectrode arrays of gustatory cortex while a rat performed a simple taste discrimination, found that individual cortical neurons responded to MSG stimulation with action potential patterns discernable from responses to sucrose, NaCl, or other stimuli. Moreover, in some cases, the responses to these stimuli were in the opposite direction. For example, even though a cortical cell increased its firing rate to increasing concentrations of MSG, the same cell could show a decrease in response to increasing concentrations of sucrose. Similar temporal analyses of gustatory nerves and brain stem structures may reveal further differences between umami taste signaling and other basic tastes in the rodent.

In humans, fMRI has also revealed that umami stimuli can activate unique areas of the human FOI, as well as areas shared with other basic tastes. In studies comparing MSG with NaCl and other taste stimuli, significantly different activation patterns in the FOI were evoked by umami, NaCl, and sucrose stimuli (Han et al., 2018; Singh et al., 2011; Prinster et al., 2017). De Araujo et al. (2003) found activation of the rostral FOI, the caudolateral OFC, and the rostral anterior CG by taste stimulation with 1 M glucose, 0.05 M MSG, 0.005 M IMP, or the combination of MSG and IMP. Careful analysis of a 30-voxel area of the left OFC showed evidence of activation by the MSG-IMP mixture consistent with synergy between the two umami substances (de Araujo et al., 2003). In a follow-up study, McCabe and Rolls (2007) examined fMRI activation with 0.1 M MSG and a savory vegetable odor presented individually or as a mixture. Subjects subjectively rated the pleasantness of the MSG-odor combination as greater than MSG alone. Cortical activation by the

combination was significantly greater in the medial OFC and the pregenual CG than expected by the summed activation of the individual stimuli and correlated with pleasantness ratings by individual subjects. Importantly, these data illustrate how glutamate can increase the palatability of a food when combined with a consonant, savory odor (Rolls, 2009).

Neuroimaging studies have also given us insights into cortical control over higher-order or "top-down" cognitive functions on the perception of umami. Secondary taste cortices such as areas of the prefrontal cortex and the CG are the main regions involved in these functions, especially as they affect the pleasantness of umami stimuli. As predicted from monkey electrophysiological research described above, fMRI studies have shown that the response of the human OFC to umami stimuli decreases with satiation, an effect not seen in the FOI (Luo et al., 2013). In addition, an area of the OFC exhibits synergistic activation to the combination of MSG and IMP (de Araujo et al., 2003) and receives input from the olfactory system (McCabe & Rolls, 2007). Collectively, these findings indicate the OFC is strongly involved in determining the perceived pleasantness and flavor of taste stimuli.

Cognitive modulation of pleasantness is mediated by other areas of the brain as well. For example, the affective dimension of the pleasantness of umami appears to activate areas of the pregenual CG and the ventral striatum, areas that receive input from the OFC (Grabenhorst et al., 2008). Moreover, the degree of activation of these areas and the behavioral responses associated with the affective property of umami can be modulated by word labels. Depending on the nature of the task, attentional processes can selectively enhance activation of these areas (Grabenhorst et al., 2008). For example, activation of OFC, but not the FOI, is increased when the task focuses on the pleasantness of umami. However, if the task focuses on evaluating the intensity of umami stimuli, activation of the FOI, but not of the OFC, is increased (Grabenhorst et al., 2008). Understanding how umami affects cognitive processes may have important clinical implications (Magerowski et al., 2018). When umami is added to food items, subjects increase their preference for and intake of these foods (Bellisle, 1998, 1999). This information could help patients with dietary challenges, such as the elderly, those affected by cardiovascular disease, or those with taste deficits from chemotherapy or toxic agents.

3.11 Umami Signaling in the Gut: Gastrointestinal System

In one sense, the gastrointestinal (GI) tract can be viewed as a long, convoluted tubular chemosensing structure with different chambers specialized for digestion and absorption. Glutamate sensing in the oral cavity activates the cephalic phase of digestion, but glutamate is sensed again in the gut, which enhances digestive processes (vago-vagal reflex) and influences cognitive processes related to umami perception via the gut-brain axis. Throughout the GI tract, enterochromaffin sensory cells detect the chemical composition of ingested food and chyme. These enteric endocrine cells secrete serotonin and certain gut hormones, including

cholecystokinin, gastric inhibitory peptide, glucagon-like peptides (GLP-1, GLP-2), peptide YY, and others. The enteroendocrine cells have different names (e.g., endocrine I cells and endocrine L cells) depending on the peptide they secrete.

Vagal afferents do not directly innervate gut sensory cells but, rather, are activated by paracrine hormonal signals released by enteroendocrine sensory cells typically expressing a receptor also found in the oral cavity (Akiba & Kaunitz, 2011; Raka et al., 2019). For example, the metabotropic glutamate receptor mGluR1, initially found in the oral cavity, is also expressed in certain gut neuroendocrine cells (San Gabriel et al., 2005, 2007; Nakamura et al., 2010; San Gabriel & Uneyama, 2013). L cells also express receptors found in the oral cavity, such as T1R, T2R, and calcium-sensing receptor (CaSR) families capable of detecting sweet, umami (and other amino acids), and bitter compounds (Uematsu et al., 2011; Raka et al., 2019). Similar to taste cells in taste buds, these cells also have GPCR proteins and signaling pathways. When activated, L cells release GLP-1 and GLP-2. I cells express T1R1/T1R3 and CaSR receptors, which when activated release cholecystokinin. These peptides activate other enteroendocrine cells and vagal afferents. Abdominal vagal innervation extends from the esophagus to the upper GI tract and serves as the primary neuroanatomical component of the gut-brain axis. It relays information about gut content to the brain, which can modulate GI functions (e.g., digestion, absorption, emptying) and conscious sensations (e.g., satiety, taste perceptions) (Tome, 2018). Intragastric loading studies typically show that gut sensing of ingested substances either adds to or subtracts from signaling of the oral pathways.

Postingestive effects of umami stimuli on taste perception appear to be quite potent and more wide-spread than previously thought. Intragastric infusion with MSG in mice and rats, when paired with an aversive agent, can lead to learned avoidance of glutamate or, if paired with a flavor, can enhance flavor preferences (Ackroff & Sclafani, 2016). Although the associative processes underlying these effects are not known, fMRI studies in mice detected neural activation in the dorsal vagal nucleus, the NST, and the insular cortex following GI infusion of glutamate. GI activation of these areas can be combined with activity induced by oral sensations and the lateral hypothalamus and thereby influence cortical regulation of eating behaviors. This activation is reduced by vagal nerve cut and is abolished by a variety of serotonin inhibitors and by a nitric oxidase inhibitor, suggesting this signal is mediated by serotonin and nitrous oxide (Tsurugizawa et al., 2009, 2010; Uematsu et al., 2010, 2011; Torii et al., 2013). In humans, the postoral ingestive effects of MSG and other taste compounds were examined using a naso-oral tube to bypass the oral cavity during a memory task (Meyer-Gerspach et al., 2016). fMRI revealed that in the sessions in which MSG was administered, more activation was observed in FOI areas (primary taste cortex), the CG, Brodmann's area 7, and precuneus cortical areas (associated with emotional, mnemonic, and conscious informational processing of taste stimuli) than with sucrose or NaCl. These results suggest that MSG may have stronger effects on areas involved in working memory than seen with other taste compounds. It is unclear if these effects are comparable to those found in rodents, but they suggest that glutamate and the gut-brain axis may play a larger role in cognitive processing than previously suspected.

3.12 Summary and Conclusions

The savory taste and mouthfeel of umami compounds, notably MSG, are generated by receptor cells and neurons of the gustatory sensory system, complemented by inputs from cells lining the GI tract. The existence of specialized GPCRs unique for umami compounds (T1R1 + T1R3, taste-mGluR1, taste-mGluR4) in taste buds and GI tract cells reinforces the notion that umami is indeed a basic taste alongside sweet, sour, salty, and bitter. Neuronal responses to umami compounds at all levels of the gustatory system in the CNS and peripheral nervous system often overlap somewhat with responses to NaCl (salty) and sucrose (sweet). This suggests that the neural circuitry for umami, sweet, and salty taste may partially overlap. Nonetheless, there is substantial evidence that substances that elicit an umami taste generate afferent signals that are both complex and unique and that these signals are the basis for differential processing of umami taste in rats, mice, nonhuman primates, and humans.

To date, the focus of much of umami research has been to determine if umami taste is worthy of the status of a basic taste. However, this may well have caused researchers to ignore a more complex and quite possibly much more significant question: how do glutamate, IMP, and other umami stimuli affect the taste of other substances? The interactive nature of the community of cells within a taste bud is just now becoming apparent (Roper & Chaudhari, 2017; Rodriguez et al., 2021) and may play an important role in umami-related enhancement of taste signaling within the oral cavity. However, the overlap of umami, salt, and sweet neural pathways, a feature of the CNS taste system that has made it so difficult to find umami-best neurons, may be key to umami's ability to interact with other tastes. A reasonable and testable hypothesis is that umami signaling can modify neural signals generated by complex taste mixtures and natural stimuli at one or more levels of the CNS. If so, then the challenge is to determine how the umami signal interacts with other taste signals within these CNS structures to modify taste perception.

At least two directions suggest themselves as fruitful starting points to explore umami taste processing in the brain. One approach would be to investigate the temporal pattern of taste-evoked neural responses ("taste code") elicited by the interaction of MSG/IMP and other taste stimuli at the several levels of gustatory signal processing in the brain, perhaps through ensembles of neurons in these overlapping pathways (e.g., Stapleton et al., 2006; Katz et al., 2002; Di Lorenzo & Victor, 2003; Di Lorenzo et al., 2009; Roussin et al., 2012; Sammons et al., 2016). A second approach would be to use natural foods rich in umami as gustatory stimuli and investigate how signals generated by these stimuli are processed at all levels in the gustatory nervous system, from taste buds to the cortex (e.g., Delay & Kondoh, 2015; Sammons et al., 2016; Pilato & Di Lorenzo, 2018). Studies such as the above not only would reveal important information about the basic physiology of umami taste but also would increase our understanding of how umami might be utilized with human populations—such as the elderly or patients with dietary issues—to improve nutritional intake.

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Dr. Eugene R. Delay earned a BS Degree in Psychology at the University of Idaho in 1972. While at the University of Georgia, he earned an MS Degree in 1977 and a PhD in 1979 in Biological Psychology. He held faculty positions at Regis University (Denver, CO) and the University of Vermont (Burlington, VT). His research career began in psychopharmacology before shifting focus to recovery of function after brain injury. In 1991, he began a long-standing collaboration with Dr. Roper examining receptor and transduction mechanisms underlying umami taste. Recently, he studied the effects of chemotherapy drugs on the taste system, including umami.

Stephen D. Roper received a Bachelor of Science Degree at Harvard College in 1967, his PhD from University College London in 1970, and a postdoctoral training at Harvard Medical School until 1973. Dr. Roper then held faculty positions at Harvard Medical School, University of Colorado Medical School, Colorado State University (where he was Chairman of Anatomy and Neurobiology), and presently Miller School of Medicine, University of Miami. In 1996, Drs. Roper, Delay, and N. Chaudhari identified the first taste receptor, the umami receptor, and subsequently have investigated the molecular, cellular, and behavioral aspects of umami taste.

Chapter 4
Umami and Salty: A Cooperative Pair

Aubrey Dunteman and Soo-Yeun Lee

4.1 Introduction

A specific preference for substances exhibiting a salty taste, typically originating from foods containing salt (NaCl), has been identified in humans. Salt is used in food for a variety of purposes, largely falling into the categories of preservation, flavor, and processing function. While salt is useful in food products, when consumed in excess, it may increase the risk of many chronic diseases, such as cardiovascular disease and hypertension. In attempts to reduce the high-sodium content of many processed and prepackaged foods, the addition of umami flavor has been increasingly investigated due to its potential to enhance saltiness, as well as other favorable flavor attributes. Much investigation has focused on glutamates, primarily monosodium glutamate (MSG), although other frequently studied umami substances include soy and yeast derivatives. The many options available to impart umami taste have varying results, generally positive overall. Despite the variety of investigations into using umami to reduce sodium in food, there are several gaps in the research that would benefit from future study. Examples include how to enhance umami in solid food matrices aligned with sodium reduction and how greater reductions in sodium content can be achieved by combining umami enhancement and physical modification methods.

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4.2 Role of Salt in Food

4.2.1 Relevance of Salt

It has become commonplace that, when food is bland or unappetizing, salt is added in an attempt to improve flavor. Given the ubiquitous presence of salt and its extensive use in various cuisines, it comes as no surprise that humans have a specific preference for substances with a salty taste. Whether this preference originates from an innate appetite for salt or is largely a learned behavior remains unclear (Círillo et al., 1994; Mennella, 2014). The affinity for salty foods may also be partially explained by the biological necessity of sodium in the diet for survival, which is most easily accessible through sodium chloride, popularly known as salt (Beauchamp & Engelman, 1991; Liem, 2017). Regardless, the inclination for humans to consume salty foods is apparent, as demonstrated by the preference for salted over unsalted foods and the prevalence of sodium overconsumption (Beauchamp & Engelman, 1991; Verma etal., 2007).

4.2.2 Major Roles of Salt

Extending past salt appetite, dietary sodium intake is also driven by functional roles of salt (hereafter referred to as NaCl) in food. By grouping certain roles together, three main uses of NaCl can be observed: preservation, processability, and flavor (Kilcast & den Ridder, 2007) (Fig. 4.1).

4.2.2.1 Preservation

NaCl has been used throughout history as a preservative, with many traditional fermented, brined, and pickled products relying on its ability to preserve foods (Everis & Betts, 2019; Kim et al., 2017). While NaCl itself does not confer significant

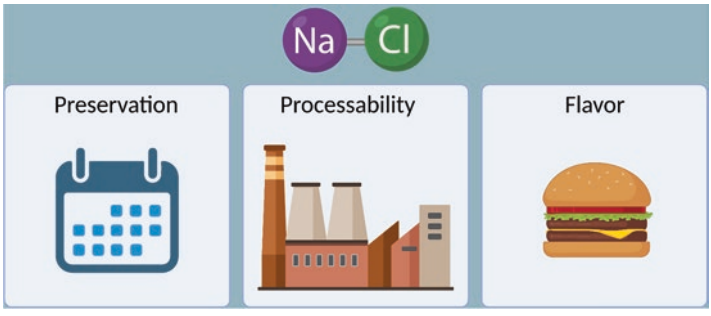

Fig. 4.1 Main roles of NaCl used in food products. (Created with BioRender.com)

antimicrobial activity, its ability to create an inhospitable environment for microorganisms and pathogens effectively extends a product's shelf life by preventing rapid spoilage. NaCl confers stress on microbes in part by reducing water activity, which limits unbound water available for microbial growth, and by increasing osmotic pressure, which can inhibit microbial growth and survival by inducing osmosis (Albarracín et al., 2011; Henney et al., 2010; Kim et al., 2017). These mechanisms are pivotal to interrupting harmful microbial processes; hence, NaCl is an easily accessible and inexpensive method of preservation.

4.2.2.2 Processability

Another major role of NaCl in foods relates to its functionality during the processing of certain food products. For example, in the manufacturing of bread, NaCl is necessary for adequate gluten development in dough, due to its ability to strengthen gluten, increase dough elasticity, and decrease dough extensibility (Noort et al., 2012; Simsek & Martinez, 2016). The presence of NaCl also impacts the fermentation process: by increasing NaCl levels in dough, yeast activity can be reduced, and as a result, the rate of fermentation decreases (Cauvain, 1998). NaCl is also important for the production of certain meat products, influencing water-holding capacity, activating enzymatic activity, and potentially generating ripening pigments (Albarracín et al., 2011). Similarly, NaCl is added to cheese to alter the water-binding activity of casein, to modify protein conformation by controlling certain enzymatic activity, and to regulate the growth of the lactic acid bacteria used in production (Albarracín et al., 2011; Floury et al., 2009). The examples listed above may also be relevant to the production of other products as well, and the functional role that NaCl plays in the processing of food is not limited to these examples.

4.2.2.3 Salty Taste

The effect that NaCl has on flavor is likely its most recognizable role in food. Evident from the name of the taste, salt confers a salty taste, one of the five identified basic tastes alongside sweet, sour, bitter, and umami, and has been found to have flavor-enhancing qualities. When NaCl is omitted from certain foods, the flavor quality is often found to suffer. Resulting food products may be described as tasteless, bland, or insipid (Cauvain, 1998; Kilcast & den Ridder, 2007). To reduce sodium levels in food, other chloride salts have been suggested in anticipation that they may also impart the easily identifiable salty taste. While many chloride salts exist and have been used in food manufacturing, only NaCl and LiCl have been found to impart a salty taste (Van Der Klaauw & Smith, 1995). With a goal of reducing sodium, LiCl appears to be an appropriate replacement for NaCl as it imparts saltiness in a manner similar to sodium's ion channel utilized with NaCl. However, due to the toxicity of lithium ions, LiCl has been eliminated as a possible replacement (McCaughey, 2019).

Although NaCl's use to impart a salty taste has not been successfully replicated, other compounds yet to be investigated likely have the potential to add saltiness to food. Looking ahead, it is sensible to consider that the activation of the sodium receptor mechanism may not be the sole determinant of salty taste perception—we should not assume there is only a single receptor, with only one transduction cascade, for such a basic taste (McCaughey, 2019). Considering how taste cells also contain separate sweet- and umami-responsive receptors or pathways that are independent of the canonical T1R3 receptor (Damak et al., 2003), the salty taste mechanism may also involve multiple receptors and has yet to be completely characterized.

4.2.2.4 Flavor Modification

Although NaCl is best known for conferring a salty taste, its influence on flavor extends past that singular taste modality. The sodium in NaCl can act as a bitter blocker and can enhance sweet tastes. The ability for sodium and NaCl to suppress bitter taste has been demonstrated alongside such bitter compounds as quinine hydrochloride (Schifferstein & Frijters, 1992) and caffeine, magnesium sulfate, amiloride, potassium chloride, and urea (Beauchamp et al., 2001; Breslin & Beauchamp, 1995), to various percentages of maximum bitterness sensation. This suppression of bitterness is likely a result of suppression at the periphery, in the oral cavity, where tastes interact with receptor cells and where, consequently, sodium and NaCl can inhibit taste receptor function (Wilkie et al., 2014). This is supported by the ability of sodium and NaCl to suppress bitterness when there is minimal salty taste perception (Keast & Breslin, 2002), but not when bitter and salty stimuli are applied to opposite sides of the tongue simultaneously (Kroeze & Bartoshuk, 1985).

In contrast to evidence of NaCl acting as an effective bitter blocker, some research has reported sodium or NaCl to be ineffective at reducing caffeine bitterness perception (Kamen et al., 1961), possibly suggesting that the suppression effect depends on such factors as the specific sodium compound and its concentration and the bitter compound and its concentration. Similarly, sodium's or NaCl's effectiveness may be affected by the consumer's taste phenotype: those who perceive 6-*n*-propylthiouracil (PROP) as more bitter experienced bitter blocking from sodium compounds, when tested with Brassicaceae vegetable, to a greater extent than those unable to taste PROP at all (Sharafi et al., 2013).

The ability for sodium or NaCl to suppress bitterness may also enhance favorable flavors by releasing tastes from the mixture suppression effect: the suppression of bitter tastes by sodium salts releases sweet tastes from being suppressed by bitterness (Beauchamp et al., 2001; Breslin & Beauchamp, 1997; Kemp & Beauchamp, 1994). The phenomenon can be particularly useful for increasing vegetable intake, as the increased sweetness and decreased bitterness may increase consumer liking (Sharafi et al., 2013; Wilkie et al., 2014).

4.3 Sodium Intake and Health

4.3.1 State of Sodium Consumption

The overconsumption of sodium, well above recommended intake limits, has become commonplace worldwide (Brown et al., 2009). Despite the recommendation by the Dietary Guidelines for Americans for sodium intake to be limited to less than 2300 mg per day (U.S. Department of Agriculture and U.S. Department of Health and Human Services, 2020), and the World Health Organization's recommendation of less than 2000 mg/day (Brown et al., 2009), the average sodium intake for American adults is roughly 3400 mg/day; thus, sodium has been designated as a nutrient of health concern for overconsumption (Dietary Guidelines Advisory Committee, 2020).

4.3.2 Sodium Sources

An estimated 75% of sodium intake in North American and European diets has been found to originate from processed or restaurant foods; roughly 10–12% can be traced each to sodium occurring naturally in foods or from discretionary use at the table (James et al., 1987; Mattes & Donnelly, 1991). Most sodium intake in developed countries results from consumption of "hidden" sodium in processed foods. However, some countries also struggle with high-sodium intake from different origins. For example, in the People's Republic of China, over 75% of dietary sodium has been found to come from salt added in home cooking (Anderson et al., 2010; Zhai, 2006).

4.3.3 Sodium's Effects on Health

Evidence of associations between excess sodium consumption and a multitude of adverse health effects has been demonstrated by meta-analyses and systematic reviews (Institute of Medicine, 2005; Malta et al., 2018). Figure 4.2 displays a selection of these health effects. A growing body of literature on dietary sodium intake and health has found a linear relationship between sodium intake and risk of developing hypertension (Bock & Cottier, 1961; Hermansen, 2000; Kim & Andrade, 2016), which further increases the risk of developing such conditions as coronary heart disease, congestive heart failure (Butler et al., 2015), stroke (Strazzullo et al., 2009), and renal disease (Keiko, 2017). Research also suggests that excessive salt intake leads to increased risk for certain cancers, including gastric cancer (Sheng et al., 2012) and liver cancer (Sun et al., 2020), further demonstrating the need to reduce the general population's sodium intake.

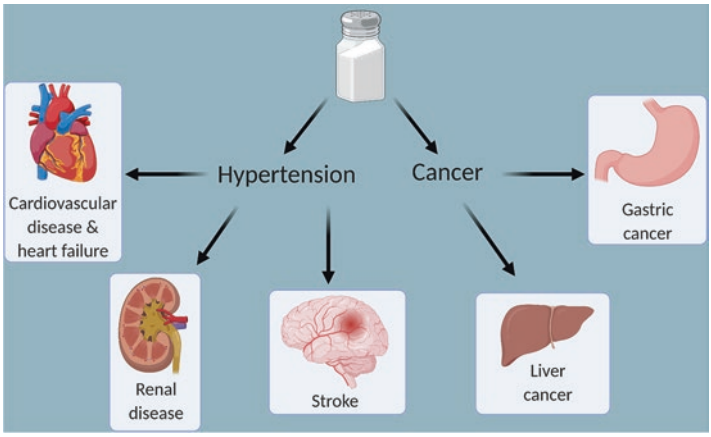

Fig. 4.2 Some increased health risks from overconsumption of sodium. (Created with BioRender.com)

4.4 Strategies to Reduce Sodium Intake

4.4.1 Stealth

Many methods have been investigated to reduce sodium overconsumption, such as leading consumers to healthier choices and manipulating high-sodium foods to contain reduced-sodium levels. While a sudden reduction in the amount of added salt in a recipe can lead to lower acceptance by consumers, a stepwise reduction in sodium—the stealth method—may alleviate some of the effects on consumer perception without requiring additional ingredients. The stealth method can be effective in reducing sodium overconsumption by developing foods that remain liked by consumers through progressively reducing the sodium content of the food or of a consumer's diet over time and, consequently, reducing preference for higher levels of salt intensity. This shift in preference can become evident anywhere from a few days to a few months after the shift in sodium intake (Bertino et al., 1982; Dötsch et al., 2009; Girgis et al., 2003; Quilez & Salas-Salvado, 2012).

4.4.2 Physical Modification

Another method of reducing sodium in foods that can be used without including additional ingredients is physical modification. Methods for physical modification of foods for sodium reduction are diverse (Fig. 4.3) and include using different salt crystal morphologies (Rama et al., 2013; Rodrigues et al., 2016), altering the texture of a food (Pflaum et al., 2013), and inhomogeneous distribution of salt in a food

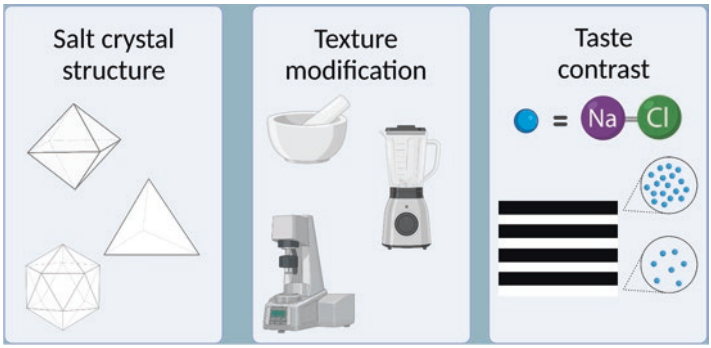

Fig. 4.3 Physical modification methods used to reduce sodium in food products. (Created with BioRender.com)

product to produce taste contrast (Noort et al., 2010). While physical modification methods have generally had promising results, costs associated with new or upgraded machinery to produce those methods may be an obstacle for many manufacturing companies.

4.4.3 Flavor Modification

In flavor modification, the flavor of a food is modified by adding another compound or food ingredient. Described below are only a subset of the wide range of flavor modification strategies available, primary detailing salt replacement and umami-based strategies.

4.4.3.1 Salt Replacement

The most widely investigated flavor modification method involves salt replacers. Although many materials have been investigated for their potential as a salt replacer, such as phosphates (Pandya et al., 2020; Seman et al., 1980), sulfates (Davaatseren et al., 2014), and citrates (Braschi et al., 2009), the most promising are mineral salts, in particular, potassium chloride (KCl) (Grummer et al., 2012). Although KCl can contribute only slightly less saltiness than sodium chloride, it has also been commonly described to have a bitter taste, which further exemplifies the need for improved methods for salt reduction (Rogério Tavares Filho et al., 2020). As noted above, LiCl has been found to confer a salty taste similar to sodium chloride, but it has been deemed unsafe to consume and thus is not a viable salt replacement option (Hand et al., 1982).

4.4.3.2 Umami-Based Strategies

Fundamentals of umami Strategies

In 1985, a groundbreaking meeting to discuss umami was held. At this meeting, *umami* was selected as the scientific term for the specific taste attributes generated by glutamates, particularly monosodium glutamate (MSG), as well as the 5′-ribonucleotides guanosine monophosphate (GMP) and inosine monophosphate (IMP) (Tepper & Yeomans, 2017). Research has shown that significant differences exist regarding individuals' ability to detect MSG and that some may lack the ability to detect MSG relative to NaCl (Lugaz et al., 2002; Raliou et al., 2009).

MSG is likely the most investigated umami-imparting substance for use in sodium reduction. Despite the evidence of its safety (Fernstrom, 2007), stigma still surrounds it from the "Chinese restaurant syndrome" it has been erroneously accused of causing (Husarova & Ostatníková, 2013). While other glutamates similar in structure to MSG, such as monoammonium glutamate (MAG), monomagnesium di-L-glutamate (MDG), and calcium diglutamate (CDG) (see Fig. 4.4), have been studied for their potential in maintaining acceptance or saltiness of reduced-sodium foods, with some level of success, publications are limited (Ball et al., 2002; Carter et al., 2011; Daget & Guion, 1989). IMP and GMP, as well as their respective derived acid salts, disodium inosinate and disodium guanylate (Fig. 4.5), have also been investigated for sodium reduction. Research has shown that they can be used as an alternative to MSG, thus avoiding the stigma surrounding MSG. Disodium inosinate and disodium guanylate are also used in a 50:50 mixture, referred to as I + G, which then may be used in conjunction with glutamates to impart a synergistic effect and yield a highly savory taste with minimal concentrations. These nucleotide compounds are produced by microbial fermentation, derived by animal origin or, more often, all-vegetable tapioca starch, so their use may be more accepted by the public than the well-known MSG.

Detection Thresholds of Umami Substances and Sodium Chloride

The detection thresholds of umami substances differ from that of sodium chloride both in concentration and in threshold variability. The concentration required to detect NaCl in water is lower than the concentration for MSG, first reported to be 1/400 and 1/3000, respectively (Ikeda, 2002). Studies on the interaction between umami and the basic tastes at threshold have yielded conflicting results, although it is more often reported that MSG does not change threshold values for sucrose or sodium chloride (Lockhart & Gainer, 1950; Yamaguchi, 1998) but reduces thresholds for sour and bitter tastes (Mosel & Kantrowitz, 1952). The impact of different umami substances on detection thresholds of other compounds that elicit primarily umami tastes, such as MSG or the 5′-ribonucleotides, is notable: both in clear soup

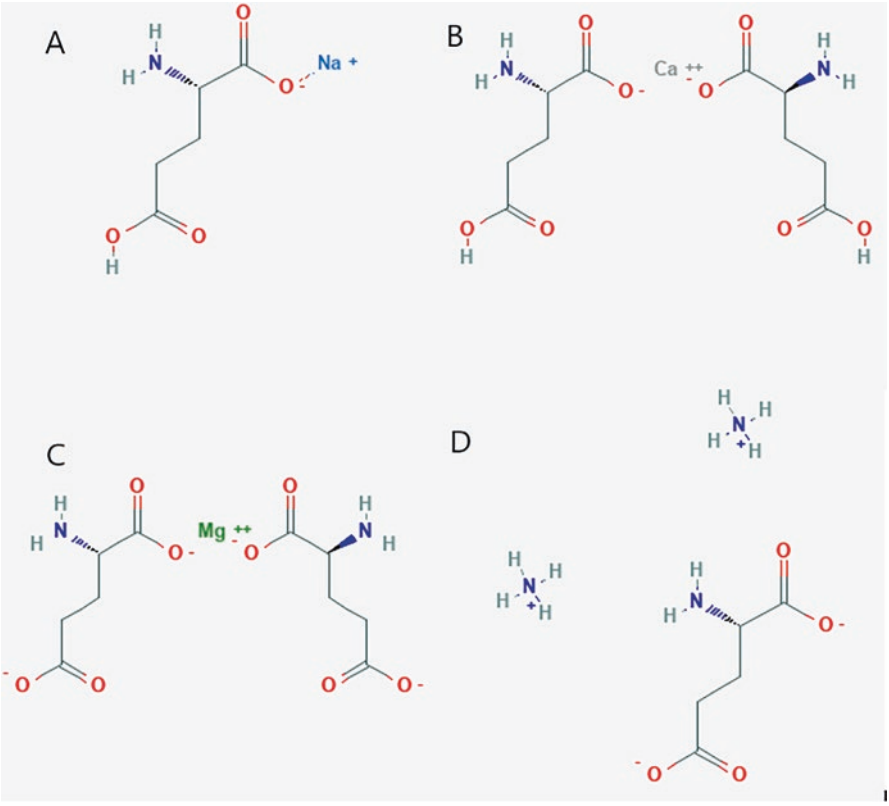

Fig. 4.4 Compound structures of glutamates: monosodium glutamate (**a**), calcium diglutamate (**b**), monomagnesium di-L-glutamate (**c**), and monoammonium glutamate (**d**). (National Center for Biotechnology Information, 2021a, b, c, d, e, f, g, h)

(Luscombe-Marsh et al., 2008) and in solution (Yamaguchi, 1998), when the solvent contains IMP, the detection threshold for MSG is lowered significantly. This also occurs with the IMP detection threshold when evaluated in an MSG-supplemented solution, as MSG and IMP are known to have a strong synergistic effect (Yamaguchi, 1998). When evaluated in solutions containing other basic taste substances, the detection threshold of MSG did not increase except when sucrose concentration was high. Because of the synergistic ability for the MSG detection threshold to be reduced and the relative ease of distinguishing umami in the presence of other tastes, it has been suggested that, among the five basic tastes, MSG is the most sensorily perceived substance (Yamaguchi, 1998). This is a point of contention, though, as the intensity of umami sensation is considered inferior compared to substances characterized by extremely strong tastes, including alkaloids or saccharin (Ikeda, 2002).

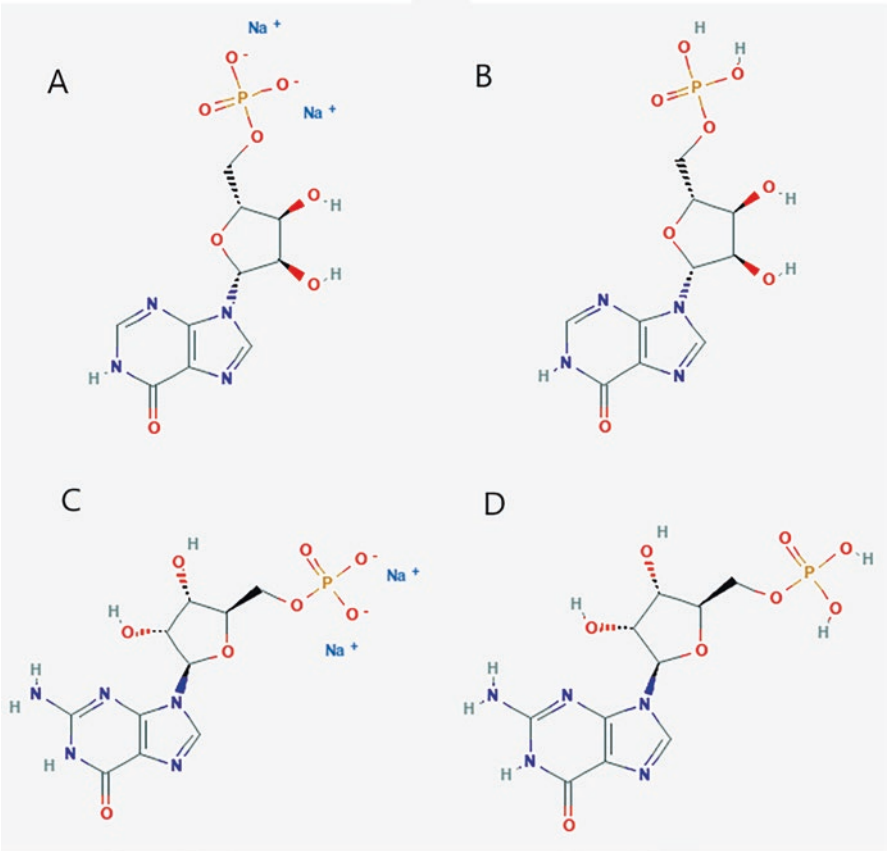

Fig. 4.5 Compound structures of ribonucleotides: disodium inosinate (**a**), inosine monophosphate (**b**), disodium guanylate (**c**), and guanosine monophosphate (**d**). (National Center for Biotechnology Information, 2021a, b, c, d, e, f, g, h)

Taste Profile of Umami Substances

Statements used to describe the taste and flavor of MSG vary greatly. From the first symposium on MSG in 1948, many descriptions of pure MSG were reported, including "a desirable meat-like taste," "all four components: sweetness, sourness, saltiness, and bitterness," and "a persistent lingering flavor reaction," to name a few (Beauchamp, 2009). MSG has been described as having a slightly sweet and salty taste (Lockhart & Gainer, 1950), but it has also been described as eliciting sweet, sour, salty, and bitter tastes (Mosel & Kantrowitz, 1952). Despite numerous studies investigating MSG taste, a clear consensus on its sensory properties is still lacking (Kemp & Beauchamp, 1994; Beauchamp, 2009).

The temporal profile of tastes in solution varies depending on the substance and whether it is alone or combined with other tastes. When evaluating a single primary taste solution at a time, salty and umami tastes show similar temporal time-intensity

profiles and temporal dominance of sensations (Rocha et al., 2020). These two tastes were also similar in that the duration of the taste solutions, MSG for umami and NaCl for salty, increased in a concentration-dependent manner.

Saltiness of Umami Compounds

The saltiness of MSG is approximately 30% that of NaCl by molar sodium concentration and 10% of NaCl by weight (De Souza et al., 2013; Yamaguchi, 1998). IMP has a saltiness equivalence of approximately 50% molar sodium concentration of NaCl and 7% by weight. Combining both MSG and IMP results in a taste that is largely umami due to their synergistic actions and thus is negligible in saltiness (Yamaguchi, 1998).

Interactions Between Salty and Umami Tastes

The effect of combining MSG and NaCl on saltiness has been examined over the years. A compensatory relationship between the two has been suggested, where more MSG is necessary as NaCl is reduced and vice versa. In soups, the optimal combination of NaCl and MSG has been reported as approximately 2:1 ratio of NaCl to MSG (Chi & Chen, 1992; Jinap et al., 2016; Yamaguchi & Takahashi, 1984), although the dynamics of palatability and saltiness vary for differing matrices (Baryłko-Pikielna & Kostyra, 2007; Kim et al., 2014). It has also been demonstrated that enhanced palatability from MSG largely depends on the presence of NaCl, as MSG alone reduced hedonic perception in rice, whereas MSG plus NaCl mitigated palatability loss from MSG (Yamaguchi, 1987; Yamaguchi & Takahashi, 1984).

In NaCl and MSG mixtures, a temporal sequence of basic taste perception was evident: the dominant taste prior to swallowing was saltiness, whereas umami was the dominant taste after swallowing (Kawasaki et al., 2016). In NaCl and MSG mixtures, umami duration in MSG solutions decreased with additional NaCl (Lioe et al., 2005), while saltiness duration in NaCl solutions increased with additional MSG (Kemp & Beauchamp, 1994). Such findings demonstrate a mixture-duration suppression effect for NaCl in NaCl+MSG mixtures and that saltiness of concentrated NaCl has a greater impact on umami taste duration than on enhanced umami taste (Kawasaki et al., 2016).

The ability for umami compounds to enhance salty taste in solution has also been evident using the glutamate MAG and the nucleotides IMP and GMP. At every NaCl concentration, saltiness enhancement was greater using MSG and MAG than using either IMP or GMP, although all umami flavor enhancers displayed similar sensory profiles (Rocha et al., 2020). Saltiness enhancement was also more apparent when NaCl concentration was reduced in smaller amounts, indicating that these substances may be most appropriately suited for foods requiring less drastic reductions in sodium content (Rocha et al., 2020).

4.4.3.3 Umami Compounds as Flavor Enhancers in Sodium-Reduced Products

Glutamates

Liquids

Glutamates have frequently been evaluated for their potential in sodium-reduced liquid foods over the years. In pumpkin soup, CDG and MSG have been demonstrated to maintain or increase ratings in liking, flavor intensity, familiarity, and richness under reduced-sodium conditions (Ball et al., 2002). Similar results were demonstrated using CDG in sodium-reduced chicken broth, where liking and pleasantness were maintained (Carter et al., 2011). Chicken broth containing a variety of different glutamates, including MSG, CDG, MDG, potassium diglutamate, and ammonium glutamate, were investigated previously with varying levels of success. All except ammonium glutamate and pure glutamic acid were preferred, according to preference ranking (Daget & Guion, 1989).

MSG has been the most researched glutamate for sodium reduction in liquid foods. In spicy soup, an approximate 32% reduction in sodium was feasible with MSG replacing a portion of the salt (Jinap et al., 2016). Promising results for MSG in sodium-reduced foods were also evident for tomato sauce (Rogério Tavares Filho et al., 2020), clear soup (Yamaguchi & Takahashi, 1984), chicken soup (Wang et al., 2019b), and certain vegetable soups (Roininen et al., 1996).

Semisolids

The use of MSG and KCl in margarine allows an approximate 47% reduction in sodium content while maintaining salty taste and overall impression (Gonçalves et al., 2017). When used in combination with KCl and either I + G or amino acids, MSG successfully maintained liking at 50% and 75% salt reductions (dos Santos et al., 2014). In mozzarella cheese supplemented with MSG and KCl, a 54% reduction in sodium was feasible while maintaining sensory quality (Rodrigues et al., 2014). While KCl has been demonstrated to have a closer saltiness equivalence to NaCl than does MSG, MSG does not enhance undesirable tastes in butter, as had been evident with KCl (De Souza et al., 2013).

Solids

MSG has been demonstrated to enhance liking in reduced-sodium potato chips and puffed rice snacks compared to their full-salt counterparts and to either maintain or increase liking when consumers were informed of the reduction in sodium (Buechler & Lee, 2019, 2020). The effect of informed versus blind tasting is not consistent, however, as contrasting results were found in potato chips. In another study, the full-salt treatment was least liked compared to the MSG treatments under blind conditions, yet once participants were informed, the MSG treatments became less liked

(Kongstad & Giacalone, 2020), suggesting consumers may still have a bias against certain flavor-enhancing compounds such as MSG. The use of MSG in reduced sodium white and multigrain bread was found to have similar acceptability and sensory characteristics when compared to their full-salt counterparts, although in contrast to aforementioned studies, information about sodium reductions and MSG inclusion had not impacted consumer perceptions (Dunteman & Lee, 2023a, b) indicating the possibility that consumers are placing less importance on clean labeling of their foods than before.

5′-Ribonucleotides

Liquids

Although MSG is the most investigated umami-imparting substance for reducing sodium, the use of 5′-ribonucleotides IMP and GMP, as well as their respective derived acid salts, disodium inosinate and disodium guanylate, has also been the focus of investigation. As noted above, disodium inosinate and disodium guanylate are also used in the 50:50 mixture I + G, which then may be used in conjunction with glutamates to yield a synergistic effect and impart a highly savory taste with minimal concentrations.

Research has shown conflicting feasibility for use of 5′-ribonucleotides in liquid applications. In vegetable soup at both low- and high-salt content, the inclusion of an umami mixture consisting of IMP, GMP, and MSG (Roininen et al., 1996) evoked increases in pleasantness, taste intensity, and ideal saltiness. Further evidence for using these nucleotides was identified with chicken noodle soup: inclusion of a mixture of MSG, IMP, and GMP led to increased intensity for such attributes as overall flavor, umami taste, and mouthfeel (Leong et al., 2016). In contrast, when an umami mixture of IMP, GMP, and KCl was incorporated into tomato sauce, the flavor acceptance was significantly reduced compared to the control sauce. On the other hand, when only KCl and IMP were added to the tomato sauce, there was no reduction in the acceptance of the evaluated attributes (Rogério Tavares Filho et al., 2020). The contrasting effectiveness of these nucleotides appears partially influenced by the food application: while I + G in mushroom, red beet, and asparagus soups contributed considerably to palatability enhancement, inclusion of MSG and I + G in green pea cream soup largely incurred a negative effect on palatability (Baryłko-Pikielna & Kostyra, 2007). Finally, IMP plus MSG enhanced perception of savory taste and flavor intensity and increase consumer acceptance in reduced-sodium chicken noodle soup (Miyaki et al., 2016).

Semisolids

When incorporated into a sodium reduction strategy for semisolid food matrices, nucleotides and/or their derivatives appear to mitigate quality loss resulting from sodium reduction or undesirable attributes characteristic of KCl in salt replacement.

Addition of KCl with IMP and GMP to sausage patties allowed up to 75% NaCl replacement before acceptability was reduced (Pasin et al., 1989). In sausages containing KCl as salt replacement, the addition of IMP and GMP with certain amino acids led to higher quality ratings than for sausages with KCl alone and resulted in no differences compared to the full-salt control (Campagnol et al., 2011a, b, 2012).

The addition of MSG to sausages reformulated with IMP, GMP, and certain amino acids allows for further reductions in sodium content, masking undesirable sensory changes resulting from replacing up to 75% of NaCl in the samples with KCl and allowing for greater than 65% reduction of sodium (dos Santos et al., 2014). The use of I + G and IMP alone with KCl salt replacement in reduced-sodium tomato sauce was also effective in masking metallic notes (Rogério Tavares Filho et al., 2020). The promising quality of GMP for masking negative attributes from KCl has also been reported in nonmeat products, such as reduced-sodium cheddar cheese. While cheeses with KCl and IMP were less accepted across all attributes evaluated, those with KCl and GMP either maintained or increased attribute acceptance compared to the control cheese (Grummer et al., 2013).

Solids

Little research has been done on solid foods using nucleotides as a strategy for sodium reduction. One study reported potato chips and puffed rice snacks seasoned with IMP, GMP, and MSG to have higher ratings of liking compared to the full-salt control samples (Buechler & Lee, 2019). When consumers were informed of the sodium reduction, the puffed rice snacks containing IMP, GMP, and MSG were rated as the most liked, while potato chips maintained their liking ratings. Descriptive analysis of the chips containing IMP, GMP, and MSG revealed that ratings for umami aftertaste and meaty aftertaste were higher and ratings for salty aftertaste were lower compared to the full-salt control chips. External preference mapping indicated that this treatment of potato chips was well liked. In rice puff snacks, the majority of evaluated attributes significantly differed across treatments, and external preference mapping indicated that those seasoned with IMP, GMP, and MSG were most liked (Buechler & Lee, 2020).

Other Amino Acids

Liquids

While research has been limited thus far on amino acids in liquid foods, those that have been have not had a positive impact on reduced-sodium foods. Soup with glutamic acid was characterized by a low overall quality, an acid taste, and a reduced chicken flavor (Daget & Guion, 1989). Similarly, lysine used as a bitter blocker in conjunction with KCl in reduced-sodium tomato sauce was ineffective: the treatment sample had increased bitterness and metallic taste compared to the full-salt control (Rogério Tavares Filho et al., 2020).

Semisolids

Glycine, lysine, and taurine have been evaluated in conjunction with salt replacement and MSG- and nucleotide-supplemented semisolid food matrixes, with differing results. Glycine has been used in reduced-sodium frankfurters with acceptable consumer perception (Wilailux et al., 2020). Lysine in reduced-sodium reconstructed ham successfully maintained overall acceptability, appearance, taste, and mouthfeel liking compared to a full-salt control (Guo et al., 2020). Lysine and taurine in reduced-sodium fermented sausage, with 50% NaCl replaced with KCl and supplemented with MSG, IMP, and GMP, produced suitable sensory qualities (dos Santos et al., 2014). Lysine and taurine were also reported to increase taste acceptability in fermented sausages in which KCl replaced a portion of the NaCl; taurine in particular had promising results, as all attributes evaluated maintained acceptability compared to the full-salt control (Campagnol et al., 2011a, b). Results were similar with lysine addition: consumer acceptance of color, taste, aroma, and texture in reduced-sodium sausages was maintained, although once 50% of NaCl was replaced with KCl, certain sensory defects could not be mitigated (Campagnol et al., 2012).

In cheese, amino acids were used in conjunction with other sodium reduction methods, such as added umami substances, physical modification, and salt replacement. Arginine has opposing results. Studies have shown reduced-sodium cheese with KCl and arginine to be less liked than full-salt cheese without KCl or arginine (Silva et al., 2017) and to have decreased saltiness and cheese aroma and increased sour and bitter tastes (Silva et al., 2018). In contrast, reduced-sodium cheese containing KCl and arginine had acceptable cheese flavor and overall acceptance compared to reduced-sodium cheeses with KCl alone (Felicio et al., 2016). Substitution of 35% salt with KCl in combination with glycine in rice porridge was feasible: ratings for overall liking, overall flavor, saltiness, and other attributes did not differ significantly from the full-salt control (Sriwattana et al., 2016).

Solids

At the time of writing, no research has been conducted on the use of amino acids to reduce sodium in solid foods. This is a research area that needs to be explored in the future.

Other Umami Substances

A great variety of ingredients with naturally occurring umami tastes have been identified. Select ingredients used for their umami-conferring properties in sodium-reduced foods are displayed in Fig. 4.6.

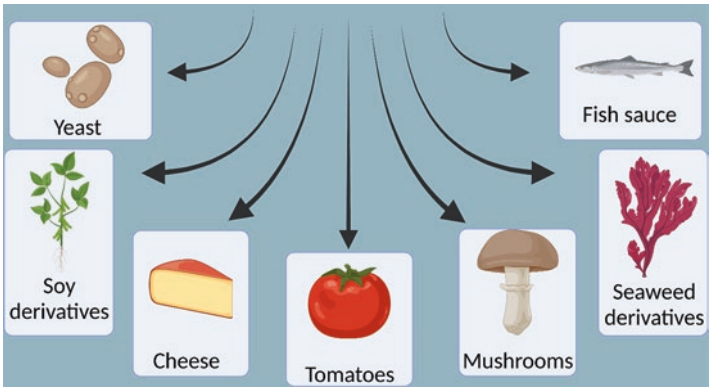

Fig. 4.6 Umami-containing ingredients investigated to reduce sodium in food products. (Created with BioRender.com)

Liquids

The use of umami substances in liquid foods to aid in maintaining quality alongside sodium reduction has been investigated in several studies. Partial replacement of salt with fish sauce, a natural source of glutamate and 5′-ribonucleotides, was demonstrated to successfully maintain overall taste intensity and deliciousness in chicken broth, tomato sauce, and coconut curry, at rates of 25%, 16%, and 10% NaCl reduction, respectively (Huynh et al., 2016). Soy sauce, despite contributing some sodium, has been found to allow for salt reductions of up to 50% in salad dressing and between 17% and 33% in tomato soup without significant reductions in overall taste intensity or pleasantness (Goh et al., 2011; Kremer et al., 2009). Other research has also demonstrated the potential for salt replacement by soy sauce for sodium reduction in tomato soup, with results suggesting levels of 24–33% to be feasible (Kremer et al., 2013b).

Other umami substances investigated in liquid foods include yeast extract, mushroom concentrate, and tomato concentrate. While not incorporating sodium reduction into their treatments, researchers have found that overall liking and overall flavor liking in chicken soup increased with the addition of yeast extract and were maintained with mushroom concentrate and tomato concentrate, thus suggesting the investigated umami ingredients may be used to produce reduced-salt soups with attributes deemed acceptable by consumers (Wang et al., 2019a).

Semisolids

A variety of different umami substances have been used in semisolid foods to aid in sodium reduction, including, but not limited to, yeast derivatives, soy derivatives, and ingredients naturally high in glutamates like tomatoes, mushrooms, seaweed, and cheese. Yeast derivatives are often used in combination with KCl for a variety of purposes, such as to reduce bitterness perception, increase saltiness intensity, and increase consumer acceptance. Yeast extract in bread with partial salt replacement

by KCl allowed for 67% sodium reduction without affecting bread consumption or causing sodium intake compensation with sandwich fillings (Bolhuis et al., 2011). Fermented sausages also benefited from yeast extract to mitigate quality defects from KCl and reduce sodium by 50% (Campagnol et al., 2011a, b). Similarly, *Debaryomyces hansenii* yeast inoculation improved taste quality of 17–20% salt-reduced dry fermented sausages (Corral et al., 2014). Reduced-sodium prato cheese with KCl salt replacement and supplementation with yeast extract and *Lactobacillus casei* increased consumer liking and saltiness intensity and decreased bitterness intensity and bitterness aftertaste compared to the same treatment without yeast extract, to the same ratings as the control, allowing for an approximate 35% reduction in sodium content (Silva et al., 2017, 2018).

Soy derivatives have been used for sodium reduction in semisolid foods such as bread and stir-fried pork. Over an exposure period of 15 days, liking of reduced-sodium bread with soy sauce did not decrease, whereas liking of the full-sodium control bread decreased; however, no differences were found in perceived saltiness intensity (Kremer et al., 2013a, b). In stir-fried pork with soy sauce, a 29% reduction in sodium content was feasible without significant losses in ratings of product pleasantness or overall taste intensity (Goh et al., 2011; Kremer et al., 2009). Frankfurters have also benefited from soy sauce, allowing for a 20% reduction in salt content without reduced ratings for quality or sensory characteristics; when treatments included KCl in addition to the soy sauce, a 35% reduction was feasible (McGough et al., 2012a, b). Additionally, no differences in overall liking or saltiness liking were observed for bacon, beef jerky, or ham with a 30% reduction of sodium and incorporation of KCl and soy sauce (Shazer et al., 2015).

Mushrooms have been used in many studies of reduced-sodium semisolid foods, although their purpose tends to focus on replacing other meats. In carne asada, substitution of a portion of beef with mushroom had no effect on flavor intensity, and in beef taco blends, incorporating 50–80% ground mushroom increased overall flavor intensity. Despite this, inclusion of mushroom did not fully mitigate saltiness reduction in the reduced-sodium blend (Myrdal Miller et al., 2014), but when 20% of beef was replaced with mushroom, overall liking was maintained with a 25% reduction in salt (Guinard et al., 2016). On a similar note, consumers preferred the reduced-sodium filling with 45% mushroom over both the full-sodium control with all meat and the full-sodium control with 45% mushroom (Wong et al., 2017). Mushrooms were also successfully used in reduced-sodium beef patties at 20% replacement levels: ratings for overall liking and saltiness liking were maintained with an approximate 25% reduction in sodium (Wong et al., 2019). Mushroom extract has also been investigated for sodium reduction in beef patties, where a 50% reduction in salt in the presence of the 20% mushroom homogenate extract increased acceptance of a variety of sensory attributes and enhanced salt perception to levels similar to that of the full-salt control and to levels greater compared to the 50% reduced-sodium treatments with 5% or 12.5% mushroom homogenate extract and the 75% reduced-sodium treatments (Mattar et al., 2018).

Other umami ingredients such as tomatoes, cheeses (Dos Santos et al., 2020; Xiang et al., 2017), fish sauce (Huynh et al., 2016), hydrolyzed vegetable proteins

(Khetra et al., 2019), and seaweed derivatives (Barbieri et al., 2016; Vilar et al., 2020) have also been investigated for use in reduced-sodium foods, with mixed results, although results trended toward acceptable products by either maintaining or increasing quality attributes.

Solids

At the time of writing, no research has been conducted on the use of umami substances to reduce sodium in solid foods. This is another research area in need of exploration.

4.5 Conclusion

This chapter has discussed certain gaps in knowledge surrounding the use of the umami taste in relation to salt and sodium reduction. While glutamates, particularly MSG, are well studied, there is limited research into other approaches that would align with consumer expectations. Soy and yeast derivatives, ingredients naturally high in glutamates, and potentially certain amino acids may all be preferred by the general public compared to glutamates or the 5′-ribonucleotides, given the familiarity and perception consumers likely have surrounding these substances.

Research including both blind and informed conditions on umami-based sodium reduction methods is largely absent from the literature yet would provide valuable insights into the potential of each method once available on the market. There is also a large gap in how these methods may fare in solid food products—studies currently are limited to potato chips and puffed rice snacks. While this may reflect the fact that most high-sodium foods are either liquids (e.g., soups) or semisolids (e.g., cured meats), further investigation into other product categories would be valuable, as future food trends cannot be predicted. Research on umami in solid foods would also help increase our knowledge of sodium reduction methods in solid foods.

Lastly, while much research has used umami-based methods in combination with other umami substances or with the salt replacer KCl, other sodium reduction methods achieved by modifying the physical form or processing conditions in conjunction with umami taste have not been well studied; this approach may enable larger reductions in sodium content than currently available.

Despite the diversity in sources of umami taste and sodium reduction presented throughout this chapter, certain limitations have arisen during writing. Not every piece of literature investigating the umami taste has been reviewed; gray literature that is difficult to identify may be present yet inaccessible. Similarly, not every literature review on the topic has been included owing to limitations in space and in the scope of this book. Although this chapter provides a detailed look into how umami and salt are related, further connections may have not been identified as a result of the tendency to present each taste independent of the others, without sufficient literature review and discussion.

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Chapter 5
Umami and Satiety

Martin R. Yeomans

Umami is today recognized as one of the five basic tastes, complementing the more widely known salty, sweet, sour, and bitter tastes. In all five cases, the taste percept (i.e., the conscious experience of the taste quality) arises from oral detection of nonvolatile chemicals dissolved in saliva that bind to specific taste receptors on the tongue. An important feature of all five basic tastes is that their qualities are unique: that is, it is not possible to generate a different taste quality by mixing other tastes (perceptual independence). In the case of umami, the primary receptor is known to be a heterodimer of two proteins, TAS1R1 + TAS1R3, that has a unique role in taste sensing (Damak et al., 2003; Li et al., 2002), and recent studies suggest strong positive selective pressure for the genes for both TAS1R1 and TAS1R3 in human evolution (Valente et al., 2018). These same receptors are found in other parts of the digestive tract, but only those in the mouth give rise to the perceptual experience of umami taste. A key question, then, is why we have evolved the ability to detect umami? To understand this, we first need to consider the potential evolutionary advantage of umami sensing.

Evolution shapes physiology to adapt to specific challenges for survival. For omnivores, including humans (as cogently argued as the "omnivore's paradox" in (Rozin, 1976)), the key problem is how to identify which of the many potential foods that occur in nature are safe and nutritious. On that basis, it has long been argued that our ability to taste certain compounds in potential foods evolved to meet that challenge, with the mouth the gatekeeper that directs decisions on whether a potential food is ingested or rejected (Tanaka et al., 2007; Kim et al., 2004), interpreting taste as the "nutritional sense" (Bartoshuk, 2018). Accordingly, our ability to sense bitterness ensures we are cautious when ingesting substances that could be harmful (Shi et al., 2003; Breslin, 2013), and there is clear evidence of how diet

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shaped the evolution of bitter taste perception (Li and Zhang, 2014). Similarly, sweetness may signal a safe source of energy (Beauchamp, 2016), and most recently sourness has been proposed to help identify key vitamins in states of vitamin deficiency (Teng et al., 2019). From this evolutionary perspective, what may be the reason that humans can detect umami taste? The answer, based on the nature of the foods that contain the compounds that generate umami taste, is that umami may have evolved to help us sense sources of protein, an idea dating back to the original discovery of umami taste (Ikeda, 1908) and then developed by other researchers (e.g., Naim et al., 1991; Kurihara, 2009; Geraedts et al., 2011). But our ability to detect umami compounds in the mouth and later in the gut could have a function beyond the simple sensing of the presence of protein. Sensors in the mouth and gut are also key components of appetite control, and recent evidence suggests that umami taste not only allows us to sense the likely presence of protein but also helps the body regulate protein intake. This chapter evaluates current state of play for research that has tested the role of umami in satiety.

5.1 Why We Taste Umami: Lessons from the Diet

The original idea of umami relating to protein sensing was based on consideration of where in the diet we find the chemicals that activate umami taste receptors. Umami taste can be traced back to the initial isolation of glutamic acid from seaweed and the subsequent discovery in 1908 that it, and particularly its sodium salt, monosodium glutamate (MSG), conveys a unique "flavor." MSG is now known to be the main molecule that stimulates human umami taste receptors. Subsequent research found that the umami taste generated by MSG was greatly potentiated by the presence of ribonucleotides, most specifically by disodium 5′-inosine monophosphate (IMP) and disodium 5′-guanosine monophosphate (GMP) (Kuninaka, 1981; Fuke & Ueda, 1996). Notably, neither IMP nor GMP elicits a strong umami taste alone, but both act synergistically with MSG to elicit a stronger umami taste than predicted by the sum of the individual components (Yamaguchi & Ninomiya, 2000; Fuke & Ueda, 1996). To understand why we have evolved the ability to taste umami, we need to consider where in our food supply we find MSG, IMP, and GMP: in a wide range of foods that we classify as savory. Indeed, it was Ikeda's (1908) observation that these foods have a distinct "savory" taste that led to his use of the word *umami* to describe this.

The most concentrated levels of free glutamate are found in a wide variety of foods, including some vegetables (e.g., mushrooms, potatoes, cabbage, corn, onion, spinach), fruits (e.g., tomatoes, avocado), some fish and seafood (e.g., prawn, clam, crab, oyster), seaweed, egg yolks, ripened cheeses, human breast milk, and fermented soya beans and in lower concentrations in commonly consumed meats (e.g., beef, pork, chicken) (Kurihara, 2009; Ninomiya, 1998; Drake et al., 2007; Fuke & Shimizu, 1993; Hajeb & Jinap, 2015; Ghirri & Bignetti, 2012). From a nutritional standpoint, all of these provide valuable nutrients, but at first sight there appears to

be no obvious strong nutritional link across these foods that could have driven the evolution of umami as a preferred taste.

However, ribonucleotides are distributed rather differently. IMP in particular is a constituent of most of the meat sources that provide most of the protein humans consume (beef, lamb, pork, chicken, fish, and goat). Moreover, although the protein found in those foods has a relatively weak taste profile in its natural state, once hydrolyzed, the protein has a characteristic umami taste carried predominantly by glutamate and ribonucleotides. Notably, the processes of aging, heating, and curing these foods releases both free MSG and IMP, greatly enhancing the level of umami taste (Sasaki et al., 2007; Rotola-Pukkila et al., 2015; Maga, 1994). This has led to important speculation that our penchant for umami taste evolved at a time when humans were switching to cooking as the primary process to prepare food for ingestion (Wrangham, 2017; Valente et al., 2018). Thus, in the form that we consume these foods, umami may provide an oral signal of the likely presence of protein, an idea first noted by Ikeda (1908).

It is therefore possible to develop a hypothesis that we evolved umami taste as a way of detecting protein in cooked foods. However, unlike other basic tastes, umami is strongly influenced by other flavor elements, making the sensing of umami more complex than sensing MSG and ribonucleotides alone (Mouritsen et al., 2017). This complexity of umami taste, with the strongest umami taste found only when sources of MSG and IMP/GMP are combined with other flavor elements (McCabe & Rolls, 2007), may have had a particularly profound impact on the development of cuisine worldwide, underlying the use of umami-rich seasonings (Mouritsen et al., 2017) and shaping how we combine ingredients to better enable sensing of protein (Ninomiya, 2015). The general idea that the overall savory character of a food is then related to protein content has been supported by some studies that asked participants to rate the savory character of foods and then explored how these ratings related to actual protein content (van Dongen et al., 2012; Martin et al., 2014). Other studies, however, suggest this relationship is relatively weak (Teo et al., 2018) or not significant (Buckley et al., 2018). Overall, both the content of free glutamate and umami-related nucleotides in foods and consumer evaluations of food products suggest umami taste may function, at least in part, to locate protein in the diet, although more work is needed to fully clarify this relationship.

5.2 Umami and the Regulation of Protein Intake

The argument developed in this chapter is that umami taste may go beyond a mechanism for simply sensing potential sources of protein in our diet to actually playing a key role in the regulation of protein intake. To understand this, the evidence that protein intake is regulated, followed by the effects of protein on satiety, is reviewed. Then the literature that has examined how the presence of umami taste modifies our experience of appetite is explored, focusing in particular on evidence that umami may enhance satiety when protein is ingested. Studies that tested liking for umami

tastes as a function of protein need state provide further evidence for a role of umami in satiety, suggesting that umami is liked more when we are in short-term need of protein and, conversely, that liking is suppressed when we are protein replete.

5.2.1 Regulation of Protein Intake

Nutritionally, protein is one of the three main macronutrients and is an essential component of the human diet, needed for the formation and repair of muscle tissue and to provide essential amino acids to produce key neurotransmitters, hormones, enzymes, and receptors, among other key cellular functions. Both fat and carbohydrate can be stored as reserves if intake exceeds current energetic needs, but protein cannot be stored in the body. This inability may explain why the proportion of protein in the diet is remarkably similar in human cultures with very different dietary habits. An analysis of the percentage of energy consumed as protein across 175 countries (Fig. 5.1: based on data published in Ritchie & Roser, 2017) gave an average of 11.1%, with more than 50% of countries having protein intake between 10.5% and 12.5% of total energy intake and only 10% of countries having more than 12.6% of total energy from protein. Remarkably similar overall protein intake was seen in countries where more than 65% of protein intake comes from animal sources or 85% comes from plants. These data provide striking evidence of how tightly controlled human protein intake is and adds credence to the idea that oral sensing of protein in food, likely involving umami taste, is a critical part of appetite control.

The evidence that protein intake is regulated more tightly than are fat and protein has important implications for understanding our habitual food intake. According to

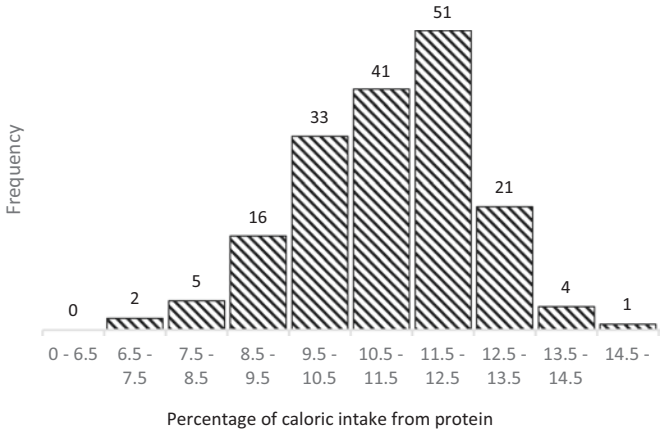

Fig. 5.1 Average protein intake, as a percentage of total caloric intake, in 175 different countries and dependencies (numbers at tops of columns). (Data from Ritchie and Roser (2017))

the protein leverage hypothesis, the absolute need for a certain level of protein in our diet could drive overconsumption where available levels of protein are reduced (Simpson & Raubenheimer, 2005; Gosby et al., 2014). A full evaluation of that hypothesis is outside the scope of this chapter, but in the present context, the key message is that protein intake is tightly regulated, and for that to be true, the body has to have a mechanism for sensing and monitoring protein intake. Umami taste offers a potential sensory component that could achieve this.

5.2.2 Protein: The Most Satiating Macronutrient?

Satiety could potentially be explained by a broader sensing mechanism that monitors overall energy intake relative to energetic needs. At its simplest level, that proposition suggests that energy is the key controlled variable, and the prediction then follows that intake of the three main sources of energy (fat, carbohydrate, and protein) would have satiating effects, once matched for energy. However, humans generally experience greater satiety, that is, stronger suppression of appetite and subsequent less ingestion at the next meal, after consuming protein-rich foods than after energy-matched fat- or carbohydrate-rich foods (see Anderson & Moore, 2004; Dhillon et al., 2016; Johnstone, 2013; Morell & Fiszman, 2017; Paddon-Jones et al., 2008; Veldhorst et al., 2008 for reviews).

In this context, most short-term studies examining satiety use the preload design (Yeomans, 2018), where participants ingest a fixed amount of different versions of a test food, as the main manipulation, and their appetite is tested afterward to assess satiety. A large number of preload studies using different foods and drinks, different protein sources, and varying times between the preload and the ad libitum test meal have shown greater satiety after protein than after other energy sources (e.g., Anderson & Moore, 2004; Bertenshaw et al., 2008; Chungchunlam et al., 2012; Martens et al., 2013). Notably, however, a number of well-designed studies failed to find any greater satiety for protein than for other macronutrients (e.g., Geliebter, 1979; Raben et al., 2003) and in some cases even found no evidence that any macronutrient source generated short-term satiety relative to a low-energy control (e.g., de Graaf et al., 1992). Although small methodological differences (study power, satiety measures, etc.) could have influenced these outcomes, the variability in outcome itself could suggest something important about how protein is sensed and controlled. Crucially, to enable clear claims about protein, most protein-satiety studies take great care to disguise the presence of protein at a sensory level. In doing so, these studies may inadvertently remove the very signals the body uses to sense and control protein intake—including, critically, umami taste.

This idea that the sensory characteristics of protein-rich products at least partially explain the higher levels of satiety they generate was tested explicitly (Bertenshaw et al., 2013). Their earlier studies had confirmed both that a whey-protein-enhanced beverage was more satiating than an equicaloric carbohydrate-enhanced beverage (Bertenshaw et al., 2008) and that the effects of whey protein on

satiety were dose dependent (Bertenshaw et al., 2009). However, the flavor characteristics of whey protein (which includes an umami component) made it impossible to fully disguise the addition of protein. Thus, they surmised that perhaps the greater effectiveness of protein than carbohydrate to induce satiety may have been due to the sensory characteristics cuing an expectation of protein, which in turn generated the stronger satiety response. To test this, they contrasted the effects of the same high-whey-protein preload with two alternative high-energy preloads: a carbohydrate preload adjusted to the same perceived thickness, with cream flavoring added to match sensory characteristics of the whey preload, and a second protein preload using a different form of whey protein that lacks these sensory characteristics (Bertenshaw et al., 2013). Notably, when sensory matched, the high-sensory whey and sensory-matched carbohydrate induced the same levels of satiety (evidenced by lower-energy intake at a test meal; Fig. 5.2), but the equicaloric low-sensory protein preload produced significantly less satiety. However, this study did not include any specific manipulation of umami taste. Thus, studies that examine whether satiety is greater in the context of umami taste can test the umami-satiety hypothesis.

5.3 A Role for Umami in Protein-Based Satiety?

How might the possible effects of umami on appetite be tested? To date, a number of different approaches have been used, and although the picture is far from complete, several lines of evidence suggest that umami may have some role in generating postmeal satiety. This research is described in the following sections, grouped by the approach taken: human experimental preload-satiety studies with adult volunteers, insights from the studies of feeding by human infants, and consideration of how acute protein need state modifies responses to umami taste.

5.3.1 Umami-Enhanced Satiety: Human Experimental Studies

To date, 10 studies conducted with human adult volunteers, reporting 13 experiments and representing research from 6 different research groups, have tested the effects of added MSG or a combination of MSG with nucleotides including IMP on satiety (see Table 5.1). These studies provide the most direct test of the idea that umami enhances satiety and so warrant detailed evaluation. These studies are presented in chronological order since the findings changed as the design of studies became more sophisticated.

The first study that directly assessed the effects of umami using a laboratory-based satiety test in human volunteers looked at the effects of a relatively high concentration of MSG (20% w/w) added to a minimal-energy beef consommé in three related experiments (Rogers & Blundell, 1990). There was no evidence that addition of MSG-enhanced satiety in these three experiments, with no effect on the

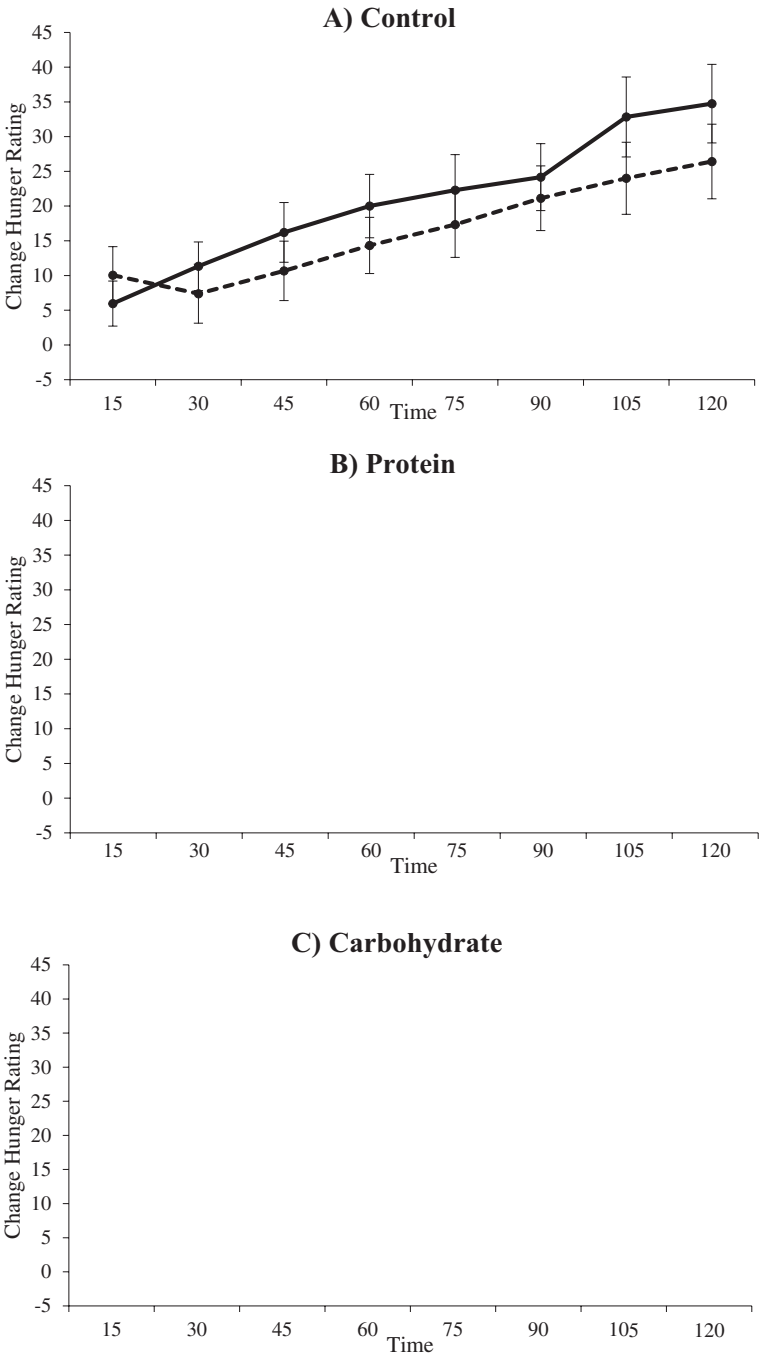

Fig. 5.2 Recovery of hunger after consuming one of six versions of a naturally low-glutamate soup (Masic & Yeomans, 2013): lower-energy (126 kcal) soup (**a**), higher-energy soup (310 kcal) primarily with added protein (**b**), or a similar higher-energy soup (303 kcal) with added carbohydrate (**c**), either with (broken lines) or without (solid lines) added MSG

Table 5.1 Preload-satiety studies investigating effects of manipulated umami taste in human adult volunteers

Study	Experiment design	Umami manipulation	Participants[a]	Key outcomes
Rogers and Blundell (1990)	Effects of three preloads on rated appetite over 60 min: No preload or low-energy (<10 kcal) beef consommé with or without nnn	20% MSG	32 healthy volunteers	No significant difference in appetite or fullness between MSG and control soup
Rogers and Blundell (1990)	Effects of four preloads on intake at a test meal consumed 30 min later: No preload or low-energy (<10 kcal) beef consommé with 0, 10, or 20% added MSG	10% or 20% MSG	32 healthy volunteers	No significant effects of added MSG on test meal intake (trend for small increase)
Rogers and Blundell (1990)	Effects of three preloads on intake at a test meal consumed 2 mins later, plus subsequent rated appetite: No preload or low-energy (<10 kcal) beef consommé alone or with MSG	20% MSG	32 healthy volunteers	No significant effects of added MSG on test meal intake. More rapid recovery of appetite after the soup with MSG
Luscombe-Marsh et al. (2009)	Effects of five preloads on appetite, satiety-related hormones, and intake at test buffet 30 min later: Water control and four isoenergetic test preloads combining noodle soup + one or two filled rolls (overall nutrient content not detailed: Portion sizes adjusted to provide 20% of estimated daily energy needs): Soup + roll alone, + MSG, + MSG/IMP, + MSG/IMP sham-fed	0.6% MSG, 0.25% IMP	10 men, BMI 26.5 ± 1.2, age 44 ± 6 years; 12 women, BMI 23.7 ± 1.4, age 32 ± 6 years	No significant effects of any MSG manipulations on rated appetite: Significantly greater food intake after the preload with MSG (but not with MSG + IMP) than without either additive

(continued)

Table 5.1 (continued)

Study	Experiment design	Umami manipulation	Participants[a]	Key outcomes
Carter et al. (2011)	Effects of four chicken-broth preloads on appetite and test meal intake: Low-energy (15 kcal) control, low energy + MSG, low energy + MSG and nucleotides, or high energy (163 kcal; energy added as fat). Each soup was consumed twice, at 0900 and 1115 h, prior to test meal at 1200 h	0.5% MSG, 0.0013% nucleotides	35 healthy women: BMI 21.6 ± 0.3, age 24.7 ± 0.8 years	No effects of MSG on test lunch intake, which was reduced in the high-fat condition. Significant reduction in hunger and desire to eat after MSG at second preload
Finlayson et al. (2012)	Effects of equicaloric mushroom-flavored sweet, savory (+ MSG), or bland milk-based preloads on intake at buffet lunch 30 min later	Not specified	30 healthy women: BMI = 22.7 ± 0.4, age 21.9 ± 0.5 years	Lower intake of high-fat foods after MSG-enhanced savory than after sweet foods; no other effects of savory manipulation
Masic and Yeomans (2013)	Effects of six low-MSG vegetable soup preloads (covert nutritional manipulations) on rated appetite over subsequent 2 h: Low energy (126 kcal, control), higher-energy carbohydrate (303 kcal), or higher-energy protein (310 kcal), with or without MSG	1% MSG	24 healthy men: BMI 24.0 ± 0.5, age 21 ± 1.4 years	Significantly slower recovery of hunger after MSG than after control in protein condition; trend for slower recovery of hunger after MSG in low-energy condition; no effect of MSG in carbohydrate condition
Masic and Yeomans (2014a)	Effects of six low-MSG vegetable soup preloads (covert nutritional manipulations) on intake at a test meal 45 min later: Low-energy (126 kcal, control), higher-energy carbohydrate (303 kcal), or higher-energy protein (310 kcal), with or without MSG	1% MSG	35 healthy men: BMI 22.0 ± 0.2, age 21 ± 0.2 years	Reduced test meal intake after protein but not after carbohydrate manipulation, with compensation for covert energy enhanced by the presence of MSG

(continued)

Table 5.1 (continued)

Study	Experiment design	Umami manipulation	Participants[a]	Key outcomes
Masic and Yeomans (2014b)	Effects of four low-MSG vegetable soup preloads on intake at a test meal 45 min later: Low-energy (126 kcal, control) or higher-energy protein (310 kcal), with or without MSG	1% MSG + 0.25% IMP	11 men and 16 women: BMI 22.7 ± 0.4, age 21.8 ± 0.6 years	Significant reduction in test lunch intake after umami manipulation relative to control and after protein relative to low energy. Significantly higher compensation for added nutrients in MSG (70%) than for control (40%)
Imada et al. (2014)	Effects of three low-energy (8 kcal) chicken-broth preloads on appetite and intake at multi-item test meal served 15 min later: Broth alone (control), broth + MSG, or broth + MSG/IMP	0.5% MSG, 0.0005% IMP	86 healthy women: BMI 22.2 ± 0.2, age 37.9 ± 0.5 years	MSG, but not MSG + IMP, significantly reduced overall energy intake at the test, with reduced energy from sugar and fat from the test buffet. No significant effects on rated appetite
Miyaki et al. (2016)	Effects of two low-energy (47 kcal) soup preloads on test meal intake: Control soup or soup + MSG	0.5% MSG	68 women, BMI 28.6 ± 0.4, age 38.8 ± 1.2 years	Significantly lower food intake at test lunch, but not at an afternoon snack, after soup + MSG
Anderson et al. (2018)	Effects of four low-MSG vegetable soup preloads, plus water control, on rated appetite and test meal intake 120 min later: Low-energy (281–293 kcal, control) or higher-energy protein (402–418 kcal), with or without MSG	1.0% MSG	52 healthy young men	More sustained fullness after protein + MSG compared to all other conditions; reduced desire to eat in the low-energy MSG condition. No significant effects of MSG on food intake

(continued)

Table 5.1 (continued)

Study	Experiment design	Umami manipulation	Participants[a]	Key outcomes
Anderson et al. (2018)	Effects of four low-MSG vegetable soup preloads, plus water control, on rated appetite, test meal intake 120 min later, and selected satiety hormones: Low-energy (281–293 kcal, control) or higher-energy protein (402–418 kcal), with or without MSG	1.0% MSG	52 healthy young men	Lower subjective appetite after protein + MSG than in other conditions. Reduced lunch intake after protein + MSG but no after protein alone. Increased release of insulin and C-peptide and reduced blood glucose after protein + MSG

[a]Average participant age BMI are only reported here if detailed in the relevant paper

experience of appetite over the ensuing 2 h (experiment 1) and no significant effect of 10% or 20% MSG on test meal intake (experiments 2 and 3). The only significant effect on any of the measures of appetite was for more rapid recovery of hunger after consuming the soup with 20% MSG followed 10 mins later by a meal (experiment 3). Thus, these experiments provide no evidence of any effects of MSG on satiety and, indeed, found instead limited evidence that MSG could stimulate appetite, although the levels of MSG used were notably high and outside the physiological range consumers would experience from normal foods.

The next study (Luscombe-Marsh et al., 2009) likewise failed to find any evidence that umami caused satiety. Here, appetite and intake at a test meal were contrasted between a water control and a high-protein meal, with four variations: unaltered, with added MSG (0.6%), with added MSG + IMP, or with the MSG/IMP version sham-fed (i.e., chewed but not swallowed). There were no significant differences in changes in appetite ratings across time between the three high-protein meals, all of which generated greater satiety (i.e., reduced rated appetite) than did the water control or the sham-fed preload. Contrary to the predictions of enhanced satiety, more was consumed after the meal with added MSG (but not added MSG + IMP) than after the unaltered meal. Thus, the conclusion from these first two studies would be that umami does not enhance satiety; rather, to the contrary, MSG might cause a small increase in appetite. However, in the next study (Carter et al., 2011), when a low-energy broth was consumed twice prior to a test meal, with umami manipulated by the addition of MSG or MSG + IMP, MSG slowed the recovery of hunger after the second soup preload. Although the umami manipulations had no significant effects on food intake, this study did suggest a possible, albeit small, effect of umami on satiety, and notably, this was seen at much lower levels of added MSG than in the earlier studies. The approach in the next study was different: Finlayson et al. (2012) tested whether consumption of a preload that was bland,

sweet, or savory in flavor modified food selection and intake at a subsequent buffet meal. The relevance here was that MSG (level not reported) was used to modify the flavor of the savory condition. Overall, there was little effect of the sensory manipulations, but notably, intake of high-fat foods was significantly lower after the MSG-enhanced savoury than the sweet preload.

Building on the findings of reduced recovery of hunger after an umami-enriched soup (Carter et al., 2011), and the finding that carbohydrate could have the same effects on satiety as protein if the sensory characteristics were similar (Bertenshaw et al., 2013), Masic and Yeomans (2013) tested the effects of a realistic level of MSG added to a low-energy, low-glutamate soup, and the same soup with either added protein or added carbohydrate. As in an earlier study (Carter et al., 2011), there was evidence that MSG could slow the recovery of hunger after ingestion, but only after consuming the soup with added protein (Fig. 5.2), in contrast to the results of Carter et al. (2011), who only manipulated MSG content of a low-energy (15 kcal) broth. The implication is that the MSG signal appears to be most effective when it is experienced in the context of actual protein ingestion. This might suggest that umami acts as a signal of the likely presence of protein, thus aiding more efficient processing of ingested protein, an idea further supported by a follow-up study that examined test meal intake after low- and higher-energy soup preloads with and without added MSG (Masic & Yeomans, 2014a). In that study, addition of protein to a low-energy, low-glutamate soup reduced test meal intake more than did an equicaloric carbohydrate preload. To further characterize satiety, the satiating efficiency of the two macronutrient manipulations, with and without added MSG, was calculated (Kissileff, 1984; Bellisle & Blundell, 2013). Satiating efficiency is calculated by determining what percentage of the energy difference between a treatment and control preload is compensated for by reduced intake at subsequent meals. Hypothetically, imagine someone consuming a low-energy (e.g., 100 kcal) preload on 1 day and a high-energy (e.g., 400 kcal) on a second day. If they then consumed 300 kcal less at lunch after the high-energy than after the low-energy preload, the satiating efficiency of the high-energy preload can be said to be 100%. In practice, perfect compensation in preload-satiety studies is very rare (Almiron-Roig et al., 2013; Chambers et al., 2015). Notably, when these values were calculated (Masic & Yeomans, 2014a), compensation for the added energy was significantly greater after the protein-rich soup with added MSG (62%) than in the equivalent carbohydrate condition (24%). This study therefore added to the evidence that umami can enhance satiety but that it does so particularly in the context of protein intake.

So far all of the umami-satiety studies in our laboratory had relied solely on the manipulation of MSG content only. However, earlier it was noted that cuisine favors combinations of ingredients that result in the presence of MSG + IMP, and the first study to suggest there may be a role of umami in satiety included an MSG + IMP manipulation (Carter et al., 2011). Therefore, Masic and Yeomans (2014b) examined the effects of MSG + IMP on protein-induced satiety by contrasting appetite and intake after consuming a low-glutamate soup with added energy (principally as whey protein) and a combination of MSG + IMP. In this case, there was evidence both for the expected effect of protein on satiety, with less consumed after the

high-energy protein soup than after the low-energy soup, and an overall effect of umami, with less consumed when umami was enhanced by the addition of MSG + IMP in both the low-energy and protein-enriched preloads (Fig. 5.3). They again calculated satiating efficiency and found that added protein plus MSG + IMP produced significantly greater compensation (70%) than did added protein alone (44%).

Since the series of studies in our laboratory, we are aware of a further three publications that have further investigated the possible effects of umami on satiety using the preload-satiety model. In the first of these (Imada et al., 2014), participants consumed a low-energy (8 kcal) chicken broth either alone (control), with added

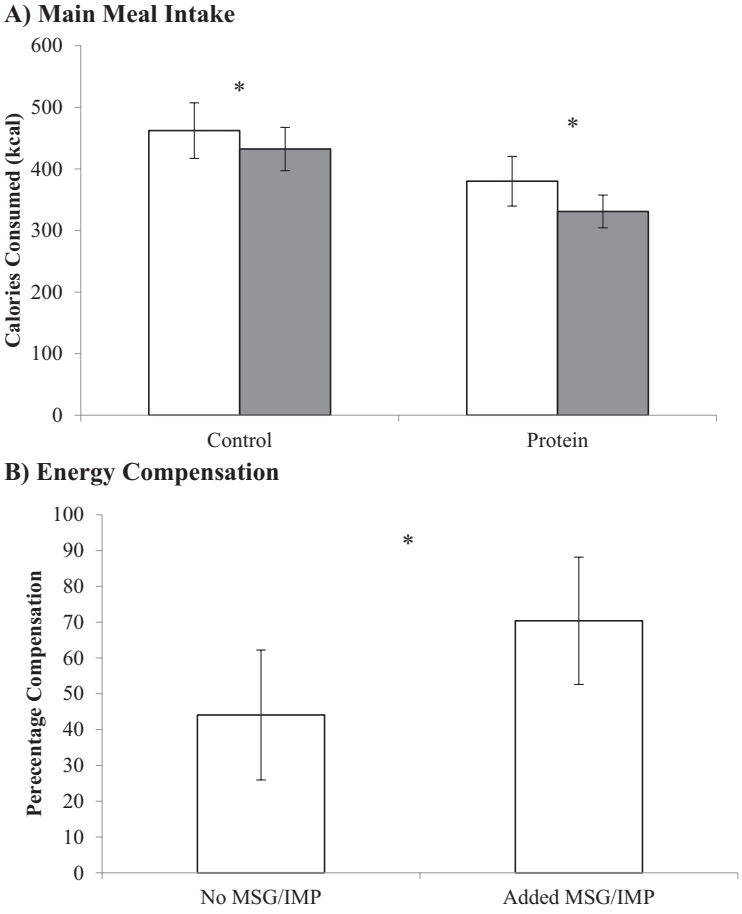

Fig. 5.3 (**a**) Intake at lunch after consuming a low-energy (12 kcal) control soup (left) or a higher-energy (310 kcal) soup, with energy mainly from protein (right), either with (white columns) or without (gray columns) added MSG/IMP (Masic & Yeomans, 2014b). (**b**) Percentage of the preload energy compensated for by reduced lunch intake after the high- relative to the low-protein preload in the control and MSG/IMP conditions. * $p < 0.05$

MSG (0.5%), or with added MSG + IMP prior to a multi-item buffet meal. Overall energy intake at the meal was lower after consuming the soup with added MSG, but not with added MSG + IMP, than in the control condition, due primarily to the reduced selection and intake of sweet and high-fat snacks. Thus, this study did suggest some direct satiating effects of a low concentration of MSG but found this in the context of a minimal-energy broth. A subsequent study by the same group tried to extend the findings from the study by Carter et al. (2011) using the two-soup intervention model in overweight individuals, with a soup naturally low in glutamate (Miyaki et al., 2016). Again, addition of 0.5% MSG to this soup reduced subsequent food intake at a test meal and also reduced rated hunger between soup ingestion and the start of the meal.

In the most recent two experiments to examine the effects of umami on satiety, Anderson et al. (2018) attempted to replicate and extend the earlier findings of Masic and Yeomans (2014a). The key differences were the use of a slightly larger preload (500 mL instead of 300 mL), a longer gap between preload and test meal (120 min instead of 45), and measurement of satiety-related hormones as additional measures of satiety. In their first experiment, the high-protein soup with MSG sustained fullness for a longer period than did all other treatments, but MSG had no significant effects on intake at the test meal. In their second experiment, subjective appetite was significantly lower after the protein soup with added MSG than after all other conditions, and intake at the next meal was significantly lower for the protein + MSG but not protein-alone conditions than in the lower-energy and water control conditions. Both experiments thus found some evidence to support a role for umami in satiety, replicating earlier studies. The second experiment also found some changes in physiological markers that further supported these behavioral satiety findings: the protein + MSG preload but not the protein-alone preload resulted in increased levels of insulin and C-peptide (an early-stage marker for insulin synthesis) and also lowered blood glucose.

At face value, of the 13 experiments examining effects of MSG on satiety, 9 reported at least some evidence supporting a role for umami in satiety, and of the 4 that did not, 3 were from the first study to examine this question. Closer inspection of the designs of these studies gives clues to why some did not find evidence of umami-enhanced satiety. The first key design issue appears to be the dose of MSG used to manipulate umami: the dose used in the earliest three experiments (Rogers & Blundell, 1990) was considerably higher (10–20%) than in the more recent experiments finding evidence of satiety (typically 0.5–1.0%). The levels of MSG in those early studies were considerably higher than those found in normal food products, and it is notable that studies using more realistic levels of MSG found evidence of satiety enhancement. This further implies that satiety is not enhanced as a linear function of MSG concentration. The second design issue may be the size of the preload: all of the successful studies used relatively low-energy preloads (maximum of ~300 kcal), nearly always as a soup manipulation. In contrast, the study by Luscombe-Marsh et al. (2009), which found no significant effect, used a much larger preload, comprising soup plus one or two savory rolls, with the portion size adjusted to deliver 20% of the estimated energy requirements for each participant.

The effects of umami may have been masked by the much stronger satiety from the larger preload. This in itself raises important questions about the nature of the satiety signal umami generates, discussed in depth further below. A final issue worth noting is that many studies did not fully control the level of umami taste in the control conditions of these studies, which hinders interpretation. For example, if the level of umami in the control was already sufficient to signal the possible presence of protein, then additional MSG might not add any new information that could affect appetite.

5.3.2 Glutamate and Satiety in Human Infants

Although it is less possible to conduct direct studies of the role of umami in satiety in infants and children, further insights into the potential impacts of umami on satiety have been provided by studies exploring differences in weight gain associated with breast-feeding and bottle-feeding practices in humans. In relation to umami taste, one of the most surprising observations is that human breast milk has as much as 19 times the free glutamate content of cow's milk (Van Sadelhoff et al., 2018). That observation allowed researchers to consider what role umami might have in control of infant feeding (Mennella et al., 2011; Ventura et al., 2012, 2015), in the context of the well-established finding that human infants who are bottle-fed a diet of standard cow milk formula (CMF) typically gain more weight than do babies who are breast-fed (reviewed by Appleton et al., 2018).

In addition to the difference in free glutamate, there is a notable difference in overall protein content of the two main milk sources fed to human infants: CMF has more protein overall than does human breast milk, and consequently, formula-fed infants have much higher protein intake (55–80% more, adjusted for body weight; Alexy et al., 1999) than do breast-fed infants. Because protein is more satiating than other macronutrients, we might expect that CMF would be more satiating than is breast milk and that the faster weight gain seen in CMF-fed infants cannot be attributed to a lack of satiety from feeding. However, while CMF has higher overall protein content, it has lower overall levels of free amino acids, most notably glutamate. When the growth rate of human infants was contrasted between standard CMF and a formula with protein that had been extensively hydrolyzed (EHF), which consequently had a much higher free amino acid content (Mennella et al., 2011), those fed on EHF had more normative weight gain than those fed standard CMF, and their growth rates were in line with predictions for breast-fed infants (for further details, see Chap. 5 in this volume). Hydrolyzing the protein in the formula had a particularly large effect on levels of free glutamate, with 106.5 mg/100 mL in the hydrolyzed formula compared to just 1.8 mg/100 mL in CMF. These short-term effects were subsequently verified in a larger randomized controlled trial to more fully determine the direct impact of standard CMF and EHF on infant growth (Mennella et al., 2018). Replicating the initial finding, that study found evidence of sustained slower growth in body weight for infants fed with EHF, which persisted

across the first year of life, because infants ingested more CMF than EHF, driven at least partly by a reduced intake of EHF, which was more satiating.

More remarkably, the same group extended this work to contrast whether the presence of free amino acids affected actual infant feeding (Ventura et al., 2012). Infants attended the laboratory on three occasions to consume two meals with each of three formula diets: CMF, EHF, and CMF with added MSG. Infants fed both with EHF and MSG-enhanced formula consumed less at the first meal than they did with CMF, and a longer interval elapsed before they signaled readiness for their second meal, and they did not compensate by consuming more at that second meal. Thus, both reduced immediate intake and delayed demand for the second meal are consistent with an effect of umami taste on satiety in human infants, adding further weight to the idea that umami has a clear role in regulating human appetite. A subsequent study explored the feeding style of infants fed standard and CMF with added glutamate (Ventura et al., 2015). Infants consumed less of the glutamate-enhanced CMF and tended to feed for shorter times. Although detailed analysis of feeding behavior (from video analysis) found few differences between diets, there was evidence that the distinct end-of-meal behaviors seen later in meals became evident sooner with the glutamate-enhanced formula. The reduction in intake, shorter feeding duration, and earlier switch to end-of-meal behaviors might be consistent with increased satiety from the glutamate-enhanced CMF.

5.3.3 Protein Need State, Satiety, and Liking for Umami Taste

The evidence to date suggests a likely role for umami taste in satiety in humans but is far from conclusive. The inconsistent results among studies that explicitly explored umami taste and satiety in particular (see Table 5.1) suggest that any such role of umami may be specific to very defined conditions, and so whether this realistically contributes to satiety in real life may be questionable. However, if umami acts as a signal for the likely presence of protein, then biologically it would make sense for sensitivity to that umami signal to also vary depending on individual protein need state. If so, the variability in study outcomes could relate to differences in acute and habitual protein intake across study designs and individual participants.

As discussed earlier, regulation of protein intake appears much more tightly controlled than fat and carbohydrate, and this may in turn mean that sensitivity to umami taste, including its effects on satiety, may also vary with both habitual protein intake and acute protein need. Thus, the final set of studies explored in this chapter tested how responses to umami taste and/or wider savory evaluations vary in relation to both acute and longer-term protein intake. The focus again is on human studies because of the suggested evolution of a specific role for umami coinciding with when humans first started to cook food (Hartley et al., 2019; Valente et al., 2018).

In support of responses to MSG varying with protein need state, a number of older studies in humans reported stronger preferences for foods with higher MSG content in both adults (Murphy, 1987) and children (Vazquez et al., 1982) when in

protein-deficient states or with poor nutritional status compared to well-nourished controls. Some studies have also reported that liking for savory flavors varied with acute protein status. In this context, one study in particular suggested that participants' ability to respond to experimentally manipulated acute protein deficit (by provision of low-protein breakfasts) has to be learned: participants who were acutely protein deprived came to prefer a dessert flavor that was previously paired with the delivery of more protein relative to participants tested and trained in the absence of acute protein lack (Gibson et al., 1995). That study did not specifically manipulate umami taste, but the demonstration that acute protein need heightened sensitivity to sensory characteristics of a protein-rich product fits the wider idea that umami promotes protein choice in the protein-deprived state. Specific evidence that acute protein deprivation modifies the response to MSG came from a study that examined responses to umami, salty, and sweet tastes in participants in relation to acute protein need (by manipulating earlier protein intake) and habitual protein intake (Masic & Yeomans, 2017). In that study, acute protein deprivation increased liking regardless of MSG concentration (Fig. 5.4a), and crucially, this effect depended on habitual protein intake (Fig. 5.4b). Here, liking for the strongest (1%) MSG soup decreased as a function of habitual protein intake after consuming a protein-rich breakfast, but not after the low-protein or baseline (habitual) breakfast. Because the high-protein breakfast would have been predicted to generate higher satiety, the implication is that expression of liking for umami is suppressed by protein-induced satiety. This suggests that umami's role in appetite control is fine-tuned to control protein intake, with increased preference for umami driving protein intake in the context of either habitual low-protein intake or acute protein need. Moreover, if the

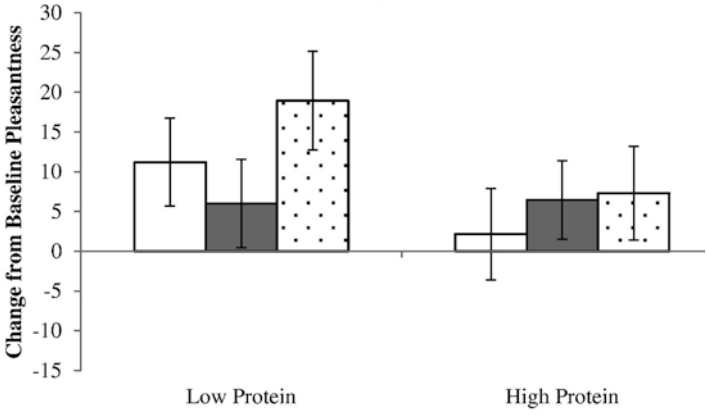

Fig. 5.4 How acute and habitual protein intake modified hedonic responses to umami taste (Masic & Yeomans, 2017). (**a**) Overall changes in liking from baseline for a low-glutamate soup with 0% (white columns), 0.6% (gray columns), or 1.0% (dotted columns) added MSG evaluated 2 h after consumption of a low- or high-protein breakfast. * $p < 0.05$. (**b**) Absolute liking for soup with 1% added MSG as a function of habitual protein intake on the baseline (normal breakfast) day (black line) and after days when participants consumed a specific low-protein (dark gray line) or high-protein (light gray line) breakfast

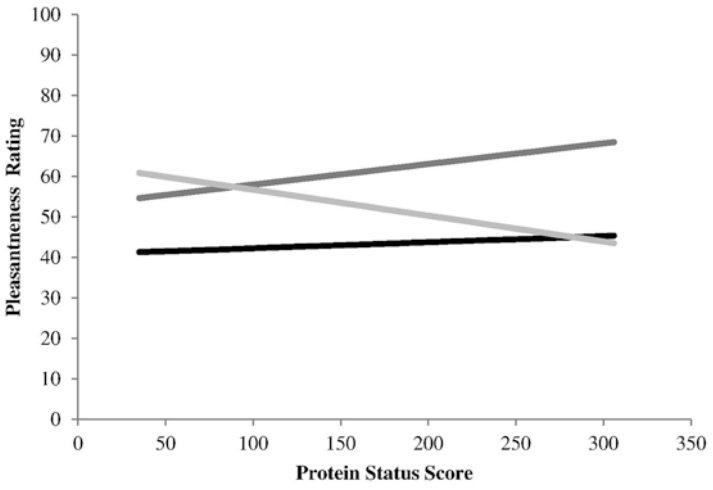

Fig. 5.4 (continued)

body monitors protein intake, at least in part, through experience of umami taste, then increased exposure to umami taste may in turn result in reduced preference for umami, an idea supported by a recent study where repeated exposure to umami resulted in a generalized decline in liking for umami taste (Noel et al., 2018).

5.4 Possible Models for Umami-Enhanced Satiety in Humans

If umami taste does have a role in short-term regulation of food intake, particularly associated with satiety in the context of regulation of protein intake, a key question is how this might work. The original idea that umami taste evolved to allow us to sense protein in our diet (Ikeda, 1908) would not necessarily suggest that umami should play a role in satiety: umami might direct food choice to protein-rich sources, but the control of intake could be achieved through other satiety processes. However, as discussed in detail above, intake of protein appears to be much more tightly regulated than intake of other macronutrients. Thus, the effects of umami on satiety might suggest umami taste has a role beyond food choice to help regulate protein intake. How might that regulation be achieved?

Protein has been shown to be more satiating than other macronutrients, but this is most evident where the sensory characteristics of the ingested food include cues that predict the likely presence of protein (Bertenshaw et al., 2013). Umami taste may be one of the most reliable predictors of protein in the context of the cooked foods that most humans consume. This is supported by the positive findings of most studies that examined the effects of umami taste on satiety and included a protein-rich manipulation (Table 5.1). Although these effects were relatively subtle, these studies found at least some evidence (in terms of altered intake and/or enhanced

subjective satiety) that the combination of MSG + protein was more satiating than would be predicted from the sum of the separate effects of protein and MSG alone. Although how umami taste magnifies the satiating effects of protein is not clear, two possible models are presented here that might be explored in future research.

The first model builds on increasing evidence that the orosensory experience of foods generates consumer expectations about the level of satiety they will experience postingestion (Chambers et al., 2015). There is now a wide variety of evidence that both sensory and cognitive characteristics of ingested products can modify these satiety expectations and that these expectations then interact with actual nutrient consumption to generate satiety. Beyond umami, at a sensory level, two examples are (1) where perceived thickness and creaminess of a beverage generated predictable expectations about satiety (McCrickerd et al., 2012), and these same expectations then modified the degree of satiety generated by a disguised nutrient load (Yeomans & Chambers, 2011), and (2) where differences in oil-droplet size likewise altered satiety expectations (Lett et al., 2015) and actual satiety (Lett et al., 2016). To date, studies have not explicitly tested how manipulation of umami modifies satiety expectations, but the prediction would be that the increasing savory characteristics of umami-rich foods would generate stronger satiety expectations. However, if umami simply generated satiety expectations, then any nutrient-rich food that has some level of umami taste should be more satiating than the same nutrients without umami taste. What is more complicated with umami is that the effects seem to be protein specific, which argues against a generalized expected satiety model. However, if the expectations generated by umami were confirmed by protein sensing in the gut postingestion, this model offers a plausible account. It is now well established that the TAS1R1 and TAS1R3 receptor units that underlie umami taste when glutamate is detected in the mouth are also present throughout the gastrointestinal tract (Kondoh et al., 2009; San Gabriel & Uneyama, 2013), although as with other postoral taste receptors, activation of these receptors does not result in our "tasting" food in our gut. Instead, it is widely believed that these gut-based receptors monitor nutrient levels (e.g., Shirazi-Beechey et al., 2014; Raka et al., 2019), perhaps fine-tuning digestive processes depending on the balance of ingested nutrients.

If the impact of umami on satiety was mediated through expectations, then we would predict that umami taste would enhance behavioral measures of satiety expectations and have measurable effects in brain areas associated with these expectations. To date, there has been no detailed evaluation of effects of umami on expected satiety, and likewise, the neural representation of expected satiety has not been elucidated. However, a number of studies with human volunteers have looked at neural responses to umami taste, which allow some inference of the plausibility that umami enhances protein-induced satiety by generating expected satiety. Early studies established that umami taste is represented in the primary and secondary gustatory cortex, incorporating the anterior insula, frontal operculum, and the orbitofrontal cortex (OFC: e.g., Schoenfeld et al., 2004; McCabe & Rolls, 2007; Singh et al., 2015). The OFC has also been shown to have a role in sensory-mediated satiety (O'Doherty et al., 2000). More importantly, the OFC has been shown to have

a critical role in predicting reward value (e.g., O'Doherty, 2007; Hare et al., 2008; McDannald et al., 2012), and because satiety expectations are neural predictions of the potential impact of ingestion on satiety, it would be predicted (but as yet not tested) that OFC neurons would play a critical role in satiety expectations. Thus, although no studies to date have formally tested an expected satiety model of umami-enhanced satiety, current knowledge of encoding of umami taste and broader prediction are both consistent with an expectation-based model.

An alternative to the expectation-mediated effects of umami on satiety would be a more direct effect of umami on the physiological systems known to be involved in satiety. Of principal interest are the specific hormones released in the gut in response to nutrient ingestion (see Chaudhri et al., 2008; for reviews Zanchi et al., 2017), which include cholecystokinin (CCK), pancreatic polypeptide, glucagon-like peptide, and polypeptide-YY. CCK is of particular interest, since studies in vivo and in nonhuman animals have provided some evidence that stimulation of the intestinal TAS1R1 + TAS1R3 complex can stimulate CCK release (Daly et al., 2013; Tian et al., 2019). If this is the cause of the enhanced satiety seen in some human appetite studies, then it would be predicted that circulating CCK levels would be raised after consuming umami-tasting foods, particularly in the context of protein consumption. In this context, it is notable that one study in human volunteers found evidence of reduced hunger, but not increased CCK, following intragastric infusion of umami tastants (Van Avesaat et al., 2015). A more recent study examined effects of umami taste and ingestion on glucagon-like peptide and again found no evidence of any change in hormone levels (Anderson et al., 2018). Thus, the only two studies that examined changes in satiety hormones after umami did not find evidence in humans to support the suggested effects of umami on CCK release reported elsewhere. Overall, while a direct effect of umami taste on gut-based satiety signaling cannot be discounted, to date there is no evidence for this.

Finally, although the expectation-based and gut signaling-based models of umami-based satiety are discussed here as separate potential models, in practice control of appetite is multifaceted and integrated. Notably, there is increasing evidence of top-down control of gut-based satiety signaling (e.g., Crooks et al., 2021) and, in particular, that sensory characteristics of products that generate satiety expectations may also enhance gut-based release of CCK (Yeomans et al., 2016).

5.5 Uncertainties and Future Directions

This chapter reviews evidence that umami may enhance satiety in humans and identifies important shortcomings in our current knowledge. The wider idea that umami is an alimentary taste (Keast et al., 2021) that may have evolved in humans in the context of our use of fire to modify protein prior to ingestion complicates the investigation of umami-induced satiety since it implies that the role of umami in humans may differ from that in other species. Usually findings in humans are verified by more detailed physiologically based studies in nonhuman animals, but in this case

such studies may not be appropriate tests of the role of umami in satiety in humans. Instead, more detailed human studies are needed to meet specific shortcomings in the literature, including (but not limited to) the effects of umami taste on satiety expectations, more detailed evaluations of neural responses to umami taste in relation to satiety, and more highly powered and sustained studies of the effects of umami-enriched products on satiety. A further complication is that many products already have appropriate levels of satiety signals that match the relevant nutrient content; adding umami taste in that context could lead to a mismatch between the sensed taste and nutrient content, an issue that has been noted in the context of sweet taste and carbohydrate-based calories (Veldhuizen et al., 2017).

5.6 Conclusions

This chapter evaluates the evidence that umami taste may impact satiety in humans. The evidence that umami predicts protein, as originally suggested by Ikeda (1908), does not look convincing until the cooked state of the food humans ingest is taken into consideration. In the context of cooked food, the idea that umami predicts protein is plausible and also fits with evidence of how the system of sensing umami taste evolved. Although not all studies reviewed found evidence of enhanced satiety, the balance of evidence, particularly where the level of umami enhancement is physiologically realistic, does suggest a subtle effect of umami on satiety. In particular, the evidence suggests that umami increases the degree to which protein is satiating, which may explain why protein has been found in general to be more satiating than other macronutrients. Future research is needed, however, to understand the mechanisms through which umami enhances satiety. This chapter offers the suggestion to focus on two models, one based on prediction error and expectations and the other on physiological satiety cues.

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Chapter 6
Umami Taste: Inborn and Experiential Effects on Taste Acceptance and Satiation During Infancy

Ana San Gabriel and Julie A. Mennella

The sensation of taste, which has been classically delineated into the five basic taste qualities of sweet, sour, salt, bitter, and umami (Beauchamp, 2019), has attracted great interest in recent years as a major determinant of what we eat—an overlooked aspect of nutrition (Kershaw & Mattes, 2018). Taste plays a critical role as the gatekeeper of what enters the body, guarding against ingestion of dangerous substances (e.g., bitter-tasting poisons) (Glendinning, 1994) while encouraging consumption of foods important for growth and development (Kurihara, 2015; Gabriel et al., 2018), including mother's milk, readily available glucose in energy-containing plants (e.g., sweet fruits) (Beauchamp, 2016), a needed mineral (salt) (Beauchamp, 1987), and proteins (umami)—particularly the taste of the amino acid L-glutamate (Glu) and 5′-ribonucleotides (Beauchamp, 2009). In the context of feeding, these taste sensations naturally co-occur with other sensory modalities, including olfaction and chemesthesis.

This chapter focuses on umami taste in infancy. As a basic taste, the scientific investigation on umami has received perhaps the least attention in developmental studies, especially when compared to the ontogeny of sweet and salty tastes (Mennella et al., 2016a; Beauchamp & Mennella, 2009). We provide an overview of the basic biology of umami taste, from the distribution of umami taste receptors throughout the oral cavity and gastrointestinal system to its role in flavor, palatability, and food intake. We then summarize the scientific evidence on early routes of umami exposure and children's inborn and learned responses to its taste and satiating properties. We focus on the first year, when infants make the drastic transition from eating an all-liquid diet of human milk, artificial milk (infant formula), or

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both, to one containing both liquid and solid foods (Grummer-Strawn et al., 2008). This body of scientific evidence derives from a variety of precise and detailed measurements of infants' orofacial responses and well-controlled paradigms that measured their behavioral responses, intake, and satiation (Ventura & Mennella, 2017). Often the umami stimulus studied was L-glutamate, in the form of the sodium salt monosodium glutamate (MSG).

6.1 Umami Taste in the Oral Cavity and Alimentary Canal

One century after Kikunae Ikeda's description of the fifth basic taste of umami (Ikeda, 2002), scientific breakthroughs revealed its perception is mediated by activation of heterodimeric G-protein-coupled receptors (GPCRs) encoded by members of the type 1 family of taste receptor genes, *TAS1R1* and *TAS1R3* (Nelson et al., 2002; Bachmanov et al., 2016) (see Chaps. 1 and 2). In addition to the TAS1R genes, other GPCRs act as umami receptors: truncated taste versions of the metabotropic glutamate receptors (mGluRs) found in many neuronal cells, mGluR4 (Chaudhari et al., 2000a) and mGluR1 (Chaudhari et al., 2000a; Yasumatsu et al., 2015; San Gabriel et al., 2009). These umami receptors, located throughout the oral cavity and alimentary canal, are activated only by free amino acids (FAAs), not by amino acids bound in the form of proteins (Keast et al., 2021). The locations of these receptors underlie their different roles in signaling the presence of taste-reactive FAAs, which not only generate the perception of umami taste but also modulate complex digestive processes such as gastric emptying and satiety.

6.1.1 Oral Cavity and Taste Psychophysics

The T1R1 + T1R3 heterodimer receptor and mGluRs are located at the tip of taste cells distributed across the tongue (Yasumatsu et al., 2015). When activated by free L-amino acids (e.g., free Glu), 5′-ribonucleotides, or salts of glutamic acid (e.g., MSG), these receptors transmit signals to the brain. The taste of Glu is synergistically enhanced by the sodium salts of 5′-inosine monophosphate or 5′-guanosine monophosphate.

Psychophysical studies revealed that MSG imparts a "savory" and "satisfying" sensation (Rogers & Blundell, 1990), increasing the palatability of a variety of foods, due in part to its ability to block bitter tastes (Mennella et al., 2014a). Beauchamp (2009, 2019) suggests that umami also increases palatability by functioning as a flavor enhancer (Beauchamp, 2009; Hartley et al., 2019), but the food matrix in which umami-tasting compounds are experienced is important. Although unpalatable when tasted alone or in aqueous solution, umami compounds are palatable in broth and improve the flavor of a variety of foods and flavors (Beauchamp, 2009; Yeomans et al., 2008; Yamaguchi & Takahashi, 1984), imparting a pleasant

"mouthfeel" sensation of fullness (Prescott, 2004). Glu occurs naturally in many foods, such as meats, cheeses, broths, and tomatoes, and imparts a savory taste (Gabriel et al., 2018; Ninomiya, 2003). It is notable that many cultural food traditions intended to preserve food or increase its nutritional value (e.g., extraction, curing, aging, fermentation) often increase the food's FAA, including Glu, content (Ninomiya, 2015).

6.1.2 Alimentary Canal and Feeding Behaviors

Outside of the oral cavity, T1R1 + T1R3 receptors and mGluRs are scattered widely along the lower alimentary canal, comprising the stomach (San Gabriel et al., 2007) and small intestine, where they regulate digestion, absorption, and metabolism of nutrients, especially amino acids (Keast et al., 2021). Although perception of umami taste in the mouth is a conscious sensation indicating the presence of free Glu in foods, the detection of Glu in ingested food by the gastrointestinal tract is not (Hartley et al., 2019). Instead, when umami compounds bind to receptors in the gastrointestinal system, nerves are activated, hormones are released, or both (Kondoh et al., 2009; Daly et al., 2013; Shirazi-Beechey et al., 2014). Electrophysiological studies have revealed that binding of MSG to the stomach lining, probably via stomach mGluR1, can activate the vagus nerve by releasing bioactive molecules such as serotonin (Uneyama et al., 2006), whereas molecular and physiological studies suggest that free Glu in ingested food potentiates gastric digestion and emptying of amino acid-rich foods (San Gabriel et al., 2007; Zolotarev et al., 2009). In the intestine, the binding of free Glu to T1R1 and T1R3 receptors appears to cause secretion of the hormones ghrelin and cholecystokinin, which are known to impact gastric emptying and/or satiation (Keast et al., 2021; Vancleef et al., 2015).

Brief feeding studies in healthy adults have shown that, when added to foods such as broths and vegetables, MSG imparts a "savory" and "satisfying" sensation that enhances palatability (Rogers & Blundell, 1990; McCabe & Rolls, 2007; Rolls, 2009; Carter et al., 2011). However, results on its effect on satiation (i.e., energy intake within a meal) and satiety (i.e., energy intake during a subsequent meal) in adults have not being consistent, perhaps due in part to the wide range of experimental paradigms and participant ages and health status (Keast et al., 2021) (see Chap. 4). While some studies on healthy, noninstitutionalized adults reported that, when added to a food, MSG increased satiation and reduced intake within a meal or increased sensations of fullness (Imada et al., 2014; Miyaki et al., 2016), others reported no effects (Rogers & Blundell, 1990; Luscombe-Marsh et al., 2009; Anderson et al., 2018).

6.2 Inborn Responses to Umami Taste

At birth, human infants are well equipped to convey a range of hedonic responses to tastes, odors, and complex flavors. As reviewed by Forestell and Mennella (2017), facial expressions in particular play an important adaptive role, allowing dependent infants to convey information to caretakers about the sensations they are experiencing in their oral cavity. Head turning away and displays of gaping and puckering in response to bitter and sour tastes are often recognized as signals of disgust or rejection, whereas orientation toward the food, faster sucking, and smiling are often interpreted as a signals of liking, encouraging feeding of that particular food.

In the 1970s and 1980s, a series of pioneering studies by Steiner, Ganchrow, and colleagues revealed that, within hours after birth, newborns respond with characteristic, differential orofacial responses when small quantities of sweet-, sour-, bitter-, or umami-tasting liquids were placed on their tongue (Steiner, 1979, 1987; Ganchrow et al., 1983). Similar to infants' reactions to the taste of sugars, the facial responses to the taste of umami appear to be primarily inborn and preferred (Steiner, 1987). Newborns responded with increased sucking and mouth movements and relaxation of their face when tasting soup broth containing 0.1% and 0.5% MSG but rejected MSG when presented in water solutions. Research on older infants (2–24 months) confirmed the rejection of Glu in plain aqueous solutions (Beauchamp & Pearson, 1991) and the palatability of umami in the context of a food. Both well-nourished and malnourished 2- to 24-month-old infants preferentially ingested soup broth containing MSG relative to soup broth alone (Beauchamp & Pearson, 1991; Beauchamp et al., 1987).

This body of research highlights important aspects of the taste stimuli and methodological approaches needed to examine umami taste palatability. First, it is difficult to interpret findings when children are presented with only umami taste in plain aqueous solution (Schwartz et al., 2009). Rather, umami must be experienced in the context of other chemosensory stimuli when testing individual differences in the hedonics of umami taste in pediatric and adult populations (Beauchamp, 2009; Forestell & Mennella, 2017; Steiner, 1987). As suggested by Beauchamp (2009, 2019), umami functions as a flavor enhancer, increasing the palatability of flavors it is mixed with (Hartley et al., 2019). Second, when phenotyping orofacial taste reactivity, infants should not see the facial expression of their mothers during testing since they are sensitive to and mimic these facial expressions (Gunnar & Stone, 1984). Third, measurements of intake and acceptance should be based on infants' behavioral signaling of hunger and satiation (i.e., infant-led feeding paradigms) (Forestell & Mennella, 2017; Ventura et al., 2015) and not determined by mothers or experimenters, because they may under- or overfeed by not attending to the infant's satiation cues (Crow et al., 1980; Li et al., 2010).

6.3 Early Experiences with Umami: First Foods

Like the prenatal diet (amniotic fluid), the early postnatal diet is unique in that it is typically solely liquid based, consisting of human milk, infant formula, or both. The protein in these first foods supports infant growth, immune function, and behavioral development by supplying nitrogen and essential and semi-essential amino acids (Dewey et al., 1996). These first foods—amniotic fluid, human milk, and infant formula—as well as a variety of foods, from vegetables to meats, naturally contain FAAs, including free Glu (Yamaguchi & Ninomiya, 2000).

Infants' experiences with the taste of FAAs, and Glu in particular, can vary considerably. Table 6.1 summarizes the variation in the total FAA and free Glu content in amniotic fluid, human milk at different stages of lactation, and infant formulas from a range of studies. Although measures of FAAs in human fluids date back to the 1940s (Beach et al., 1941), we included only studies that used chromatography and spectrophotometry measures, omitting earlier ones that used microbiological

Table 6.1 Total free amino acids (FAAs) and free glutamate (Glu) content of amniotic fluid, human milk, and infant formula[a]

Sample	Concentration (μmol/L)		Selected References
	Total FAAs (number of FAA)[b]	Free Glu	
Amniotic fluid			
First and second trimesters	2036 (17)	149	Cockburn et al. (1970)
	1803 (16)	261	Lopez Ramon y Cajal et al. (2007)
	2230 (16)	149	Reid et al. (1971)
Third trimester	1070 (16)	48	Reid et al. (1971)
	1573 (16)	107	Levy and Montag (1969)
Human milk			
Colostrum	3321 (19)	1090	Zhang et al. (2013)
Transitional milk	2416 (19)	960	Zhang et al. (2013)
Mature milk	2481–2941 (19)	1175–1529	Zhang et al. (2013)
Infant formula			
Cow milk	523–864 (20)	86–109	Ventura et al. (2012a)
Soy	19,33–2450 (20)	0–11	Ventura et al. (2012a)
Partial protein hydrolysate	2329 (20)	113	Ventura et al. (2012a)
Extensive protein hydrolysate	80,375–85,445 (20)	7472–8226	Ventura et al. (2012a)

[a]Values represent normal pregnancies for amniotic fluid and term births for human milk. Data are presented as ranges of means when from more than one publication, from two stages of lactation, or from more than one brand of a given type of infant formula

[b]Total concentration based on the sum of all FAAs; numbers in parentheses indicate number of different FAAs summed

methods. Note that different studies used different numbers of FAAs to calculate total FAAs, ranging from 16 to 20 individual FAAs.

6.3.1 Amniotic Fluid

Much of the early research on amniotic fluid content aimed to help diagnose certain genetic disorders associated with aminoaciduria (Emery et al., 1970) or to identify biomarkers of inborn errors of metabolism (Reid et al., 1971) or placental dysfunction (Lopez Ramon et al., 2007). During normal pregnancies, FAA levels change dynamically in amniotic fluid (Reid et al., 1971) (see Table 6.1). In general, FAA concentrations in amniotic fluid and maternal plasma are higher during early pregnancy and lower in the third trimester and near term (Emery et al., 1970; Reid et al., 1971; Lopez Ramon et al., 2007; Athanasiadis et al., 2011; Levy & Montag, 1969; Cockburn et al., 1970). Such changes in part reflect the exchange of maternofetal fluids as the placenta and the fetus develop (Reid et al., 1971; Lopez Ramon et al., 2007). Amino acids are actively transported across the human placenta, mediated by specific transporters in plasma membranes (Jansson, 2001), and are also synthesized and metabolized through the placenta (Jansson, 2001; Cetin, 2001).

The time course and trajectory of changes in amniotic fluid during pregnancy differ among the individual FAAs (Reid et al., 1971; Guadalix et al., 1975). Overall, alanine was the most abundant amino acid in the amniotic fluid during gestation (Lopez Ramon et al., 2007). Although less abundant than alanine, free Glu is relatively abundant throughout pregnancy in humans (Table 6.1), whereas in other animals (i.e., pig), it is the most abundant FAA in both amniotic fluid and maternal plasma (Wu et al., 1995). From the perspective of early feeding and experiences, the human fetus actively swallows significant amounts of amniotic fluid, particularly during the last trimester (Underwood et al., 2005), so the varying amounts of FAAs and free Glu could result in differential exposures prior to breastfeeding.

6.3.2 Human Milk

For reasons not completely understood, the mammary tissue of many mammals produces large amounts of nonprotein nitrogenous compounds, including (protein-unbound) FAAs. Research quantifying the amino acid composition of human milk dates back to the 1940s and is a growing field of research, perhaps motivated by the need to improve the composition of infant formula, since human milk is the standard for human infant nutrition (Ballard & Morrow, 2013).

The total amino acid (both unbound and free) profile and the free Glu content of human milk at the three stages of lactation, colostrum (0–5 days), transitional milk (6–20 days), and mature milk (≥21 days), are shown in Table 6.1. Here we highlight the findings from a systematic review of 22 studies on both preterm and full-term

human milk (Zhang et al., 2013). The inclusion criteria for this meta-analysis were that the women who donated the human milk samples had to be healthy, have delivered a term infant of known age, and have to be consuming free-living diets and that the study provide adequate information for the milk samples, such as stage of lactation, method of extraction (e.g., type of pump) and storage (e.g., liquid, freeze-dried form), units of concentration, and geographic location. FAAs had to be quantified by ion exchange chromatography or an automatic amino acid analyzer and not by microbiological methods.

The systematic review revealed that total amounts of amino acids (both unbound and free) decline during the first 4 months of lactation and remain stable thereafter (Zhang et al., 2013), a pattern that parallels the changing protein needs of growing infants (Dupont, 2003). From the data in the review (Zhang et al., 2013) and other publications, we summarized the total FAA content in human milk across lactation (Table 6.1). The pattern of individual amino acids differs over time. While most amino acids were significantly lower in mature milk than in colostrum (i.e., leucine, lysine, phenylalanine, valine, threonine, methionine, isoleucine, taurine, arginine, asparagine, tyrosine, proline) or stayed the same (i.e., histidine, glycine, serine, cysteine, alanine), the FAA glutamine and Glu increased with progressing lactation. Overall, at each stage of lactation, Glu, glutamine, taurine, and alanine were the most abundant FAAs, with Glu and glutamine accounting for about half of FAAs at each stage, a finding consistent with our own research (Baldeon et al., 2014).

To graphically depict the changes in total FAAs and free Glu during lactation, we focused on our longitudinal study on adolescent and adult mothers that measured the FAAs including free Glu content in colostrum, transitional milk, and mature milk over time (Baldeon et al., 2014). Figure 6.1 shows variation in the relative amount of FAA Glu and all other FAAs in the milk of lactating woman during the three stages of lactation. What causes this variation and whether variation in the Glu content of the maternal diet plays a role remain important areas of future research.

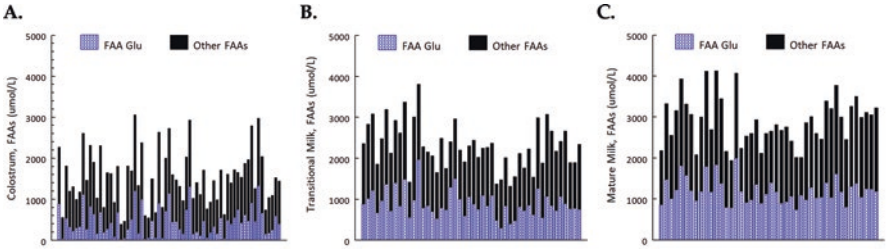

Fig. 6.1 Concentration (umol/L) of free amino acid glutamate (FAA Glu; hatched bars) and other free amino acid concentration (other FAAs; solid bars) in human colostrum (**Panel A**), transitional milk (**Panel B**), and mature milk (**Panel C**). Each bar represents an individual lactating woman (A, n = 65; B, n = 47; C, n = 45). The height of each bar represents total FAA concentration. (Data from Baldeon et al. (2014))

6.3.3 Infant Formulas

For healthy infants fed artificial milks, the four types of infant formula are currently on the market are cow milk formula (CMF), which is the most commonly consumed infant formula; soy formula; partially hydrolyzed formula; and extensive protein hydrolysate formula (EHF), a type of formula typically given to infants who have cow milk protein allergy or intolerance to intact protein (Rossen et al., 2016). Although these formulas are isocaloric and can differ in their source of carbohydrate (e.g., lactose vs. modified cornstarch), the form of the protein, the degree of hydrolysis, and in turn the concentration of FAAs are the major distinguishing factors (Ventura et al., 2012a). For example, the milk proteins (whey and casein) in hydrolysate formulas are treated with enzymes to break down their protein structure, generating FAAs, which lessens the burden of digestion and minimizes allergenicity for infants (Cook & Sarett, 1982). Thus, while infants fed any of these formulas are categorized as formula fed, they are not a homogeneous group since feeding these different formulas will lead to different exposures to proteins and FAAs, including umami-tasting compounds.

Table 6.1 presents FAA levels for the four types of infant formula. EHF had the highest levels of FAAs, averaging 120-fold higher than CMF, 39-fold higher than soy protein formula, and 36-fold higher than partially hydrolyzed formula. Compared to human milk, the concentrations of FAA and free Glu are lower in CMF but substantially higher in EHF (Baldeon et al., 2014; Ventura et al., 2012a; Agostoni et al., 2000a, 2000b). Quality control measures and manufacturing standards for infant formula minimize variations in FAA content for a given type of infant formula. For example, infants fed different brands of CMF will have a similarly low exposure to free Glu (Ventura et al., 2012a), compared to those fed breast milk, and infants fed EHF will ingest substantially higher concentrations of FAAs, experiencing different tastes (Ventura et al., 2012a). Psychophysical testing among adult sensory panels has revealed that EHF tastes less sweet, more bitter, and more savory than CMF, due in part to the differences in FAA content (Mennella & Beauchamp, 2005; Ventura et al., 2012b).

6.4 Effects of Early Umami Experiences on Taste Acceptance

Before tasting solid foods, infants are exposed to varying amounts of umami tastes in amniotic fluid, human milk, and the different infant formulas. Mennella, Beauchamp, and colleagues have used the differential early exposure to free Glu and umami flavors of infants feed exclusively human milk, CMF, or EHF as an experimental model system to study early flavor learning, food acceptance, satiation, growth, and the developing microbiome (Ventura & Mennella, 2017; Mennella & Trabulsi, 2012; Mennella et al., 2009, 2014b, 2022).

Forestell, Mennella, and colleagues (Mennella et al., 2009) used the striking differences in the taste and FAA content among human milk and infant formulas to understand how the earliest feeding experiences modify orofacial reactivity and intake of umami and other basic tastes both before and after the introduction of solid foods. At the time mothers decided to add cereal to their diets, 4- to 9-month-old infants who were exclusively fed human milk, CMF, or EHF were tested on six occasions, in counterbalanced order, for their acceptance of the basic tastes in a cereal matrix: sweet (0.56 M D-lactose), salty (0.1 M NaCl), bitter (0.24 M urea), savory (0.02 M MSG), and sour (0.006 M citric acid).

The type of milk infants were fed with affected their liking and acceptance of the basic tastes in a food matrix. Breastfed and EHF-fed infants were more likely than CMF-fed infants to smile (facial relaxation) while eating the Glu-flavored cereal, which likely reflects their exposure to the high concentrations of free Glu found in human milk (Baldeon et al., 2014; Agostoni et al., 2000a) and in EHF (Ventura et al., 2012a). However, breastfed infants do not all have the same flavor experiences early in life, because human milk has a great degree of individual variation in taste-reactive chemicals (for review, (Mennella, 2007; Spahn et al., 2019; Mennella et al., 2017)), including Glu (Baldeon et al., 2014) (see Fig. 6.1), and thus in the taste experiences of their infants, which presents difficulties in interpreting the results.

After weaning to table foods, as caloric intake from infant formula declined, infants' preferences for the basic tastes in cereal reflected the types of foods they had been fed: infants who ate pasta and other foods that contained cheese or tomatoes, which have naturally occurring free Glu, showed greater acceptance of the MSG-flavored cereal (Mennella et al., 2009).These findings are consistent with results from randomized feeding trials that revealed differences in food preferences in children fed EHF or CMF years after their last taste of the formula (Sausenthaler et al., 2010; Mennella & Beauchamp, 2002; Trabulsi & Mennella, 2012): the preference for umami flavors depended on the type of milk fed (Mennella & Castor, 2012; Mennella et al., 2011a). CMF and EHF differ in composition, in the profiles of volatile flavors, and in tastes other than umami, and the evidence suggests that palatability is personal, dependent on experience.

Experimental evidence demonstrates the plasticity in flavor learning during infancy. By experimentally manipulating the timing and length of exposure to EHF, Mennella, Beauchamp, and colleagues discovered a sensitive period for flavor programming during which feeding EHF renders this formula highly palatable and accepted throughout infancy (Mennella et al., 2004, 2011a). Infants introduced to EHF during the first 3.5 months accept its taste, but this acceptance diminishes in infants first introduced when they are older than 4 months (Mennella et al., 2014b; Mennella & Beauchamp, 1998). Infants exposed to EHF for at least 1 month during this sensitive period do not reject its taste when they are older: they feed EHF to satiation, prefer EHF to CMF, and do not display facial expressions of distaste while feeding, and mothers perceive their infants enjoy its taste (Ventura et al., 2015; Mennella et al., 2004, 2011a). Moreover, the flavors experienced during early breastfeeding and formula feeding "imprint" and remain preferred for a considerable time thereafter (Mennella et al., 2009, 2017; Sausenthaler et al., 2010; Schuett

et al., 1980; MacDonald et al., 1994; Owada et al., 2000; Liem & Mennella, 2002; Hepper et al., 2013). Whether variation in the umami content of the maternal diet during pregnancy and lactation results in differential exposure by their infants in amniotic fluid and human milk, respectively, is an important area for future research.

6.5 Satiation, Satiety, and Growth

Relative to intact proteins, hydrolyzed proteins are absorbed and metabolized more rapidly than intact proteins (San Gabriel et al., 2007). Indeed, in feeding trials, young infants ingested more CMF to satiation than they did EHF (Ventura et al., 2012b, 2015; Hyams et al., 1995; Mennella & Beauchamp, 1996; Mennella et al., 2011b). To our knowledge, only a few experimental studies in infants have investigated the effects of MSG content on satiation (intake within a meal) and satiety (one meal's effect on intake at subsequent meal) (Ventura & Mennella, 2017; Ventura et al., 2012b).

Because Glu is the most abundant FAA in EHF (Ventura et al., 2012a), we conducted a within-subject, two-meal, 3-day study to determine whether the differences in the satiation effects of CMF and EHF were due to differences in free Glu content (Ventura & Mennella, 2017; Ventura et al., 2012b). The experimental design allowed for infants to determine the timing and duration of each meal on each testing day. In randomized order, they were fed one of three isocaloric formulas during the first meal—CMF, EHF, or CMF—plus added free Glu, in the form of MSG, to approximate levels in EHF (CMF + Glu). When infants signaled hunger several hours later, they were fed a second meal of CMF.

As shown in Fig. 6.2, the infants consumed significantly less CMF + Glu and EHF than CMF during the first formula meal, whereas intake during the second formula meal did not differ across the three testing days. Thus, adding free Glu to CMF was sufficient to induce greater satiation compared to CMF alone. That is, the infants consumed less of the two formulas higher in free glutamate (EHF, CMF + Glu) (Ventura et al., 2012b) and began displaying satiation behaviors earlier compared to feeding CMF alone (Ventura et al., 2012b, 2015), and they did not compensate at the next meal (Ventura et al., 2012b). Thus, levels of free Glu in formula affect intake, suggesting that what infants are fed may be as important as how they are fed.

As stated earlier, although isocaloric, CMF and EHF differ not only in the content of FAA Glu but also in macronutrient composition. For example, EHF contains higher concentrations of FAA and has cornstarch as the carbohydrate source, whereas CMF contains mainly intact proteins and has lactose as its carbohydrate source. Nevertheless, long-term feeding trials have consistently revealed more normative weight gain and decreased risks of diseases during childhood in infants fed EHF compared to those fed CMF. The growth trajectories of EHF-fed infants were normative and comparable to infants fed human milk (Mennella et al., 2011b), whereas infants randomized to CMF experienced accelerated weight gain during

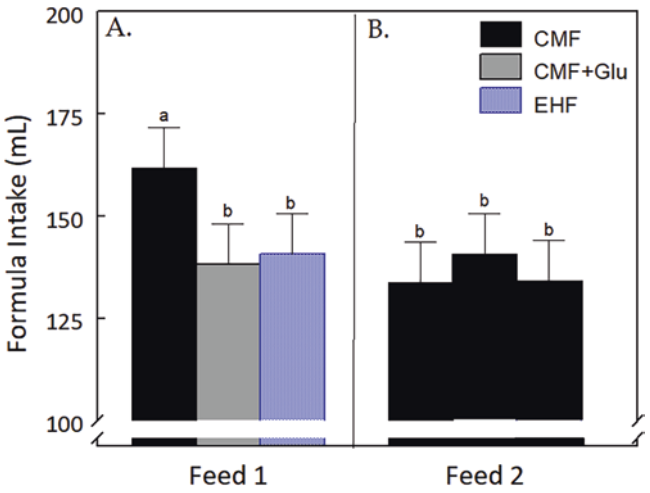

Fig. 6.2 Amount of formula (mL; mean ± SEM) ingested during three separate test sessions that occurred on three separate days. In counterbalanced order, infants were fed CMF (black bars), CMF with added Glu (CMF+ Glu; gray bars), or EHF (blue bars) during the first formula meal (A, Feed 1). Infants were fed CMF alone during the subsequent formula meal (B, Feed 2). Intake during the first formula meal, but not the second, differed across the three testing days. Different superscripts (a, b) indicate significantly different at $P < 0.05$. (Adapted with permission from Ventura et al. (2012b))

the first 4 months due to both lower energy loss and greater energy intake (Mennella et al., 2018). Two of these trials enrolled healthy infants with a family history of atopy (Roche et al., 1993; Rzehak et al., 2009) for the first 4 months (Rzehak et al., 2009) or 6 months (Roche et al., 1993), and two other trials both randomized healthy 2-week-old infants with no history of atopy to feed either EHF or CMF for 8.5 months (Mennella et al., 2011b) or 12 months (Mennella et al., 2018). In the latter trial, while within the range of typically growing infants, body weight-for-length Z scores between CMF- and EHF-fed infants remained significantly different during the first year. Because the World Health Organization standards established the growth of breastfed infants as the norm (WHO Multicentre Growth Reference Study Group, 2006), that the Z scores of infants fed EHF tracked at zero means their growth was similar to that of breastfed infants. Three other trials, each of shorter duration and with fewer subjects, did not report growth differences but did report greater satiation when infants are fed EHF than when fed CMF (Hyams et al., 1995; Vandenplas et al., 1993; Borschel et al., 2014).

Taken together, the experimental evidence reviewed herein reveals that infants respond to differences in the FAA content of their milk, in terms of intake within a meal in the short term. Whether the higher concentrations of free Glu in human milk and EHF (see Table 6.1) are the underlying mechanisms for the more normative weight gain, which is associated with lower risks of obesity in the longer term (Trabulsi et al., 2020; Zheng et al., 2018), is an important area for future research, because early rapid weight gain (Mennella et al., 2011b, 2018; Rzehak et al., 2009)

is a consistent and established risk factor for later obesity and other comorbidities (Zheng et al., 2018; Monteiro & Victora, 2005; Woo Baidal et al., 2016).

6.6 Summary

From an early age, the flavor and metabolic functions of umami taste are evident in humans. Infants are born with the capacity to detect and prefer umami taste, like they do with sweet taste, but only when it is presented in the context of a food, not in plain water, similar to findings in adults. Inherent plasticity is associated with this taste, which interacts with early experience to vary preference based on what infants are fed. Beginning with the first foods, the content of free Glu in amniotic fluid varies during pregnancy, as well as during lactation, and varies by type of infant formula. After birth, those fed human milk or protein hydrolysate formulas will have greater exposure to free Glu than those fed CMF. During early milk feedings, Glu and perhaps other FAAs can modulate satiation in the short term and growth and risks of obesity in the long term (Mennella et al., 2014b). We hypothesize that, because they are unbound, FAAs can be sensed by receptors in both the oral cavity (Chaudhari et al., 2000b) and intestinal and gastric walls (San Gabriel & Uneyama, 2013), likely conferring beneficial physiologic and metabolic effects (Ventura et al., 2012b; Mennella et al., 2011b; Burrin et al., 2008).

Experience with umami continues to evolve as children begin to eat the foods of the table. Like other flavors and tastes, these early feeding experiences "teach" children what foods are safe and what foods are eaten and preferred by their caregivers and family (Mennella et al., 2016b). In general, early experiences change not the taste quality per se but its palatability—a more labile feature of a food that drives eating behaviors and food choice (Mennella et al., 2020).

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Chapter 7
Umami and Healthy Aging

Minoru Kouzuki and Katsuya Urakami

7.1 Introduction

The World Health Organization has declared 2021–2030 as the Decade of Healthy Ageing, calling for coordinated actions by governments, civil society, international agencies, professionals, academia, media, and the private sector over the next decade to attain sustainable development goals (World Health Organization. UN Decade of Healthy Ageing, 2020). This includes ensuring that the people, families, and communities age healthily as the world's population ages at an accelerating rate. In Japan, the average life expectancy and healthy life expectancy are among the highest in the world (World Health Organization. World Health Statistics, 2021), and this is considered to be due to the high level of medical care and improvement in the healthcare system relative to the past. However, it has also been suggested that the Japanese dietary patterns play a role in reducing the mortality risk (Matsuyama et al., 2021). The typical Japanese diet is a well-balanced diet with a wide variety of ingredients that leads to the intake of many beneficial nutrients. The Japanese people have a great interest in food, and Japan has many of the world's most advanced technologies and ideas. Therefore, the contribution of the food industry to health is likely to be significant. We believe that efforts in various areas are necessary for healthy longevity, and diet is one of the most important areas.

Humans acquire nutrients predominantly by consuming food, which helps maintain homeostasis in the body. In other words, daily diet plays an important role in maintaining good health throughout one's life. Especially in older adults, it is important to maintain good nutritional status by consuming sufficient nutrients from the diet, not only to prevent diseases but also to delay the functional decline associated with aging. However, older people are more likely to suffer from

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malnutrition due to a variety of factors, including decreased food intake, changes in eating and swallowing functions (oral functions), and changes in taste, which may occur with aging (Ahmed & Haboubi, 2010; Pilgrim et al., 2015; Landi et al., 2016; Minakuchi et al., 2018; Iwasaki et al., 2021). They may also suffer from disorders that result in impaired nutrient absorption and abnormal loss of nutrients from the body. Malnutrition leads to a decrease in activities of daily living, increased risk of infectious diseases, prolonged hospitalization, and increased mortality (Lonterman-Monasch et al., 2013; Marshall et al., 2016; Katona & Katona-Apte, 2008; Hao et al., 2019; Cederholm et al., 1995). This can have a serious impact not only on the person but also on the society, because of the possible medical and nursing care costs.

Among the several approaches for improving nutrition in older adults, this chapter focuses on umami taste. L-Glutamic acid and its salt, a type of amino acid, were discovered in Japan as flavors and flavor enhancers, and its sodium salt, monosodium L-glutamate (MSG), is used as umami seasoning (see also Chap. 1). Umami taste is accepted as the fifth basic taste, in addition to salty, sweet, sour, and bitter, and the potential of umami ingredients for enhancing the taste and appetite among vulnerable individuals has gained attention. Umami for seniors can be discussed from two points of view: its relationship with appetite, salivation, and taste in older adults and the effects on nutritional status, quality of life (QOL), and cognitive function from continuous MSG intake. However, few studies have investigated umami with older adults as the target group or interventions with MSG in particular. Therefore, in this chapter, we discuss how umami can be used to improve the health of older adults by introducing studies that have been conducted not only on older people but also on the general adult population.

7.2 Umami in Older Adults for Nutritional Health

Undernutrition results from an imbalance between the intake (or absorption) of specific nutrients and their required amounts, in addition to necessary energy and protein, and is followed by sequential changes in metabolic function and body composition. Factors that have been correlated with lower food intake and malnutrition in older adults and are associated with aging are impairment of chewing and swallowing, compromised digestion and absorption rates, and decline of physical activity. These factors are also associated with depression, dementia, loneliness, and isolation (Robinson et al., 2018; Nieuwenhuizen et al., 2010). As a result, health problems may rise from malnutrition, or malnutrition may cause health problems.

Older people often suffer from some form of disease that may deteriorate their nutritional status. On the other hand, age-related changes may also lead to problems with nutrient intake, such as compromised digestion and absorption. This section considers the following age-related changes: oral function, digestion and absorption function, dietary intake, and sensory function. Although umami taste alone is not a "one-size-fits-all" solution for malnutrition, interventions utilizing umami have reported improved salivary secretion, a factor that causes dysphagia, which affects

the promotion of digestion, meal enjoyment, and taste sensation, which in turn relate to appetite and dietary intake. Treating taste disorders may lead to higher interest in the diet and solve nutritional problems by enabling the sensation of various tastes, including umami.

7.2.1 Umami for Food Enjoyment and Appetite Enhancement Among Older Adults

Improving the enjoyment of eating and appetite is important to prevent malnutrition and health problems. MSG is a seasoning agent that improves the flavor and palatability of foods. For example, one study investigated whether enhancing flavor increases appetite (Mathey et al., 2001). One of four flavors, chicken, beef bouillon, turkey, and lemon butter (fish), was added (1 ± 0.2 g) into the main dish using a spice shaker to enhance flavor. Each 100 g of added flavor contained about 60 g sugars/starch and 30 g MSG, as well as protein, fat, salt, and so on. Thus, the added flavor had a high MSG content. After a 16-week intervention targeting people older than 65 years living in a nursing home, the body weight of the flavor-enhanced group increased (mean ± standard deviation: 1.1 ± 1.3 kg) compared with that of the control group (−0.3 ± 1.6 kg). Daily dietary intake was significantly decreased in the control group, whereas no significant change was observed in the flavor-enhanced group, which remained relatively stable. In the flavor-enhanced group, the consumption of flavor-enhanced cooked meals significantly increased, degree of daily hunger increased, and the subjective sense of smell improved. Since the sense of smell plays an important role in meal enjoyment, it is possible that providing the participants with a meal with a good aroma enhanced their enjoyment of the meal, which in turn led to increased food intake and weight gain, thereby improving nutritional status. The results suggest a favorable effect of MSG-containing seasonings on flavor enhancement.

Several studies have examined the effects of adding only MSG. A study that investigated changes in food palatability, perceived saltiness, and food intake among young people (18–39 years old) with MSG supplementation in the diet (Bellisle et al., 1989) found that, depending on the type of meal, the addition of 0.6% MSG was preferred in spinach mousse, and 0.6% or 1.2% MSG was preferred in beef jelly. However, as the concentration of MSG increased, the degree of perceived saltiness also tended to increase, as expected. The addition of 1.2% MSG led to an increase in dietary intake on the first week of testing, whereas the addition of 0.6% MSG to the diet increased dietary intake over successive weeks. Thus, high levels of stimulation may exert rapid effects, but moderate levels may be better for lasting effects.

Another study, in which 0.6% MSG was added to two lunch menus of older people to evaluate dietary and nutrient intake in each menu (Bellisle et al., 1991), found that intake of some but not all enhanced foods increased. This is considered

to result from expecting an appetite-stimulating effect by adding MSG, but there was no increase in intake of MSG-containing soups with different menus, suggesting MSG may be compatible only with specific foods. Moreover, the influence of food choices in the diet could also have an effect, as the results were different for two lunch menus, and intake of calcium and magnesium increased in one of the menus, and intake of sodium and fats increased in the other. Sodium in MSG is about one-third that in sodium chloride (NaCl) (Bellisle, 1999), and if the amount of NaCl is reduced and an appropriate amount of MSG is added, the palatability is maintained (Morita et al., 2021; Hayabuchi et al., 2020) (see also Chap. 4 Dunteman and Lee); therefore, the effective use of MSG to reduce salt intake may help prevent hypertension and even reduce the risk of cardiovascular disease, and from a health perspective, enhancing flavor and taste with MSG is beneficial. Taken together, these studies suggest that the use of an appropriate amount of MSG is expected to increase palatability and appetite, resulting in enhanced enjoyment of eating.

The mechanism of appetite enhancement by MSG may also involve its effect of promoting the digestion of food. Glutamate is thought to regulate digestive function not only through receptors in the oral cavity but also through activation of the vagal afferent fibers from the gastric branch via glutamate receptors in the stomach (Uneyama et al., 2006; Yamamoto et al., 2009; Toyomasu et al., 2010). A study conducted in healthy men 27–45 years of age showed that adding 0.5% MSG to protein-rich liquid meals enhanced gastric emptying compared with the absence of MSG (Zai et al., 2009), suggesting it is involved in protein digestion. In another study, targeting healthy individuals 30–50 years of age, MSG or NaCl was added to lunch and dinner for 7 consecutive days, and then pre- and post-meal assessment was conducted on day 7. Results showed that MSG supplementation at nutritional doses elicits elevation of several plasma amino acid concentrations in healthy humans (Boutry et al., 2011), suggesting that adding MSG may affect uptake of amino acids in addition to digestion of protein. Adding MSG to the diet may thus increase dietary intake by promoting digestion and may also improve nutritional status due to increased nutrient uptake.

7.2.2 Effect of Umami Stimulation on Salivary Secretion in Older Adults

Dry mouth has been used as a comprehensive term to refer both to xerostomia (the subjective sensation of dry mouth) and to salivary gland hypofunction (objective findings of dry mouth), such as hyposalivation or altered salivary components (Nakagawa, 2016; Thomson, 2015; Han et al., 2015). Decreased salivary secretion may cause complaints of xerostomia; however, xerostomia may or may not be accompanied by decreased salivary secretion due to salivary gland hypofunction (Hopcraft & Tan, 2010; Napeñas et al., 2009). Reduced salivary secretion negatively affects oral health, and xerostomia affects QOL.

The proportion of patients with xerostomia and salivary gland hypofunction increases with age, and factors include high prevalence of systemic diseases and side effects of regular medications (Villa & Abati, 2011; Smidt et al., 2010; Johanson et al., 2015). Although age-related changes in the structure of salivary gland tissue have been shown (Moreira et al., 2006), many believe that aging itself does not affect salivary secretion (Hopcraft & Tan, 2010; Smidt et al., 2010). Dry mouth causes problems related to food intake, such as inability to chew food thoroughly, inability to form a bolus, and inability to swallow; therefore, this condition has a strong relation to nutritional disorders. There is a report that treating xerostomia in the context of systemic diseases enabled and improved the sensation of umami taste, improved appetite and body weight, promoted the enjoyment of eating, and improved health conditions (Satoh-Kuriwada et al., 2012a). Treatment of dry mouth is crucial considering its role in nutrition in older adults.

Saliva is secreted by the major (parotid, submandibular, and sublingual) and minor salivary glands. Most saliva secreted into the oral cavity originates from the major salivary glands. However, in some cases, xerostomia may not be accompanied by a decrease in salivary secretion, suggesting the involvement of a minor salivary gland in xerostomia. Previous studies have suggested an association between complaints of xerostomia and decreased labial minor salivary gland secretion rate, even in the presence of normal or reduced salivary output throughout the oral cavity (Eliasson et al., 2009). It has also been reported that people with xerostomia had a more remarkable decrease in lower labial minor salivary gland secretion than in chewing-stimulated whole salivary secretion and that lower labial minor salivary gland secretion measurement had superior sensitivity, negative predictive value, and diagnostic accuracy for discriminating xerostomia compared to chewing-stimulated whole salivary secretion measurement (Satoh-Kuriwada et al., 2012b).

In an attempt to treat dry mouth, a study examined the change in the amount of salivary secretion of major salivary glands and minor salivary glands by taste stimulation (Hodson & Linden, 2006). Eight healthy subjects 18–55 years of age were tested to determine whether stimulation with the basic five tastes (sweet, salty, sour, bitter, umami) increased parotid salivary flow. The relative efficacy for eliciting salivation was sour > umami > salty > sweet ≥ bitter. Another study verified the amount of stimulation by the basic 5 tastes on minor salivary glands using an iodine-starch filter paper method, in 11 healthy subjects with an average age of 31 years (Sasano et al., 2014, 2015). The order from the highest to the lowest amount of salivation by stimulation was umami > sour > salty = sweet = bitter. The salivary reaction evoked by umami stimulation lasted longer than that of other stimuli. Regarding sour stimulation, which is commonly associated with salivary secretion, a salivary secretion equivalent to the umami taste stimulation was induced immediately after the stimulation, but the amount decreased following stimulation; therefore, the effect was not sustained. Furthermore, the increase in total salivary secretion from the major and minor salivary glands was transient with sour stimulation but persisted longer with umami stimulation when 24 healthy volunteers were stimulated with sour or umami (Sasano et al., 2010).

Another study was conducted with ten older adults with a mean age of 69.5 years where saliva was collected three times at intervals of 30 min after the ingestion of food (at 0, 30, and 60 min) (Schiffman & Miletic, 1999). Test foods were chicken broth, onion soup, corn, and carrots, with and without 2.0%, 1.5%, 3.5%, and 2.0% MSG, respectively. After 30 and 60 min, the secretion rates of secretory immunoglobulin A (μg/min) after ingesting food containing MSG were high, due to increased salivary flow, because no significant differences in absolute concentration were found. Thus, repeated taste stimulation may affect immune function through increased salivary flow.

A method using kelp stock containing MSG has also been reported as a treatment for dry mouth using umami (Satoh-Kuriwada & Sasano, 2015). Twenty women with an average age of 61.9 years who complained of dry mouth were asked to drink or to gargle kelp stock five to six times a day when they felt dry mouth. Around 80% of respondents answered that their dry mouth had improved, and 67% said they felt the effect after 1 month of use. In addition to improvement of dry mouth, respondents also said that the method "improved roughness in the mouth," "prevented food clogging which made it easier to swallow," and so on. Improvement of various symptoms related to dry mouth was observed; thus, this may be a practical method to enhance salivation.

To summarize, based on available data, umami stimulation appears to promote salivary secretion and improve xerostomia in both the major and minor salivary glands, suggesting that umami stimulation can be used to improve dry mouth. However, since there are a relatively few studies in older adults, and many of these include only small numbers of subjects, further examination is needed.

7.2.3 Perception of Umami Taste in Older Adults

It is generally believed that as we age we begin to prefer stronger flavors (the combination of taste, smell, and irritant properties of foods). Indeed, a study comparing the strength of flavor and palatability of four food items (bouillon, tomato soup, chocolate custard, and orange lemonade) found that older adults tended to have a preference for higher flavor concentrations than did younger individuals (de Graaf et al., 1996). One of the reasons that older people prefer stronger flavors is a change in taste function. To date, many studies have been conducted on the relationship between taste thresholds and aging (Liu et al., 2016; Boesveldt et al., 2011; Mojet et al., 2001; Yoshinaka et al., 2016; Yamauchi et al., 2002; Methven et al., 2012; Welge-Lüssen et al., 2011). Most researchers have thus come to the conclusion that taste function decreases with age; however, which taste sensitivities are reduced differs across studies. For example, on one study, recognition thresholds for sweet, salty, sour, and bitter tastes were in the normal range, but recognition thresholds for umami were elevated (Satoh-Kuriwada et al., 2012a). Thus, age-related deterioration in taste function can be understood to vary, because sensitivity for all tastes is

not lost; rather, the detection and recognition ability for specific taste qualities may be impaired.

Low salivary volume, low serum zinc, the effect of comorbidities, and prescribed medications have been pointed out as underlying factors for decreased taste function in older adults (Sasano et al., 2014; Ikeda et al., 2008; Kinugasa et al., 2020), with a variety of factors having secondary effects. It may also result from decreased signaling mechanisms for taste in the brain. Previous studies have shown that people with Alzheimer's disease dementia (ADD), which is more likely to develop at an older ages, may exhibit a decline of taste sensitivities (Ogawa et al., 2017; Kouzuki et al., 2020). The cause of the decline is thought to be due not to impaired transmission from peripheral receptors but to a decrease in taste-perception cognitive ability that accompanies brain atrophy and neurodegeneration. In our study (Kouzuki et al., 2020), many participants, not only those with ADD but also nondementia controls (NDCs), could not recognize umami. With respect to umami, the cumulative distribution curves for detection and recognition thresholds, for the percentage of correct answers for each taste solution, differed from those of other taste solutions, especially with respect to recognition: a concentration higher than that of other taste solutions was required (Fig. 7.1). However, 21.4% of NDCs were not able to recognize of umami taste even at the highest concentration, and its recognition became worse with age.

Studies in humans do not necessarily achieve consistent results, due to differences in the background factors and living environments of the subjects, differences in the concentrations of taste solutions between studies, and the fact that some

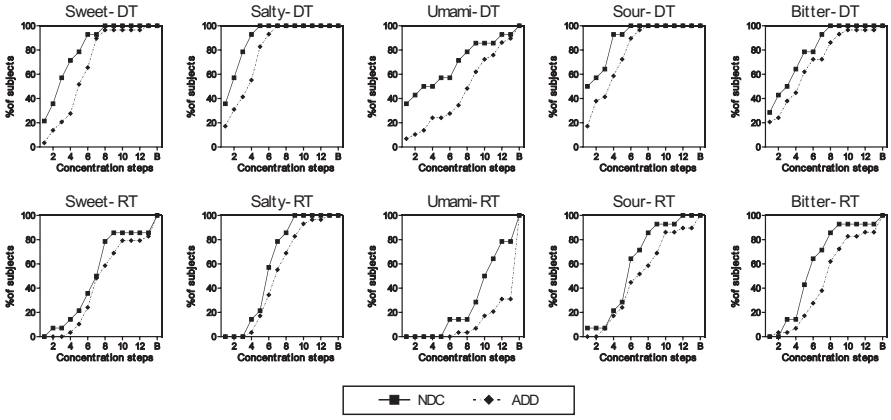

Fig. 7.1 Cumulative curves for detection thresholds (DT, top row) and recognition thresholds (RT, bottom row) in patients with Alzheimer's disease dementia (ADD) and in nondementia controls (NDCs). The taste functions of patients with ADD and of NDCs were evaluated in detail by the whole-mouth gustatory test using taste solutions for sweet, salty, sour, bitter, and umami, each diluted to 13 levels. If the participants could not detect or recognize a taste, even at the highest concentration, those results are indicated as "burst" (B) on the x-axis. (Modified from reference Kouzuki et al. (2020), licensed under a Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/))

studies evaluate only detection or recognition thresholds. However, these thresholds do not usually decrease, at least in older adults. Because elevated thresholds imply the need for more intense taste stimuli for taste detection, it can be understood that older adults prefer a stronger-tasting diet due to a lower perception of taste.

Reports on improvements to taste function indicate that taking the zinc agent polaprezinc at 150 mg/day (administered as 75 mg twice daily; 75 mg of polaprezinc contains approximately 17 mg of zinc) resulted in improvements in the mean recognition thresholds for sweet, salty, and sour tastes in 74% of older adults with taste disorders (Ikeda et al., 2008). Regarding umami, seven cases 62–78 years of age with reduced umami sensitivity were treated for xerostomia in addition to systemic disease and improved their recognition threshold for umami, as assessed by a filter paper disk test (Satoh-Kuriwada et al., 2012a). In another study, in 28 patients 45–78 years of age, with complaints of taste impairment, clinical examinations (blood tests, salivary tests, an oral candida culture test, and oral hygiene tests) and investigation of systemic diseases and drug prescriptions were carried out, and appropriate treatment was performed based on these results. After treatment, all patients showed lower recognition thresholds of umami than before treatment, indicating that loss of umami taste sensitivity can be improved with appropriate treatment (Satoh-Kuriwada et al., 2014). Evaluation of taste function and treatment for taste disorders are important because decreased interest in meals due to reduced taste function may reduce appetite and adversely affect nutritional status.

7.3 Clinical Trials for Continued Ingestion of MSG in Old Age

Here, we introduce the effects of long-term ingestion of MSG in older adults. MSG transmits gustatory signals to the brain via oral and gastric receptors, affecting digestive functions by increasing the secretion of saliva (Hodson & Linden, 2006; Sasano et al., 2014; Sasano et al., 2015) and gastric juices (Zolotarev et al., 2009) and promoting digestion (Zai et al., 2009; Boutry et al., 2011). There have also been reports that the neural organization of the primary gustatory cortex receives inputs from glutamate receptors on the tongue (Schoenfeld et al., 2004) and that umami-stimulated activation of the primary gustatory cortex (insular and opercular regions) and orbitofrontal cortex were observed in functional MRI (de Araujo et al., 2003), suggesting that ingestion of MSG may affect the brain. Although very few interventional studies have involved MSG consumption for a long time by older adults, this section introduces studies that attempted to improve the nutritional status and QOL of older adults by MSG intake (Toyama et al., 2008; Tomoe et al., 2009), as well as those that examined the effects of continuous transduction of taste signals to the brain by MSG intake on cognitive function (Kouzuki et al., 2019).

7.3.1 *Umami and Improved Behaviors and Nutritional Status in Old Age*

Here, we present a study evaluating the improvement of nutritional status and QOL of older people by long-term consumption of MSG (Toyama et al., 2008; Tomoe et al., 2009) and provide our opinion on the subject. Older individuals with malnutrition are more likely to have reduced QOL, while interventions that improve nutritional status lead to significant improvements in physical and mental aspects of QOL (Rasheed & Woods, 2013), and nutritional status of older people is a modifiable factor associated with QOL.

A study of 11 inpatients (mean age ± standard deviation: 85.8 ± 8.2 years) who consumed 0.5% (w/w) MSG added to their staple rice gruel three times daily for 2 months reported no change in body weight before and after the intervention and no change in serum total protein or albumin, an indicator of the nutritional status (Toyama et al., 2008). However, the number of lymphocytes in blood increased significantly during the intervention period and then decreased significantly 1 month after the intervention period. Low lymphocyte count is an indicator of loss of immune defenses caused by malnutrition (Ignacio de Ulíbarri et al., 2005) and is affected by increases or decreases in nutritional status. This parameter is perhaps connected with protecting the body from infection by enhancing immune function, indicating that glutamate may activate biological defense systems. Moreover, in the evaluation of daily performance by the nursing staff, "clear speech," "cheery facial expression," and "eye opening" showed more remarkable improvement, which correlated with improvements in QOL. In addition, the revised Hasegawa's Dementia Scale (HDS-R), a screening test for cognitive function, showed that five patients improved, three deteriorated, and three showed no change. These results support the hypothesis regarding positive effects of MSG intake on cognitive function.

These conclusions were subsequently supported using a similar intervention in a 3-month placebo-controlled, double-blind study (Tomoe et al., 2009). In this investigation, the group that consumed MSG (MSG group) comprised 14 inpatients (mean age ± standard deviation: 83.0 ± 8.9 years), and the control group comprised 15 inpatients (84.3 ± 9.6 years). Blood tests revealed no increase in albumin, as in the previously described study (Toyama et al., 2008), but the ratio of reduced-form albumin to total albumin, considered an indicator of redox status or quality and quantity of dietary protein ingestion in the body (Kuwahata et al., 2017; Tabata et al., 2021; Wada et al., 2020), was increased only in the MSG group, suggesting an improvement in protein nutritional status. Evaluation of daily performance by nurses without knowledge of the presence or absence of the intervention indicated improvement in the MSG group after the intervention, with results comparable to those of the earlier study (Toyama et al., 2008). On the other hand, no significant changes were observed in HDS-R scores. However, HDS-R as a screening test for dementia may have inadequate detection power to assess effects of the intervention.

In addition, to evaluate behavior of patients during the actual diet, the researchers recorded behavior during meals before and at the end of the intervention and had both videos evaluated by 13 university students. In the MSG group, activity level, eye opening (e.g., eating awake), swallowing (e.g., timing of swallowing), cheery expression, motion of arms and hands (e.g., handling of cutleries), and position holding showed improvement; overall dietary behavior was improved, and there was a tendency to try to consume independently.

In summary, these results suggest that continuous intake of MSG in the older adults may improve the immune system and nutritional status, as evidenced by improvement in some biochemical markers, and may also contribute to improvement of QOL based on behavioral changes.

7.3.2 Umami and Slower Cognitive Decline in Old Age with Dementia

Studies to verify brain activation by MSG stimulation have been reported (Schoenfeld et al., 2004; de Araujo et al., 2003). In addition, as mentioned above, HDS-R scores improved in 45.5% of patients when MSG was added at 0.5% (w/w) to rice gruel in each meal given three times a day for 2 months (Toyama et al., 2008), suggesting MSG may have a beneficial effect on the brain. Therefore, we investigated the impact of continued MSG consumption on cognitive function and interest in food in older people with dementia (Kouzuki et al., 2019). The subjects of this study were 159 dementia older persons living in hospitals or nursing homes (e.g., geriatric health service facilities, special nursing homes for the aged, and group homes). The subjects were divided into two groups: one with MSG added to their daily diet (MSG group) and the other with NaCl added as a placebo (control group); the dietary intervention was performed for 12 weeks. MSG (0.9 g/dose) or NaCl (0.26 g/dose, equivalent to the amount of sodium contained in the molecular content of MSG) was added to three meals daily: breakfast, lunch, and dinner. When applicable, MSG or NaCl was added to rice porridge, miso soup, or other soup; otherwise, these additives were mixed in the main dish. After completion of the intervention, a follow-up period without dietary intervention was provided for an additional 4 weeks, and examinations of dementia symptomatology, blood tests, daily performance, and preference for diet were conducted pre- and post-intervention and post-follow-up.

Cognitive function was tested using the Touch Panel-type Dementia Assessment Scale (TDAS) (Nihon Kohden Corporation, Tokyo, Japan) (Inoue et al., 2011) as a subjective method to assess subjects' cognitive functions. TDAS is a cognitive function test introduced to touch-panel computers by partially modifying the Alzheimer's Disease Assessment Scale, which is considered the most reliable decision-making method for progress of ADD and treatment effectiveness. TDAS scores did not differ significantly between the baseline, post-intervention, and post-follow-up groups

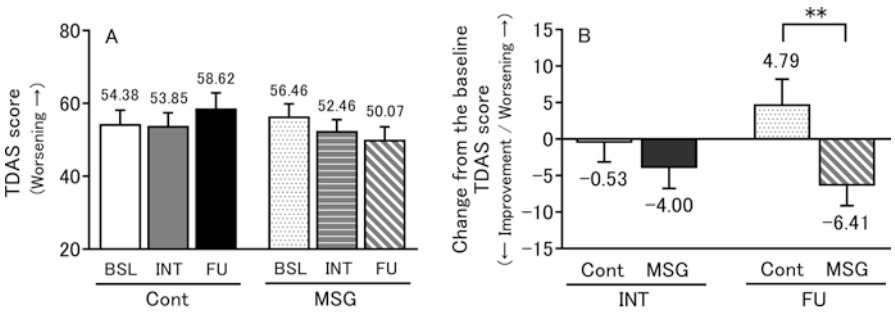

Fig. 7.2 The Touch Panel-type Dementia Assessment Scale (TDAS) score: overall (**a**) and mean change from the baseline (**b**). *BSL* = baseline, *INT* = intervention, *FU* = follow-up, *Cont* = control, *MSG* = monosodium L-glutamate. All data represent mean ± standard error; the numbers above the error bars are the mean values. $^{**}p < 0.01$. (Modified from reference Kouzuki et al. (2019), licensed under a Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/))

in either the MSG or the control group (Fig. 7.2a); however, comparisons of scores between the two groups from baseline showed significant improvement in the MSG group after follow-up (Fig. 7.2b). Thus, it is possible that improved cognitive function was observed in a test performed at 4 weeks after the intake was discontinued, thereby indicating the necessity of further investigation. In addition, when examining the correlation between changes in baseline and post-intervention TDAS scores and a food palatability survey, we found a significant association between the total TDAS score and the enjoyment of the meal in the MSG group and a trend toward a correlation between the total TDAS score and the deliciousness of the meal. In other words, the greater the improvement in food quality, the greater the improvement in cognitive function.

Although MSG enhances umami taste, we considered the effect of MSG ingestion on taste function. It has previously been reported that the percentage of people with low serum zinc levels rises with age (Ikeda et al., 2008; Kogirima et al., 2007); this tendency was also observed in subjects in this study (Kouzuki et al., 2019), with baseline mean serum zinc levels as low as 61.8 μg/dL in the MSG group and 63.5 μg/dL in the control group (reference value in the study, 64–111 μg/dL). Zinc plays an important role in taste bud homoeostasis, and patients with taste disorders have exhibited significant improvements in taste sensitivity after treatment with a zinc-containing compound (Ikeda et al., 2008; Sakagami et al., 2009). The variation in serum zinc levels before the intervention did not significantly differ between the two groups compared to variation after the intervention and at follow-up, but the MSG group showed increased serum zinc levels in the post-intervention test. Zinc is absorbed from the intestine, and the ingestion of MSG increased the secretion of gastric juice and upper gut motility via vagus nerve stimulation (Toyomasu et al., 2010; Zai et al., 2009; Boutry et al., 2011; Zolotarev et al., 2009) and enhanced digestive absorption, which may have led to a better absorption of zinc. In rats, the average life span of a taste bud cell is about 250 ± 50 h (Beidler & Smallman, 1965).

It was suggested that zinc deficiency induces delayed proliferation of taste bud cells (Hamano et al., 2006). Although we cannot make a clear conclusion, taste bud regeneration in response to increased zinc absorption during the MSG intake period might have appeared as a sustained effect even after MSG discontinuation. These results suggest that elevation of serum zinc caused the regeneration of taste buds, and the effect of MSG on the umami receptors T1R1 + T1R3, mGluR1, and mGluR4 in taste cells (Yasumatsu et al., 2015) led to a greater perception of the taste of cooked meals and affected cognitive function by enhancing the taste signaling to the brain via glutamate receptors in the oral cavity, as well as via the vagus nerve from the stomach (Tsurugizawa et al., 2008; Tsurugizawa et al., 2009).

7.4 Conclusions

Life expectancy is increasing worldwide; however, it is important for healthy life expectancy to increase concomitantly. Preventive measures to avoid becoming ill are important to maintain health, and this chapter focuses on nutrition as one of the factors associated with disease. Although age-related changes may lead to a decrease in nutritional status, a variety of methods have been shown to potentially prevent or improve malnutrition. Adding substances that elicit umami taste, such as MSG, has been proposed as a way to address malnutrition. It may also be possible to promote nutrient intake from meals by increasing interest in meals by enhancing appetite and by promoting digestion via the addition of MSG, thereby increasing the amount of salivation by the stimulatory action of MSG and improving the ability to recognize umami through appropriate treatment targeting decreased taste function. Long-term consumption of MSG by older adults is also expected to improve nutritional status, QOL, and cognitive function. One's daily diet is important for living healthily even in old age, and we believe that the approach using umami taste has many possibilities for preventing or improving various health disorders by enhancing the palatability of the diet.

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Chapter 8
Umami Taste as a Component of Healthy Diets

Ana San Gabriel and Tia M. Rains

Suboptimal diets on top of social and environmental challenges have resulted in a global nutritional crisis (Independent Expert Group, 2021). Current trends of unhealthy and unsustainable food production, together with an estimated growth in population to about 10 billion by 2050, represent a threat to food security, the health of people, and the health of the planet (Pörtner et al., 2022; Willett et al., 2019). For the shift to sustainable food systems that provide a healthy, nutritious, and sustainable diet, experts have evaluated the best available evidence (Afshin et al., 2019) and identified a need to increase ingestion of plant-based foods and to reduce consumption of animal-based foods (Willett et al., 2019). Therefore, the amount and kinds of foods we choose to eat have an impact not only on our health but also on the environment (Springmann et al., 2016).

The challenge is to make consumption of plant-based foods more appealing. The sense of taste has great relevance to nutrition: it helps identify and support ingestion of nutrients, improving the probability of survival (Mattes, 2021). In this context, the pleasant taste conferred by umami compounds could play a key role in increasing the palatability of plant-based foods and, more specifically, local plant-based crops that are part of the traditional cuisine in each region.

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8.1 Diet, Health, and the Environment

The Global Burden of Disease Study 2017 showed an association between the quantity and type of foods we eat and our health (Afshin et al., 2019). The relevance of nutrition for our health has been strongly reinforced in the last 2 years with the COVID-19 pandemic (Pörtner et al., 2022; Willett et al., 2019): individuals infected with SARS-CoV-2 that presented age-associated preexisting comorbidities, such as noncommunicable diseases (NCDs) like diabetes and obesity (Afshin et al., 2019; Michael A Clark, 2019), had a higher risk of mortality (Antos, 2021; Ssentongo, 2020; Centers for Disease Control and Prevention, 2022). In fact, the pre-COVID-19 prevalence and incidence of these chronic diseases, which are indicators of poor metabolic health (but not diseases exclusive to modern humans), have increased and continue to be the leading cause of total lives lost (Thompson, 2013; WHO, 2020a). In 2019, before the COVID-19 pandemic, seven out of ten deaths were the result of NCDs, with cardiovascular diseases at the top of the list—the most frequent chronic illnesses in an aging population (Tubiello et al., 2021).

Suboptimal diets were estimated to pose a higher risk of mortality from NCDs. Inadequate consumption of fruits, vegetables, nuts, seeds, and whole grains and excess consumption of sodium have caused 11 million deaths and 255 million disability-adjusted life-years (DALYs), a combination of years of life lost due to premature mortality (YLLs) and years of healthy life lost due to living with disability (YLDs) (WHO, 2020b). Eating at least 400 grams of fruits and vegetables (including legumes, nuts, and whole grains), more unsaturated fats, and less than 5 grams of salt per day throughout the life course was found to prevent all forms of malnutrition and lower the risk of NCDs (WHO, 2020c).

And, it so happens that these foods not only are more beneficial for our health but also have a lower impact on the environment (Chai, 2019; Clark, 2019; Springmann, 2016; Tilman & Clark, 2014): the composition of the diet strongly affects the emission of greenhouse gases. For instance, the production of plant-based foods releases a lower volume of greenhouse gases than does producing animal-based foods. However, selecting foods solely on their environmental impact may not automatically maximize human health (Tilman & Clark, 2014).

Thus, we have a diet-health-environment dilemma, in which no region of the world meets the recommended consumption of health-promoting foods, unhealthy foods are overconsumed, and unsustainable food systems are causing anthropogenic changes to Earth's climate.

8.1.1 Shift of Global Traditional Diets

As nations become more affluent, especially low- and middle-income countries, traditional diets based on coarse starchy crops with complex carbohydrates (e.g., cereals, roots, and tubers) are replaced by refined starches, added sugars, vegetable

oils, and animal fats, and plant proteins are replaced by such animal products as eggs, meats, and dairy (Drewnowski & Poulain, 2018). These changes in dietary patterns, supported by greater wealth and higher food affordability, are known as *nutrition transition* (Drewnowski & Popkin, 1997). However, the health and environmental costs seem to be hidden in inexpensive global staple grain and sugar crops, as shown by the increase in the burden of malnutrition (Fanzo, 2018; Tilman & Clark, 2014). A "Western/unhealthy" pattern has been described as having a high intake of refined grains and sweets, meat, and soft drinks (Murakami et al., 2018).

8.1.2 Umami and the Japanese Dietary Pattern

According to the WHO (2019), Japan has the longest average life expectancy in the world, which has been partially attributed to the Japanese dietary pattern. Assessed as the Japanese Dietary Index, the Japanese dietary pattern has been associated with a lower risk of all causes of death and of cardiovascular and heart disease mortality (Abe et al., 2020; Matsuyama et al., 2021). A higher adherence to this diet was associated with a longer life and longer disability-free survival (Abe et al., 2020; Zhang et al., 2019). Experts have known for some time that evaluating dietary patterns, in which foods are eaten in combination, rather than listing foods in isolation, gives better guidance for diet quality (Reedy et al., 2014). Common foods in the Japanese dietary pattern, such as seaweeds, fish, green and yellow vegetables, and green tea, contain myriad beneficial nutrients and phytochemicals, which are suspected to have a cumulative effect.

The Japanese dietary pattern traditionally known as *washoku* (a traditional dietary culture of Japan) is not the only one that lowers the risk of all causes of morbidity and mortality, but it is the only one that includes a specific taste as part of its traditional heritage: the umami taste. The guiding principles of *washoku*, designated a UNESCO intangible cultural heritage in 2013, explain that the basic structure of a customary Japanese meal includes a distinctive flavor that results from the combination in the mouth of the taste, smell, and the tactile sensation of each ingredient (Ninomiya, 2016). The core flavor of many Japanese recipes is the umami taste from dashi soup stock. The extraction of umami substances when preparing the stock from traditional ingredients—dried kelp, dried bonito, or dried shiitake mushrooms—in combination with such products as vinegar, miso, or soy sauce intensifies the flavor of seasonal and fresh local ingredients (Kumakura, 2015). The style of eating small portions of a large variety of seasonal foods, including fish and abundant vegetables, and the effective use of umami taste seem to be the basic elements that promote positive health outcomes from *washoku* (San Gabriel et al., 2018).

The modern Japanese diet has transitioned to include high intakes of refined grains (white rice and white flour), as well as vegetables, seaweeds, soybean products, fish, and green tea, together with low consumption of whole grains, nuts, processed meats, and soft drinks (Micha et al., 2015; Murakami et al., 2018). Although there are still lower rates of morbidity and mortality from coronary artery disease in

Japan than in other regions, this seems to be supported by higher consumption of plant and marine food and decreased intake of refined carbohydrates and animal fat.

In fact, the Japanese dietary pattern has been changing since the end of World War II, becoming more diversified and Westernized. The consumption of total fats and oils has increased threefold from 1960 to 2005, and the consumption of animal products (meat, poultry, milk, and dairy) increased fourfold, while the intake of white rice was reduced by half in this period. During these 45 years, the mean intake of fish and beans augmented slightly, and vegetable consumption remained constant (Tada et al., 2011). The estimated percentage of energy derived from fat in the Japanese diet has transitioned from 7.0% in 1946 to 26.6% in 2000, together with a gradual decrease on salt intake from 13.7 g/day in 1976 to 10.6 g/day in 2006. Overall, the Westernization of the Japanese dietary style has increased the number of people with higher atherosclerotic risk by augmenting the rates of obesity, dyslipidemia, and hyperinsulinemia with impaired glucose intolerance, especially among the younger population in Japan (Tada et al., 2011).

Murakami et al. (2018) used principal component analysis to identify three major dietary patterns through the Japanese National Health and Nutrition Survey from 2003 to 2015: a "plant food and fish" pattern, a "bread and dairy" pattern, and an "animal food and oil" pattern. They found an apparent continuation of the Westernization of the Japanese diet: a gradual decrease in consumption of foods in the plant food and fish pattern and a significant increase in consumption of foods in the bread and dairy and the animal food and oil patterns (summarized in Table 8.1). Interestingly, the plant food and fish pattern, which seems to be closer to the recommended "healthy/prudent" pattern, also showed a higher use of salt-based seasonings (Murakami et al., 2018). Without forgetting the need to decrease the intake of salt at the population level, experts still express the need to promote a high consumption of plant and fish foods while discouraging the consumption of refined carbohydrate and animal fat for better health outcomes (Tada et al., 2011). In this

Table 8.1 Dietary patterns in the Japanese population

Dietary pattern	Most consumed foods	Level of adherence
Plant food and fish	Rice, potatoes, sugar, pulses, green and yellow vegetables, other vegetables, pickled vegetables, fruit, mushrooms, seaweed, fish, tea, **salt-based seasonings**	Low
Bread and diary	Bread, sugar, fruit, dairy products	Moderate
Animal food and oil	Other vegetables, red meat, processed meat, eggs, vegetable oil	High

Adapted from Murakami et al. (2018) based on the Japanese National Health and Nutrition Survey (2003–2015)

The plant food and fish pattern integrates salt-based seasonings as a food group. Murakami and colleagues calculated the association of most consumed foods with each dietary pattern by principal component analysis, using intake of 31 food groups, and scored the level of adherence. We have simplified this as low, middle, and high adherence to each dietary pattern, with high adherence meaning tested individuals consumed more foods in that category

context, returning to the core flavors of *washoku* based on the umami taste of traditional ingredients could help halt the speed of Westernization of the Japanese diet and move it more toward the plant food and fish pattern while helping reduce excess salt intake with the use of the umami seasoning (see Chap. 4) (San Gabriel et al., 2018).

8.2 The Significance of Umami Taste in Food Choice

The sensory cues of foods before, during, and after eating direct our selection of foods and are at the center of palatability. Smell and taste drive palatability, depending on our hedonic evaluation of food (Drewnowski, 1997; Gervis et al., 2022; McCrickerd and and Forde, 2016; Yeomans, 1998). But while orthonasal exposure to odors through the nose combined with retronasal odors arising from the mouth provides cues about the food itself in anticipation of eating, taste seems to play a clearer role in sensing nutrients during and after ingestion of foods (Boesveldt & de Graaf, 2017). Often cited as the "nutritional gatekeeper" of the body, the sense of taste has a prominent role in voluntary food ingestion because it helps us choose what to consume and how efficiently these foods will be digested and metabolized (Breslin, 2013). In combination with smell and the tactile sensation from the texture of foods, taste produces flavors and drives a primal response of "acceptable" or pleasantness, when we detect nutrients that we consider safe to ingest, or "unacceptable" or unpleasant, when we estimate that something could be toxic. And this distinction between toxic and nutritious appears to be qualitatively defined by taste, the oral perception of chemicals in food (Breslin, 2013). Unique types of taste cells express specific receptors to detect only one of the five basic tastes: sweet, sour, bitter, salty, or umami (Chandrashekar et al., 2006). The perception of these taste qualities results from the presence in foods of hydrophilic sugars, acids, alkaloids, salts, and amino acids that dissolve in saliva and activate distinctive receptors in taste cells, the same receptors that are used to sense molecular changes in our internal milieu (Bachmanov et al., 2014; Vincis & Fontanini, 2019). The gastrointestinal tract continues detecting the presence of nutrients and harmful compounds via the same taste receptors, but in this case food substances evoke not conscious taste sensations but metabolic responses (Breslin, 2013; San Gabriel & Uneyama, 2013; Steinert & Beglinger, 2011). The brain integrates taste signals from the gustatory system with other nontaste modalities such as texture, temperature, odor, and even visceral and homeostatic signals that help us contextualize food experiences (Vincis & Fontanini, 2019). This is why tastes and flavors that are connected to nutrients and calories will become more pleasurable over time than those flavors that we associate with feeling ill from previous experience (Breslin, 2013). The integration of food signals drives our interpretation of whether a meal is pleasant and ultimately influences our eating behavior (Khan et al., 2021; Rolls, 2009; Small, 2012).

In the case of umami, the taste of monosodium glutamate (MSG) when presented alone is not pleasant (Beauchamp, 2009; Okiyama & Beauchamp, 1998), but

functional brain imaging shows that the combination of MSG with a consonant savory smell such as a vegetable odor induces higher signals of pleasantness in brain cortical regions where taste and olfactory signals converge. Thus, some describe umami as a "rich and delicious flavor" (McCabe & Rolls, 2007). In fact, among the five basic tastes, the savory umami taste of the amino acids glutamate and aspartate in combination with 5′-ribonucleotides is one of the tastes we perceive as pleasant in a food context, and these umami compounds are widespread among many of the foods we eat daily (Breslin, 2013; Ninomiya, 1998).

8.3 The Especially Human Taste of Umami

Umami receptors (described in Chaps. 1 and 2) are the means to sense the proteogenic amino acids. However, the high sensitivity of the umami receptor T1R1 + T1R3 for glutamate is very specific to humans. It is hypothesized that in early evolution, the sense of taste may have helped our ancestor hominids identify nutritious foods (Breslin, 2013; Toda et al., 2021). Modern humans lean toward the consumption of more digestible animal proteins instead of plant proteins, but for meats to acquire strong umami flavors, it is necessary to prepare or ferment them (Mouritsen & Styrbeak, 2020). Thus, in periods of low food availability, our ancestors may have had to depend on less digestible and less palatable wild plants (Milton, 2000).

A recent study that combined functional, behavioral, phylogenetic, and ecological methods has found that the umami receptor in primates has evolved at least three times in parallel with the dietary transition from insects to leaves as typical sources of protein (Toda et al., 2021). The T1R1 + T1R3 receptor in primates whose diet depends mostly on insects is most potently activated by 5′-ribonucleotides, whereas in primates whose diet mostly depends on leaves, glutamate evokes the more significant response. According to the analysis of Toda et al. (2021), glutamate is one of the most abundant free amino acids in insects and plants, but plants have lower 5′-ribonucleotide content than do insects. This is because plants do not have muscle tissue, which is a source of ATP, the precursor for free 5′-ribonucleotides (Mouritsen & Styrbeak, 2020). Together with evidence from other studies, it seems that the modern human T1R1 + T1R3 receptor evolved from early mammals to perceive 5′-ribonucleotides present in insect-based diets but later evolved higher sensitivity to glutamate to facilitate the consumption of leafy plants.

However, plants also contain many bitter metabolites that bind to a family of mainly broadly tuned bitter taste receptors, the T2R receptors (Adler et al., 2000; Behrens et al., 2007; Chandrashekar et al., 2000). Because plants contain many bitter metabolites, by considering how bitter taste functions, it is easier to understand the role of umami taste in modulating the noxious bitterness of leafy greens that are so important to reduce the risk of diet-related chronic diseases (Afshin et al., 2019; Drewnowski & Gomez-Carneros, 2000).

8.3.1 Peculiarities of Bitter Taste

Based on their agonist spectra, human T2Rs can be broadly, intermediately, or narrowly tuned (Behrens & Meyerhof, 2013). Bitter taste receptors are thought to function as warning sensors that prevent humans from ingesting noxious food molecules, responding to a vast range of compounds known to be bitter to humans. Twenty-five bitter taste receptor genes in humans (hTAS2Rs) have been identified that encode for the G-protein-coupled receptor family of type 2 taste receptors (T2Rs) (Behrens et al., 2007). They have been described as "chemosensory sentinels" because they alert us to potential threats and trigger defensive responses in the oral cavity and beyond (Harmon et al., 2021). Bitter taste receptors are also found in chemosensory cells of extraoral tissues such as the gut and airways that mediate responses from ingested or inhaled substances (Deshpande et al., 2010; Wooding & Ramirez, 2022). T2Rs are preeminent in the rejection of potentially harmful compounds that at high levels can be harmful and even fatal, making us avoid intensely bitter-tasting toxins. This is why humans normally react by spitting, evading, or vomiting strong bitter substances (Breslin, 2013). However, many bitter compounds at low levels have medicinal properties (Bayer et al., 2021). Therefore, compounds that activate T2Rs are structurally diverse and include different drugs that can be potentially toxic (Mennella et al., 2013).

The work of Meyerhof et al. (2010) indicates that the perception of most bitter compounds is not a simple association between an agonist and a specific receptor but, rather, a complex interaction with a wide set of TAS2Rs (Wooding et al., 2021). In addition, there are large individual differences in the sensitivity for bitter taste compounds. The oldest known example refers to the genetic ability to taste two bitter compounds, phenylthiocarbamide (PTC) and 6-n-propylthiouracil (PROP) (Tepper et al., 2009). Around 70–75% of individuals worldwide taste PTC and PROP as moderately to intensely bitter—they are considered "tasters"—whereas the rest (around 28%) are "nontasters": they are taste-blind to both compounds (Kim & Drayna, 2004). Psychophysical studies have shown that the population can be divided into three distinctive groups: nontasters (30%), medium tasters (50%), and supertasters (20%) (Bartoshuk et al., 1994). This is explained by three single-nucleotide polymorphisms of the human gene *TAS2R38* that cause substitution of three amino acids at positions P49A, A262V, and V296I. These substitutions produce two common haplotypes, the taster variant (PAV) and the nontaster variant (AVI) (Tepper et al., 2009). PROP-sensitive individuals are carriers of the dominant allele PAV/PAV (the supertasters) or PAV/AVI (the medium tasters), whereas PROP-insensitive individuals are carriers of the recessive allele AVI/AVI. Others have shown that the relative expression level for PAV *TASR38* mRNA among heterozygous individuals differs widely and correlates with how they rate the bitterness intensity of both PROP and broccoli juice, which contains PTC-like glucosinolates (Lipchock et al., 2013).

These differences in the *hTAS2R38* gene affect nutritional and health outcomes. The hTAS2R38 protein is considered the antithyroid-toxin receptor—it detects

thiourea moieties such as PTC-like glucosinolates, which are dietary goitrogens present in many vegetables, including broccoli. One theory is that sensitivity to the bitterness of PROP has been conserved as a mechanism to protect humans against the excessive consumption of dietary goitrogens, especially in environments with low-iodine soils, where ingestion of plant glucosinolates may aggravate endemic goiter (Sandell & Breslin, 2006). Infants and children are thought to be more sensitive to the effect of glucosinolates, which may explain their innate aversion to bitterness, to prevent the risk of consuming toxic compounds (Breslin, 2013; Mennella & Bobowski, 2015).

Many cruciferous plants of the family Brassicaceae, including such species as broccoli, Brussels sprouts, cabbage, cauliflower, watercress, radish, kale, and mustard, contain PTC-like glucosinolates (Sandell & Breslin, 2006). The amount of these bioactive compounds present in these vegetables has been shown to be a major barrier for acceptance and consumption of cruciferous vegetables (Drewnowski & Gomez-Carneros, 2000). However, PROP tasters rated as unpleasant not only the taste of cruciferous cultivated vegetables but also tastes of other foods like coffee and grapefruit. Therefore, bitter taste sensitivity to PROP seems to generalize to other bitter compounds, which may influence the foods we choose to eat. And as a result of food preference, variations of *TAS2R38* appear to be related to adiposity and vegetable consumption (Duffy et al., 2010; Tepper et al., 2009).

However, not all substances that are toxic taste bitter, nor are all bitter compounds toxic. In fact, associations between bitter taste sensitivity and various health measures, such as tobacco use, body mass index, glucose homeostasis, and susceptibility to respiratory infections, have also been found (Dotson et al., 2008; Lee et al., 2012). And it seems that bitter taste acceptance is a behavior we can learn, so taste education could play an important role in children's future health (Beckerman et al., 2017; Mennella et al., 2016).

8.3.2 Interaction of Umami Compounds and Bitter Receptors

In the case of umami taste, human psychophysical studies have shown that umami substances appear to suppress the bitterness of various compounds (Keast & Breslin, 2003; Keast & Breslin, 2002; Kemp & Beauchamp, 1994; Yamaguchi, 1998). In vitro assays revealed that MSG, inosine 5′-monophosphate (IMP), L-theanine, and umami peptides behave as antagonists of various bitter taste receptors, such as the salicin bitter taste receptor hTAS2R16 and the caffeine receptors hTAS2R43 and hTAS2R46, also confirmed psychophysically (Kim et al., 2015, 2017). But the potency to suppress bitterness does not seem to correlate to umami intensity, since each compound interacts differently with bitter taste receptors (Kim et al., 2015; Rhyu et al., 2020). Another bitter taste receptor significantly inhibited by umami compounds is hTAS2R14 (Okuno et al., 2020), the receptor activated by the tea

catechins (−)-epigallocatechin gallate and (−)-epicatechin gallate, which are partly responsible for the bitterness of tea (Yamazaki et al., 2013), and by several phenolic compounds from extravirgin olive oil (Cui et al., 2021), whose bitterness indicates the presence of phenolic compounds.

Altogether, it seems that umami compounds can block the activation of some bitter taste receptors, but its efficiency is complicated, partially due to the complex interaction of bitter compounds with TAS2Rs, due to either the broadly tuned (promiscuous) bitter receptors or the intermediately or narrowly tuned (selective) receptors (Bayer et al., 2021; Behrens & Meyerhof, 2013). As shown in Fig. 8.1, the index of promiscuity (number of substances that activate the receptor divided by the total compounds of their data set of food TAS2R agonists) is high for TAS2R14, TAS2R1, TAS2R46, and TAS2R4 and low for TAS2R31, TAS2R20, and TAS2R50. This means that the ability of umami compounds to block the activation of TASR14 or TAS2R46 may not seem specific, whereas umami compounds are probably more selective antagonists for that more narrowly tuned receptors TAS2R43 and TAS2R16. If umami compounds could antagonize the activation of most of the promiscuous TAS2Rs, we could say that umami inhibits the bitterness of most of the bitterness of the food components found in plants. However, as yet there are not enough molecular studies of other broadly tuned TAS2Rs to assume that this is the case.

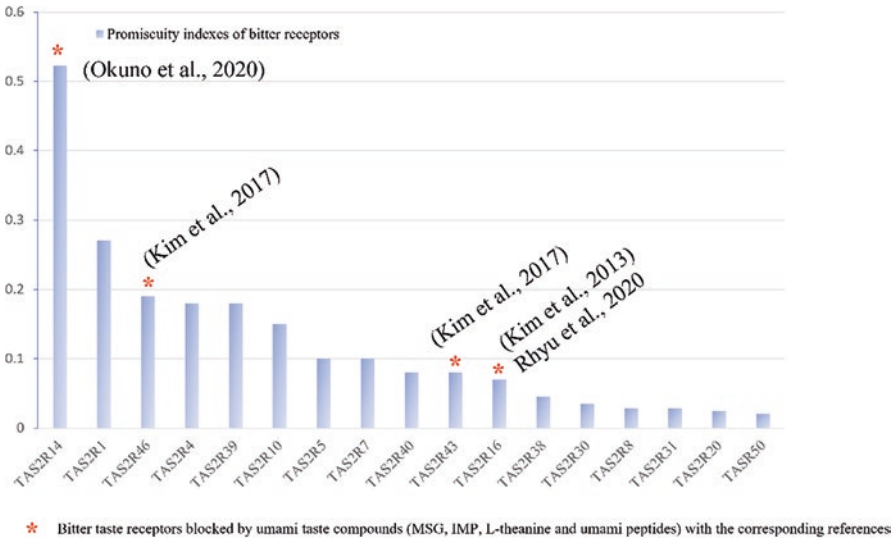

Fig. 8.1 Index of bitter taste receptor promiscuity estimated by the number of food agonists to an individual TAS2R divided by the total number of compounds in the data set. (Modified from Bayer et al. (2021). Asterisks indicate the bitter receptors for which umami compounds were able to suppress the bitterness signal in in vitro assays)

8.4 The Function of Umami for the Consumption of Plants

The importance of consuming vegetables relies on the growing evidence that vegetables provide not only nutrients and dietary fiber but also phytochemicals (nonnutritive bitter phenolic compounds) that exert various physiological mechanisms, have antioxidant activities, and modulate the immune system (Bayram et al., 2018; Drewnowski & Gomez-Carneros, 2000). These nonnutritive organic constituents, which are very diverse structurally—including phenolic compounds, carotenoids, glucosinolates, alkaloids, terpenes, and peptides—are thought to significantly contribute to the health benefit of plant-based diets (Bayer et al., 2021; Cicero et al., 2017). Yet these are also the molecules that give the astringent and bitter sensory attributes of vegetables by binding to the human T2R bitter taste receptors (Soares et al., 2018; Sterneder et al., 2021) and the reason that vegetables elicit complex perceptual stimuli (Duffy et al., 2010).

8.4.1 Umami, Salt, and Vegetable Consumption

Few sensory studies to date have evaluated the effects of umami on the perception of bitterness in foods and mixed meals, despite anecdotal evidence suggesting a benefit. As indicated in Chap. 4, there is a growing understanding of the impact of umami and specifically MSG on consumer liking and acceptance of reduced-sodium foods. Studies in that context provide some indication, at least directionally, that activating the umami receptor via the presence of glutamate attenuates the perception of bitterness within a mixed meal. For example, Halim et al. (2020) presented participants with three versions—normal salt, reduced salt, reduced salt with MSG—of four different mixed meals: roasted vegetables (carrots and eggplant), quinoa, yogurt-based dip, and pork cauliflower (with onion, peas, and carrots). The study sought to test the hypothesis that, with addition of MSG, reduced-salt versions of mixed dishes would be equally as liked as full-salt versions of the same dishes. In addition to assessing overall liking and liking of appearance, flavor, and texture/mouthfeel, several sensory characteristics were evaluated by a check-all-that-apply scale, which included "bitter" in addition to "deliciousness," "flavorful," "balanced," "bland," "rancid," "fresh," and "savory." Results showed that, directionally, the attribute of "bitter" was lower in the MSG version of the roasted vegetables, quinoa, and pork cauliflower dishes. Penalty analysis showed that bitter was a negative driver of liking overall; therefore, a shift in less perception of bitter may lead to higher liking.

However, lower bitter with MSG was shown only in the quinoa and the yogurt dip, where overall liking was higher with the MSG versions than with the standard full-salt versions. There were many limitations in this study, most notably that the dishes were not optimized for salt and MSG, and neither dish was considered

Fig. 8.2 A 1952 magazine advertisement for Ac'cent seasoning (monosodium glutamate) from the United States

particularly bitter. Yet, these results suggest that, in a practical setting, umami may favorably affect the perception of bitter, which may relate to acceptance of foods. Additional research, particularly in plant-based foods rich in bitter compounds, is warranted to better understand the relationship between umami and bitter (Fig. 8.2).

8.4.2 *Umami Perception and Dietary Patterns*

Various studies have examined the association between umami taste sensitivity and food preference and/or food consumption, with mixed results (Fluitman et al., 2021; Gervis et al., 2022; Puputti et al., 2019). Puputti et al. (2019) found that those with a higher sensitivity to umami consumed more vegetables than those least sensitive to umami. Fluitman and colleagues found that poor umami taste sensitivity related to lower adherence to the Mediterranean diet, which is abundant on foods rich in umami compounds (Fluitman et al., 2021; Ninomiya, 1998). However, in the cohort study from Gervis et al. (2022), which defined profiles of the perception of all five basic tastes collectively, older adults with high sensitivity to all tastes but umami had a higher probability of following a vegetable-rich diet than those with low bitter or higher umami perception. The difference could be explained by differences in the cohorts and the type of taste measurements (perception vs. sensitivity). But in the end, umami is implicated in specific dietary patterns, in addition to individual and age differences, so it seems important to clarify the association between umami and overall taste perception and food consumption.

8.5 Conclusion

Taste is often a forgotten element in a sustainable diet, yet it is one of the key drivers for promoting consumption of a nutritious and healthful dietary pattern (Fig. 8.3). Of the five basic tastes, umami in particular is often omitted in discussions toward

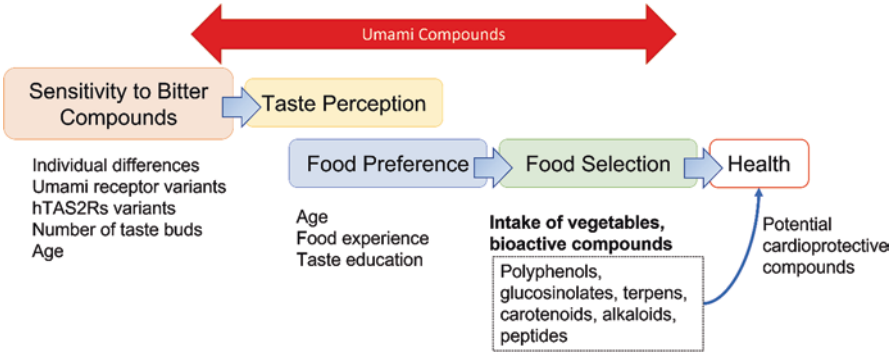

Fig. 8.3 Steps involved in food preference and food selection, which through the bitter compounds in vegetables ultimately influences cardiovascular health. Umami substances can modulate various steps by suppressing the signaling of bitter receptors, modifying taste perception, and increasing food preference, thus helping regulate food choice and vegetable intake. The effectiveness of umami compounds varies with individual differences and with age: children tend to be more sensitive to the bitterness of food, and some older adults may lose the ability to taste some bitter compounds

sustainable food systems that provide healthy, nutritious, and sustainable diets that better promote health for both people and planet. The global population continues to grow and age, increasing the prevalence of such noncommunicable diseases (NCDs) as diabetes and obesity, primary causes of disability and premature deaths worldwide that result from preventable lifestyle and dietary habits. Psychophysical, molecular, and nutritional studies continue to show how umami can block the bitterness of many phytochemicals that are cardioprotective and how umami perception is involved in the preference of healthier dietary patterns. Application of umami compounds, as has been done for centuries in the traditional Japanese diet, can serve as a tool to reduce salt and increase the intake of fresh and local plant-based foods. This aligns with the current trend to increase the ingestion of more sustainable food choices while reducing consumption of animal-based foods.

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Chapter 9
Practicalities from Culinology®: How Umami Can Contribute to Culinary Arts and Sciences

Chris Koetke, Lauren Miller, and Jonathan Deutsch

9.1 What Is Culinology®? What Is Umami?

This chapter differs from the preceding ones by focusing on umami from a practical gustatory and culinary standpoint, rather than a scientific one. It focuses on the umami experience and the traditional role that umami plays in foods loved around the globe. Umami had its place in the culinary world millennia before cooks and chefs knew what it was scientifically. The day-to-day use of umami in the kitchen predated and engendered the discoveries of umami as we currently understand it. Chefs today have the possibility of gaining a sophisticated understanding of umami, allowing a deeper understanding of the chemical properties of food, from harvest through eating, and providing tools to make food even more delicious.

This chapter, while not focused on chemistry, includes brief discussions of the scientific discoveries around umami and the synergistic interaction with nucleotides (these topics are treated in more detail in Chaps. 2 and 3 of this book). This knowledge reinforces and improves daily sound cooking practices. The intersection of culinary arts and food science is the locus that gives rise to Culinology®, or culinary science. The two disciplines inform and rely on each other. This chapter is about the intentional incorporation of umami to create balanced dishes, whether this comes from foods intrinsically rich in umami, foods manipulated by further processing to further develop umami (e.g., fermentation), or the addition of MSG (monosodium glutamate), the purest form of umami available to everyday cooks. The objective of this chapter is to apply the science of umami to daily culinary preparation.

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9.2 Umami History Through the Culinary Lens

Jean Anthelme Brillat-Savarin, author of *La Physiologie du Goût* (Brillat-Savarin, 1826, 1848), written in the early nineteenth century, is most famous for his aphorism, "Tell me what you eat, and I shall tell you what you are," often shortened to "You are what you eat." Brillat-Savarin was among the first in Western literature to document the taste we now call umami, dubbing it *osmazome*, which Brillat-Savarin defined as a water-soluble substance in meat containing all its flavors. The term was used to describe the savory taste indicative of umami. At the time *osmazome* was coined, there was no word in the French language to adequately describe the taste that Brillat-Savarin was experiencing. Not until more than a century later, as the result of scientific inquiry, did Brillat-Savarin's taste impressions become understood as umami.

In 1908 Kikunae Ikeda, a professor at the School of Science's Department of Chemistry at the Japan's Imperial University (now called the University of Tokyo), discovered that MSG was the umami in a broth of kelp seaweed (Lindemann et al., 2002). Ikeda was the first to identify glutamic acid or glutamate as the source of the savory taste Brillat-Savarin identified. He named this taste *umami* and assigned it the fifth of the five basic tastes. His discovery began in the culinary realm as he sought to better understand the characteristic tastes in his wife's dashi, a stock made from *kombu* (kelp) and *katsuobushi* (cooked, smoked, dried, mold-cured, and shaved bonito) that is foundational to many Japanese dishes. Ikeda used laboratory facilities at the university to conduct experiments aimed at the extraction of the umami factor from kelp. Ikeda found that glutamic acid was a central element in the taste of dashi. Ikeda further recognized that umami was central to many of the foods he had eaten during a stay in Europe, including tomatoes, asparagus, meat, and cheese (Yamaguchi & Ninomiya, 2009).

Based on scientific studies on the umami taste receptor on the tongue, published after 2000, proof of the existence of glutamate receptors has made it widely accepted that umami is a basic taste (Chaudhari et al., 2000), along with sweet, sour, salty, and bitter. It is important to note that taste here is limited to the receptor reaction and different from flavor, which is a broader construct that includes the perception not only of taste but mainly aroma and also feelings such as heat or cooling. For chefs, this understanding of glutamate receptors crystalized scientific conclusion underscored what they already knew but couldn't precisely explain. Chefs and cooks around the world have always cooked using umami-rich sources because they were simply delicious. Now the science caught up to explain the pleasurable umami taste from a chemosensory perspective.

One prominent example of umami in ancient cooking is that of the cuisine of the Roman Empire. Key to much of the culinary fare of ancient Rome was the fermented fish sauces used as essential seasonings throughout the culinary spectrum. The Romans had four fish sauces: *garum*, *liqumen*, *allec*, and *muria*. *Garum* was the principal sauce produced by the hydrolysis of small fish or fish innards and salt fermented for several months. *Allec* was the undissolved fish material remaining

from *garum* production. *Liquamen* was very similar to *garum* in production process and taste. *Muria* was the solution from osmosis during the salting of whole, gutted fish or slices of fish meat. At the time, these umami-rich products were just as ubiquitous and popular as wine and olive oil are today (Curtis, 2009).

The dominant free amino acid in fish sauce is glutamate. While we cannot chemically analyze the fish sauces of ancient Rome, we do know that in the current fermented fish sauces of Southeast Asia, produced through similar salting and fermenting of fish that resulted in *garum*, glutamate is present at a concentration of about 1300 mg/100 mL. Fish sauce also has an inherent nutritional value, providing other amino acids and numerous micronutrients, such as vitamin B-12 (Nakayama & Kimura, 1998, Otsuka, 1998, Yoshida, 1998).

9.3 Umami in Foods

Umami, despite its Japanese name, is not a Japanese phenomenon. Rather, it is a central part of the human taste experience that transcends history or geography. Cooks and chefs around the world gravitate toward umami-rich foods as a source of deliciousness (Lioe et al., 2010; Hajeb & Jinap, 2015). Science took thousands of years to explain what exactly this sensation is that we all crave, and chefs and cooks know so well. Examples of umami-rich foods in global cuisines include lamb daube (stew) with anchovy in Mediterranean cooking; bagna cauda (warm dipping sauce of anchovies, garlic, olive oil, and butter) from the northwest of Italy; koji-fermented soy pastes from Japan, Korea, and China; soy sauces from numerous Asian cuisines; cooked tomato and parmesan in Italian cooking; dried meat (machaca) in Mexico; ketchup on a hamburger; and dried shiitake mushrooms in meat broths in Chinese cooking.

Science has explained that the umami-rich foods enjoyed around the world are so impactful because of the presence of free glutamate. This amino acid is what our body interprets as the pleasurable taste umami. When bound to other amino acids, as is the case in proteins, glutamate is tasteless. However, certain processes, including fermentation, aging, ripening, drying, and low, slow cooking, liberate amino acids from native proteins, increasing the presence of free glutamate (Wijayasekara & Wansapala, 2017). Throughout the ages, chefs and cooks have used these tools to make superlative food. Additionally, some vegetables when ripe are more flavorful partially due to the increase in glutamate during the ripening process. Tomatoes are a good example of this (Oruna-Concha et al., 2007; Tommonaro et al., 2021).

Fermentation, responsible for the complex and heady flavors in many foods, also increases umami. Examples of fermented foods that are rich sources of umami include natto, Southeast Asian fish sauces, oyster sauce, soy sauce, miso, and kimchi fermented with seafood. A number of popular fermented products are based on either 100% fermented soy or a combination of wheat and soy (Lioe et al., 2010). Glutamic acid is the predominant amino acid in soybean and wheat proteins (Wang et al., 2018; Hou et al., 2019). During the fermentation process, a large amount of

glutamate is liberated from these proteins, resulting in a significant increase in umami. A unique mold koji (*Asperigillus oryzae*) is central to the production of many of the products listed above. When fermented with koji, which contains the enzyme glutaminase, glutamine is converted into glutamic acid. This is the traditional way of making soy sauce and miso, both of which contain high levels of umami (Otsuka, 1998; Yoshida, 1998; Lioe et al., 2010; Diez-Simon et al., 2020).

Aging in products such as cheeses, meats, and sausages also results in increased concentrations of glutamate, contributing to umami taste. For example, during the ripening of cheese, proteins are broken down into smaller peptides and amino acids, including not only glutamate but also leucine, valine, lysine, phenylalanine, and valine. These amino acids and peptides contribute to flavor complexity in cheese (Umami Information Center, 2016, 2021; Zhao et al., 2016). The increased level of glutamate (Fig. 9.1) corresponds to the heightened presence of umami. Similarly, large increases in free amino acids occur during the aging process in cured hams and other dry-cured meats (Córdoba et al., 1994; Zhang et al., 2019; Heres et al., 2021). Glutamate is one of the most prominent amino acids in these aged and cured meat products (Yamaguchi & Ninomiya, 2009).

Drying has the potential to concentrate levels of glutamate, thus making dried foods more impactful from a gustatory standpoint. An example is dry-cured ham, which combines increased glutamate from the aging process with further concentration from the drying process (Zhang et al., 2019). Drying mushrooms results in the

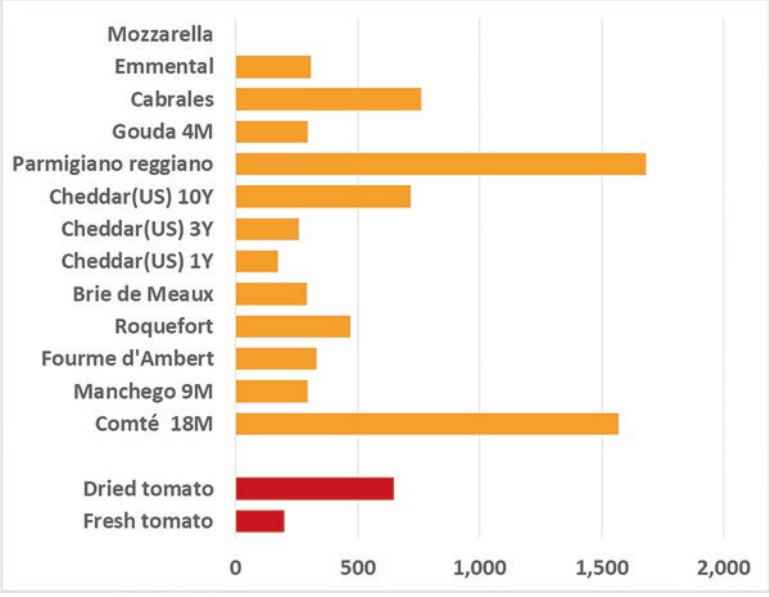

Fig. 9.1 Concentration (mg/100 g) of free glutamate in various cheeses with curation times from 4 months (M) up to 10 years (Y) and in fresh and dried tomato (Fuke & Konosu, 1991). Data were analyzed at the Japan Food Research Laboratories by the Umami Information Center

5′-nucleotide GMP (guanosine 5′-monophosphate), which has a synergistic effect on umami perception (Kuninaka, 1960; Yamaguchi et al., 1971). 5′-Nucleotides are present to varying degrees in different mushrooms. When mushrooms are dried or frozen, the cell walls are damaged, which converts nucleotides into 5′-nucleotides. The resulting GMP, combined with the mushroom's inherent glutamate, with glutamate in other foods, and/or with other free amino acids, gives a pleasurable spike in umami perception (Wijayasekara & Wansapala, 2017). A good example of this is dried shiitake mushrooms (Umami Information Center, 2016).

9.4 Concentrated Umami Sources and Products

The previous section explored the history and use of foods inherently rich in glutamate that deliver a strong umami taste. Each of those food ingredients also contributes other basic tastes, aromas, and textures—flavors that can be advantageous in various recipes. In contrast, this section looks at highly concentrated forms of umami that, aside from their strong umami character, contribute little or no additional flavors and are used in low amounts.

9.4.1 Glutamate

The ionic form of L-glutamic acid, glutamate, is an amino acid that is part of many proteins. In the production of MSG by fermentation, bacteria convert molasses or starch hydrolysates into L-glutamic acid, the non-neutralized version of MSG that tastes sour (because of its acid radical). After neutralization with sodium hydroxide, the compound adopts the form of sodium L-glutamate, and the umami taste becomes prevalent (Sano, 2009). This is how MSG is produced in its most inexpensive form—is readily available, dissolves quickly, and has immediate impact on food flavor (Lindemann et al., 2002). Before the fermentation method was adopted, L-glutamic acid was produced from wheat gluten, which contains about 25% L-glutamic acid by weight (Giacometti, 1979). The pH of most foods is close to neutral, so glutamate is almost fully found in foods in the form of the tasty sodium salt rather than the sour L-glutamic acid (Kurihara, 2009).

A good average amount for MSG inclusion is about 0.4% by weight—adding more does not necessarily render the food inedible, like a larger addition of salt would (Yamaguchi & Takahashi, 1984), but higher levels of MSG do not necessarily yield noticeably more umami character. On a practical level, MSG can be easily sprinkled onto a wide variety of savory dishes just as salt would customarily be used. It does not replace salt but is used in conjunction to provide two different taste sensations, both of which heighten overall flavor. Thus, MSG can provide an immediate and effortless increase in umami (Beauchamp, 2009).

Yet, in the culinary world, umami is not often considered when creating a dish or evaluating its overall flavor impact. For instance, chefs are trained to instinctively consider salt levels in savory dishes but rarely have they been taught to consider umami levels. When judging culinary competitions or scoring students' dishes in culinary schools, chefs often have a rubric for level of seasoning, which refers to just one taste: saltiness. Yet, considering not just saltiness but the umami axis as well, along with acid, sweet, and bitter, can provide a much more nuanced assessment of balance in tastes and flavors in a dish than simply "needing salt."

Keeping a container of MSG alongside salt and pepper is a more complete way of balancing flavor. For both chefs and cooks, it is important to remember that MSG is not a salt replacer. Although MSG does contain sodium (as its name, monosodium glutamate, reminds us), in fact MSG contains only 12.3% sodium compared with table salt's 39.6% sodium. Using MSG as a 1:1 salt substitution would result in dishes that are undersalted and therefore out of balance. That said, MSG can be effective in reducing (but not replacing) salt, as we discuss below (Morita et al., 2021).

Monopotassium glutamate (MPG), the potassium salt of glutamic acid (just like MSG is the sodium salt of glutamic acid), is produced in a similar manner. Fermentation produces glutamic acid, which is neutralized not with sodium hydroxide like MSG but with potassium hydroxide, producing MPG. Both products are very similar in glutamic acid amount.

MPG delivers concentrated umami with an impact much like MSG's and similarly dissolves quickly and can be used topically. However, while the umami impact that MSG delivers is immediate, MPG seems to bring a slightly delayed umami impact that hits the middle of the palate, leading to a more mouth-filling sensation. It is also an important ingredient in meat analogs, contributing a "serum"-like flavor note. It is less readily available than MSG and is more expensive (Kochem & Breslin, 2017; Morita et al., 2020).

9.4.2 Yeast Extracts

Manufacturing of yeast extract starts with specifically identified yeast organisms that will produce concentrated sources of umami (Chae & In, 2001). Different yeast extracts can deliver different levels of glutamate, glutathione, or nucleotides, depending on the strain. A basic, inexpensive yeast extract has low levels of everything and is used for general background savory notes. Specialty yeast extracts are more potent and deliver specific tastes and flavors, including umami notes (Jo & Lee, 2008).

A culture medium is used to grow as much yeast as possible. The yeast is then washed and goes through a lysis process to break the cell walls, either with enzymes or through a process called autolysis (Breddam & Beenfeldt, 1991). Autolysis uses high levels of salt to break the yeast apart. Older-generation yeast extracts contained high levels of sodium, but newer yeast extracts use more modern techniques that can

reduce the final levels of sodium. The cell wall material is then washed off and the remainder of the material is filtered and dried (Dimopoulosa et al., 2018). Yeast extract can also be used in a paste format—a common example of this is Vegemite spread popular in Australia. From a culinary standpoint, it is essential to know sodium levels in any yeast extract, as this will impact final taste results.

Utilization of yeast extracts in kitchen applications requires exact measurements, as they are employed in very small quantities (i.e., slightly below or above 0.15%). As a result, yeast extracts are more applicable in manufacturing settings than in daily home or foodservice environments. Using MSG is a much easier way to incorporate a concentrated umami source (Okiyama & Beauchamp, 1998). Yeast extracts are hygroscopic: when exposed to air, they will absorb moisture and clump. Yeast extracts in combination with nucleotides can have extreme impacts on flavor due to synergies between glutamates and nucleotides, as we describe below. Yeast extracts also deliver a consistent umami impact across the palate, but its overuse contributes an objectionable yeast note (Alim et al., 2019). Overall, yeast extract is less of a pure form of umami compared to MSG and MPG (J. Formanek, personal communication, September 9, 2021).

9.5 What Is Not Umami

There is a lot of confusion around what umami is, among home cooks and even among culinary professionals at high levels, who sometimes confuse the specific taste of umami with complex flavors like the unctuous sweetness of caramelized onions, the rich fatness of crispy pork belly, or the deep smokiness of Maillard-browned barbecued burnt brisket ends (Hofmann, 2005; Finot, 2006). While those foods may have many wonderful characteristics, including fattiness, unctuousness, smokiness, brown/roasted flavors, crispness, and so on, unless it was specifically prepared with umami-rich ingredients, like those described above, it probably had very low levels of umami taste, as determined both by chemical and by sensory analyses. Delicious flavor, certainly; umami taste, likely not.

There are a few reasons for the confusion around umami. It is a relative newcomer to the five basic tastes (Lindemann et al., 2002), and many people were not trained to recognize it when they were young like they did for the other basic tastes. Even at the professional level, educators have bemoaned the lack of palate training in formal culinary education (Deutsch, 2018). Without a firm understanding of umami, professional chefs do not know how to analyze their foods for optimal umami. To be umami, there must be a significant amount of glutamate that is not bound to other amino acids as a taste identified by specific umami receptors on the tongue (and elsewhere) as indicated in the previous section of *Umami History Through the Culinary Lens*. The higher the glutamate concentration in a food, the more umami will be sensed. In most cases, this sensation cannot be produced from compounds other than proteins that have glutamate—if no protein is available from which to extract the glutamate, then there can be no umami sensation on the taste

receptors. If umami receptors are not activated, food may present a delicious flavor without umami (understanding flavor as the combination of taste with all the other sensations that influence food perception, such as aroma, texture, juiciness, mouthfeel, or color) (Grabenhorst et al., 2008). So, there is additional confusion around ferments that are not protein rich. For example, cabbage is a vegetable low in protein. Kimchi recipes often add anchovies to cabbage in the fermentation, yielding an umami-rich product. Without the anchovy, or the production of glutamate by lactic acid bacteria (Yoon et al., 2021), Kimchi may be salty, sour, and delicious, but it will not be as rich in umami (Lee et al., 2021).

9.6 Synergies Between Ribonucleotides and Umami

Umami taste can be enhanced through synergistic interactions with the 5′-ribonucleotides GMP and IMP (Yamaguchi, 1998a, b) (see also Chaps. 2 and 3 of this book). IMP is found in large amounts in meat, poultry, seafood, and dairy, and guanylate is found most significantly in dried mushrooms. Both are also available in pure commercial/concentrate form (Wang et al., 2020). A small amount of inosinate and/or guanylate in combination with glutamate creates a strong umami taste (see Table 9.1).

Chefs have turned to these enhancement combinations (glutamate + inosinate/guanylate) intuitively throughout history to make food more delicious. Traditional preparations that employ this synergistic combination include the cheeseburger,

Table 9.1 Umami taste intensity of MSG + IMP mixtures of various percentages

% MSG	% IMP	Rated taste intensity
100	0	0
95	5	3.5
82	18	6.8
70	30	7.4[a]
50	50	7.5
30	70	7.3
10	90	5.3
5	95	3.7
2	98	1.8
0	100	0.3[b]

Data show responses (on a scale of 1 to 10) by trained panelists to the taste of various percent mixtures of MSG (monosodium glutamate) and IMP (5′-inosine monophosphate), generated by combining constant concentrations of 0.05 g/dL. Simplified from Yamaguchi (1967)

[a]As the percentage of MSG decreases from 100% to 70% and the percentage of IMP correspondingly increases from 0% to 30%, the taste intensity increases. A maximum is reached at this point. This forms an inverted U-shaped function with the optimal taste intensity mixture about 50% to 75% MSG and 25% IMP

[b]IMP has little or no umami taste intensity at 100% (no MSG in the mixture)

Table 9.2 Examples of food combinations for dishes that employ the synergistic effects between glutamate and IMP or GMP

Glutamate source	IMP or GMP source	Final synergistic combination
Glutamate + IMP foods		
Aged cheese	Tuna	Tuna melt sandwich
Kombu (kelp)	*Katsuobushi* (cured bonito)	Dashi
Onions, celery, carrots	Poultry	Chicken soup
Dashi	Pork	Ramen
Aged cheese	Beef	Cheeseburger
Glutamate + GMP foods		
Aged cheese	Dried porcini	Mushroom pasta
Scallop	Dried morels	Scallop with morel sauce
Kombu	Dried shiitake	Vegetarian dashi

Japanese curry, anchovies on pizza, mushroom gravy, and French onion soup. It also explains why dashi, the base stock in Japanese cooking, is so tasty despite being made from only two ingredients that are cooked for a short period of time (Umami Information Center, 2016): the *kombu* contributes glutamate, and either the *katsuobushi* contributes inosinate or, in vegetarian dashi, dried shiitake mushrooms contribute guanylate (see Table 9.2).

9.7 Benefits of Umami in Cooking

9.7.1 Aids in Salt Reduction

Flavor-enhancing and umami-rich ingredients such as MSG offer a possible sensory strategy to mitigate the low palatability of reduced salt. Medical evidence indicates that reduced sodium intake in diets can improve certain disease states such as hypertension and diabetes (Feldstein, 2002). Compliance with low-sodium diets is problematic due to the decrease in palatability (Roininen et al., 1996; Okiyama & Beauchamp, 1998; Yamaguchi & Ninomiya, 2000). MSG was acknowledged in 2019 by the National Academies of Sciences, Engineering, and Medicine as a viable strategy to reduce sodium in the food supply (Institute of Medicine, Food and Nutrition Board et al., 2010). The amount of sodium in MSG (12.28 g/100 g) is one-third that in salt (39.34 g/100 g), and the usage level as a food additive is quite low (0.1–0.8% by weight) (Maluly et al., 2017; Halim et al., 2020). Adding MSG in excess will create unbalanced flavors, decreasing palatability, so its use is self-limiting (Yamaguchi & Takahashi, 1984). This means that MSG has the potential to play a key role in reducing salt in food products while maintaining or increasing likability (see Chap. 4 of this book for more detail on this topic).

9.7.2 Provides a Bass Note in Cooking

The bass note that MSG provides in cooking may not be recognizable to average consumers, yet without it, some dishes taste like something is missing, an absence of full flavor potential. Like the bass part in music, it may not be overtly noticeable, but it provides the foundation that all the other parts build on—in dishes, MSG supports and enhances overall flavor. MSG has been described as "fullness of the mouth" and "richness" (Yamaguchi & Ninomiya, 2000) (see Chap. 2 of this book for more detail).

9.7.3 Increases Salivation

Umami, which has been shown to increase salivation (Schiffman, 1998), is notable by persistence in the palate and salivation at the end of the palate, signs of the presence of umami. This factor has been utilized in elderly patients to increase food intake (Sasano et al., 2015). The most important roles of saliva are during chewing food and in maintaining oral health. Saliva helps protect the teeth and mucosa from infection and maintain healthy taste receptors and speech communication (Uneyama et al., 2009) (see Chap. 7 of this book for more detail).

Taste dysfunction is shown to have a negative effect on health, correlating with poor appetite, reduced dietary intake, and weight loss (Sasano et al., 2014). This affects the elderly population most of all (Schiffman, 2000). Taste function and salivation are closely related, and the umami taste is shown to promote salivary secretion. A 2015 study found that treating decreased salivation reduced hypogeusia (Sasano et al., 2015), showing that salivation is essential to maintain normal taste function. The increased salivary flow rate, due to the gustatory-salivary reflex from umami taste stimulation, improved taste function, appetite, weight, and overall health in elderly people (Sasano et al., 2014, 2015).

9.7.4 Adds "Meatiness"

While it is hard to describe what umami tastes like, it is often referred to as meaty or savory. These flavor notes are particularly important in plant-based formulations for creating both meatiness and depth, pleasurable sensations that are absent in dishes that do not contain animal products (Yamaguchi, 1998a, b).

9.8 Conclusion

This chapter has focused on umami from a culinary point of view, as a basic, global taste that has played a traditional culinary role as a source of deliciousness for millennia before it was scientifically identified. The ancient Romans added umami with their fermented fish sauces, and the French gastronome Brillat-Savarin defined a water-soluble substance in meat flavors, but umami compounds—glutamate, IMP, and GMP—were not identified until 1908, by Professor Ikeda. Even so, it took another century for scientific evidence to reveal the existence of umami receptors on the tongue, identifying it as a bona fide taste element. These discoveries have helped chefs and cooks around the world understand why they traditionally gravitated toward umami-rich foods in their cuisines. Fundamental to what makes these foods delicious is the presence of glutamate and nucleotides that, from a chemosensory perspective, are a source of a fundamental, pleasurable taste. The analysis of umami compounds in foods and ingredients has given light to the cooking processes and food technologies that deliver a strong umami taste through such ingredients as MSG. For chefs and culinary students, learning how to recognize and distinguish the umami taste is an important part of their training in the kitchen, allowing the mindful application of umami-rich ingredients in recipes and menus. Understanding umami helps chefs and culinary students build balanced and complex flavor profiles. From a health perspective, this taste has been proven advantageous in reduced-sodium foods, mitigating the low palatability of low-salt products, and can aid digestion in the elderly by increasing saliva production. MSG and other concentrated umami ingredients can also provide the meaty and savory flavor notes that can be especially useful in plant-based formulations. Combined, these benefits of umami make it an attractive option to improve both health and flavor.

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