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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A. San Gabriel et al. (eds.), *Umami*, Food and Health,
https://doi.org/10.1007/978-3-031-32692-9_3

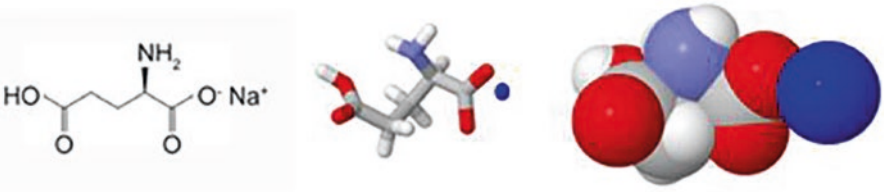

Fig. 3.1 Three different views of monosodium glutamate (MSG), showing a sodium ion (blue) near the bonding carboxylic acid. (Spacing-filling models from BioTopics. http://www.biotopics.co.uk/JmolApplet/gludisplayhalos.html)

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
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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).

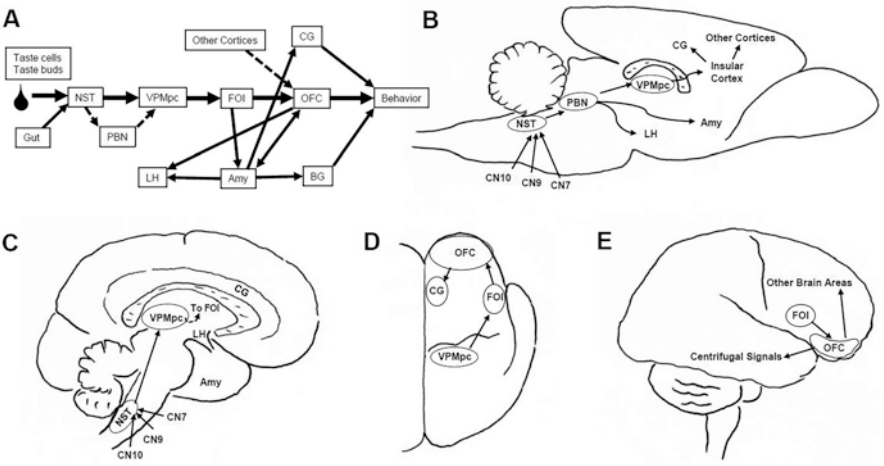

Fig. 3.3 Overview of rodent and human gustatory systems. (**a** and **b**) Schematic diagram of the major structures of the gustatory system (**a**), including sensory input from taste cells and taste buds and from the gut to the nucleus of the solitary tract (NST) and the principle ascending pathways 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.

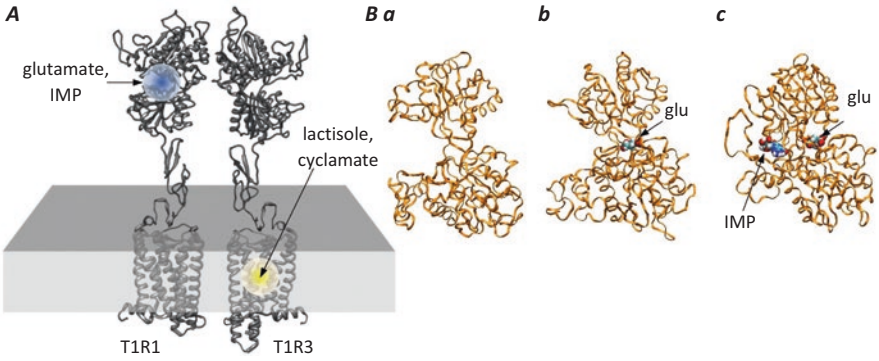

Fig. 3.4 T1R1 + T1R3 heterodimer umami taste receptor. (**a**) Glutamate and IMP bind to the large extracellular Venus flytrap domain of T1R1 in the dimeric umami taste receptor. (Modified from Laffitte, Neiers et al., 2014; Roper, 2020). (**b**) Molecular mechanism of the umami receptor: ribbon-band 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))

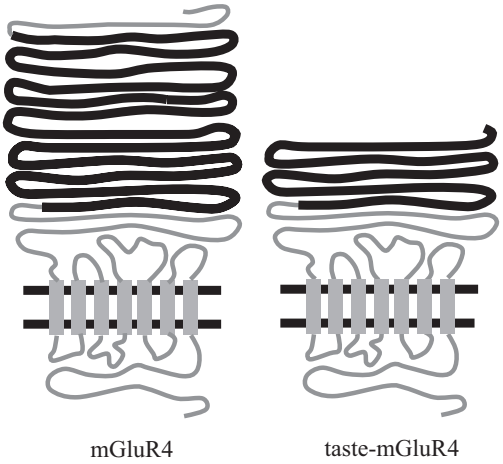

Fig. 3.5 The mGluR umami taste receptor (right) is a truncated splice variant of synaptic mGluR (left). The heavy black line shows the Venus flytrap motif, significantly truncated in taste-mGluR4. (From Chaudhari et al. (2000))

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).

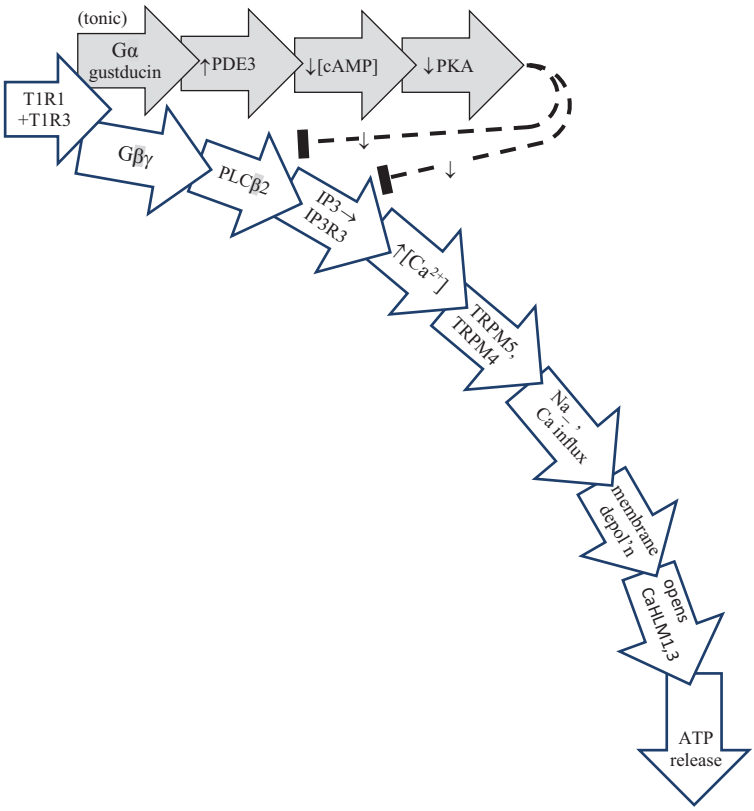

Fig. 3.6 Representation of the canonical G-protein-coupled receptor chemosensory transduction cascade. Open arrows symbolize the pathway for G-protein activation that leads to intracellular Ca^{2+} mobilization, depolarization (depol'n), and neurotransmitter (ATP) release. Gray arrows at the top depict 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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