Receptor and Transduction Processes for Umami Taste<sup>1,2</sup>

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ABSTRACT The unique taste of umami argues for a specific receptor at the taste cell level. The taste synergism between monosodium glutamate (MSG) and certain 5′-ribonucleotides provides a pharmacologic test for hypothetical mechanisms of umami taste. Early neurophysiologic and biochemical studies demonstrated specific recognition of L-glutamate by taste tissue and suggested that the synergism found with certain 5′-ribonucleotides was due to a peripheral event. The search for a receptor for umami relies at present on the data in the literature on central nervous system (CNS) glutamate receptors. These data distinguish several classes of receptors on the bases of pharmacologic properties and mode of action. Two hypotheses now seek to explain umami taste transduction. One states that umami is transduced by an N-methyl-D-aspartate (NMDA)-type glutamate ion channel receptor, the other that this taste is transduced via a metabotropic-type glutamate receptor. Evidence for the first hypothesis derives from earlier reconstitution studies, revealing a glutamate-stimulated ion channel conductance whose kinetics were affected by 5′-ribonucleotides. Additional evidence is provided from more recent calcium-imaging and patch-clamp studies, both showing that an ionotropic-type receptor on rodent taste cells mediates glutamate-induced depolarization. Evidence for the second mechanism derives from studies that located the message for a metabotropic-type (mGluR4) receptor to rat taste buds, and from whole-cell patch-clamp recordings that revealed sustained cellular conductances to glutamate and an mGluR4 agonist. It appears likely that both mechanisms are involved in umami taste transduction, suggesting the possibility that transduction of the umami signal constitute a collective property of a number of cells within the taste bud. J. Nutr. 130: 942S–945S, 2000.

KEY WORDS: • umami • glutamate • taste • nucleotides • calcium imaging • glutamate receptor

The basic taste of umami continues to be documented (Kawamura and Kare 1987, Kawamura et al. 1991, Yamaguchi 1998). Whether a taste can be described as primary depends on a number of mutable criteria. Such criteria may include the following: 1) psychophysical and descriptive data that tend to isolate one primary taste from another on the basis of statistical criteria; 2) electrophysiologic evidence that reports unique neural transduction features of the putative taste modality; and 3) biochemical and molecular biological evidence that identifies and localizes unique receptors and cellular responses to the candidate primary modality. These criteria have generally been fulfilled for the modalities of sweet, sour, salty and bitter (Brand 1997), and parallel studies are now meeting these criteria for umami as well. The criterion involving unique receptor processes has seen much support within the past few years. The fact that the major prototypical stimulus for umami taste is the sodium salt of L-glutamic acid raises the hypothesis that the receptor(s) for this modality may be related to one or more of the many known receptor types for glutamate found in the central nervous system (CNS) (Furrieron 1991, Hollmann and Heinemann 1994, Monaghan and Wenthold 1997, Fin and Bockaert 1995).

A variety of CNS neurotransmitter receptors for glutamate have been identified (Conn and Patel 1994, Hollmann and Heinemann 1994, Monaghan and Wenthold 1997). These may generally be placed into two structural categories, i.e., stimulus-gated ion channels and the metabotropic receptors. The ionotropic receptors induce signal transduction by altering ion flux through an ion channel directly coupled to and gated by a glutamate binding site. Metabotropic receptors are G protein–linked receptors in which glutamate binding in-
ducides changes in intracellular messengers that then alter the balance of intracellular ions. Studies of the taste receptor for glutamate should, like their counterparts of the CNS, strive to make use of any unique pharmacology of these glutamate-responsive systems. For example, most of the glutamate receptor types in the CNS are distinguishable through their specificity toward certain agonists and antagonists. Thus, of the ionotropic glutamate receptors, classes can be delineated roughly by their differential sensitivity to glutamate analogs such as α-amino-3-hydroxy-5-methyl-isoxazole-4-propionate (AMPA), kainic acid and N-methyl-D-aspartate (NMDA) (Hollmann and Heinemann 1994).

It is appropriate to determine the agonist/antagonist responses of glutamate taste receptors as well, allowing inferences to be made as to the type of receptors involved with umami taste. In addition, the unique properties of a putative umami receptor should be reflected in the response and pharmacology of that receptor. In taste, for example, certain 5′-ribonucleotides can enhance the intensity of the taste of the sodium salt of L-glutamate (MSG) in a true taste synergy (Rifkin and Bartoshuk 1980, Yamaguchi 1967, Yamaguchi et al. 1971). The umami taste receptor is also less sensitive to glutamate than are most of the CNS glutamate receptors, with the taste response appearing in the millimolar concentration range for glutamate. Successful characterization of the umami taste receptor must therefore include a functional explanation for this synergy and match the sensitivity of the receptor to the known psychophysics of umami taste.

This review will examine previous biochemical and biophysical studies documenting the probable existence of a putative umami taste receptor. It will also attempt to integrate these observations into a working hypothesis to describe the receptor processes for umami taste.

Interaction of glutamate with receptor sites

Several reports recording responses from the innervating sensory taste nerves are compatible with the hypothesis that umami is a unique taste. Using a conditioned taste aversion paradigm, Ninomiya and Funakoshi (1989a) demonstrated that MSG imparted a taste to the Slc:ICR strain of mouse that is different from those conferred by sweet, sour, salty and bitter stimuli. They also showed that certain fibers of the glossopharyngeal (CN IX) of the mouse were uniquely sensitive to MSG and that these fibers displayed a synergistic response to MSG plus guanosine-5′-monophosphate (GMP) (Ninomiya and Funakoshi 1989b). These data indicate that this strain of mouse can discriminate MSG from other basic tastes and that this discrimination is based primarily on information carried from the periphery by fibers of CN IX. Equally convincing were studies in dogs from Kurihara’s laboratory (Kumazawa and Kurihara 1990, Kumazawa et al. 1997 and 1998). These cells responded to L-glutamate and glycine, which are two important umami stimuli in dogs. The taste response appearing in the millimolar concentration range for glutamate. Successful characterization of the umami taste receptor must therefore include a functional explanation for this synergy and match the sensitivity of the receptor to the known psychophysics of umami taste.

Transduction models for umami taste

Although binding of MSG to presumed receptor sites has been demonstrated, subsequent transduction steps are still being explored. To date, two hypotheses have been put forth to account for transduction of the binding event to release of neurotransmitter. One states that the receptor is a stimulus-gated ion channel-type receptor. This hypothesis received initial support from studies showing that a glutamate-stimulated ion channel could be reconstituted into a lipid (azole-tin) bilayer from a partial membrane preparation of mouse (C3H strain) vallate and foliate taste tissue. Results showed that in other silent bilayers, the addition of millimolar concentrations of L-glutamate led to an increase in conductance of the bilayer (Brand et al. 1991, Teeter et al. 1992). This conductance increase was graded with glutamate concentration, was distinct from any sodium-induced currents and could be enhanced by the addition of 5′-GMP, a known enhancer of the glutamate response in this mouse strain. These findings suggested that the taste receptor for glutamate in the mouse may be of the stimulus-gated ion channel type, perhaps similar to an NMDA-type glutamate receptor channel.

Subsequent studies have used imaging dyes to monitor both intracellular calcium and membrane voltage in isolated taste cells from mouse (C3H) vallate and foliate taste tissue (Ha-yashi et al. 1996 and 1997). These cells responded to L-glutamate with either increases or decreases in intracellular calcium (Fig. 1A). Membrane depolarization was generally accompanied by increases in intracellular calcium, suggesting an inward current. The glutamate analog, L-2-amino-4-phos-
metabotropic glutamate receptor. This hypothesis was based on work of Chaudhari et al. (1996). Their studies reported that a cDNA library, constructed from rat vallate tissue, included sequences similar to known CNS glutamate receptors. Several clones were found, including ones that coded for NMDA-type receptors. In situ hybridization studies showed that one of these, a low abundance clone for a metabotropic receptor of the mGluR4 family, could be localized specifically to the taste buds of rat vallate. A conditioned taste aversion study in rats found that l-AP4 generalized to MSG, whereas NMDA did not, suggesting that to the rat, l-AP4 tasted like MSG. Imaging and patch recordings of isolated taste cells using the stimulus, l-AP4, an agonist of the mGluR4 family, supported the finding that this type of glutamate receptor is present in the taste system. Patch recordings from taste cells of rat vallate indicated that in most cells studied, glutamate (and l-AP4) induced an outward current, whereas in a small number of other cells, glutamate induced a transient inward current (Bigiani et al. 1997).

It is apparent that both hypotheses are tenable. Both NMDA-type and mGluR receptors are present on the membranes of taste cells. Yet, like their counterparts in the CNS, both lead to opposite transductional responses. How are these excitatory and inhibitory signals integrated within the taste bud so that an excitatory signal is sent to the CNS?

**SUMMARY**

Collectively, these data suggest that the receptor process for umami may involve responses from both ionotropic- and metabotropic-type glutamate receptors. Because taste cells signal the presence of stimuli with excitatory responses, it would at first appear likely that the receptor for umami is a stimulus-gated ion channel. In this type of receptor, a binding site on the complex recognizes glutamate, and this recognition induces the opening of a presumed cation channel. This depolarization induces further modulation of voltage-sensitive channels, leading to cellular depolarization sufficient to induce neurotransmitter release (Fig. 2A). It is also possible that the metabotropic receptor functions in taste transduction because inhibitory responses could be important in taste processing, particularly at the level of the taste bud. The mGluR4 receptor is one that alters levels of intracellular messengers, in this case, causing decreases in cAMP by inhibiting the action of adenyl cyclase. A G_i/o-type G protein is likely involved (Fig. 2B).

It is possible that both of these receptor types could act in concert, with the metabotropic receptor providing an inhibitory signal in some cells to enhance the contrast with excitatory cells. One might consider the analogy with visual reception in which an activated cell inhibits surrounding cells, presumably enhancing visual acuity. Alternatively, the mGluR4 inhibitory response may signal a following cell (perhaps the Merkel-like cells known to be present in taste buds of certain animals (Delay et al. 1997), which, as in the visual system, then transforms the initial inhibitory signal into an excitatory one. It is also possible that the actual umami receptor is one of a subset of metabotropic receptors for glutamate whose properties are not yet explored because its low abundance has not yet allowed excitatory responses to be observed.

The receptor and transductional processes for umami are just beginning to be explored. Future studies will clone an NMDA-type receptor in taste cells, and single cell poly-A chain reaction can be used to determine whether more than one type of receptor is expressed in a single taste cell. Until now, all reported single taste cell biophysical responses have shown cell segregation of mGluR- and

**FIGURE 1** Responses of taste cells from mouse vallate and foliate to glutamate and analogs, L-2-amino-4-phosphonobutyrate (L-AP4) and N-methyl-D-aspartate (NMDA). Right axis (R) shows fluorescence ratio values (normalized) for the voltage sensitive dye, di-8-ANEPDS, represented by solid squares in the figures. Left axis, [Ca^{2+}]_i (mmol/L), is the calculated intracellular calcium activity (nmol/L) represented in the figures by the solid triangles. Stimuli or Ringers was added at the time point shown by the vertical lines on each graph. The stimulus reaches the cell with a delay of 5–20 s. (A) Addition of 1 mmol/L L-glutamate; (B) addition of 1 mmol/L L-AP4; (C) addition of 1 mmol/L NMDA. With permission, from Hayashi et al. (1996).

phonobutyrate (L-AP4), a stimulator of metabotropic glutamate receptors, elicited primarily decreases in intracellular calcium, accompanied by little or no change in membrane depolarization (Fig. 1B). The analog, NMDA, elicited only increases in intracellular calcium, accompanied by a depolarization (Fig. 1C). L-Glutamate (1 mmol/L) plus GMP (1 mmol/L) elicited primarily increases in intracellular calcium. These data suggest, therefore, that there may be at least two types of glutamate receptors in taste cells, i.e., one an excitatory receptor, likely similar to a stimulus-gated ion channel NMDA type, and another of the metabotropic type, which may be primarily an inhibitory signal.

The second hypothesis states that the umami receptor is a
Note Added in Proof: Recently published studies have further clarified the likely dual role for metabotropic and ionotropic mechanisms for umami taste. Using isolated taste bud cells from rat fungiform, Lin and Kinnamon (J. Neurophysiol. 82: 2061–2069, 1999) show three types of glutamate induced responses: one being a depolarizing NMDA-type, the other two being either hyperpolarizing or depolarizing responses from mGluRs. In a cloning study, Chaudhari et al. (Nature Neurosci. 3: 113–119, 2000) reveal a full-length, N-terminus truncated form of an mGluR4 (“taste-mGluR4”) that when expressed in heterologous cells responds with decreases in cAMP to millimolar levels of glutamate.

LITERATURE CITED


