Responses to Di-Sodium Guanosine 5′-Monophosphate and Monosodium L-Glutamate in Taste Receptor Cells of Rat Fungiform Papillae

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Lin, Weihong, Tatsuya Ogura, and Sue C. Kinnamon. Responses to di-sodium guanosine 5′-monophosphate and monosodium L-glutamate in taste receptor cells of rat fungiform papillae. J Neurophysiol 89: 1434–1439, 2003. First published December 4, 2002; 10.1152/jn.00994.2002. The 5′-ribonucleotide guanosine 5′-monophosphate (GMP) is used widely as an umami taste stimulus and a potent flavor enhancer as it synergistically increases the umami taste elicited by monosodium glutamate. Transduction mechanisms for GMP and its synergy with glutamate are largely unknown. Using whole-cell patch-clamp and Ca2+ imaging, we examined responses to GMP, glutamate, and a mixture of GMP and glutamate in taste-receptor cells of rat fungiform papillae. Our electrophysiological results showed that GMP induces responses that are similar to those of glutamate, e.g., an outward current, an inward current, or a biphasic response. Our Ca2+ imaging results showed that applications of GMP, glutamate, and the mixture increased intracellular Ca2+ levels. Interestingly, both patch-clamp and Ca2+ imaging showed that some taste cells can respond to GMP and glutamate independently, indicating that glutamate and GMP likely activate different receptors. Simultaneous application of GMP and glutamate resulted in synergistic responses in a subset of cells; both response intensity and number of responding cells were increased. Most responses to GMP, as well as the synergy between GMP and glutamate, were suppressed by 8-bromo-adenosine 3′,5′-cyclic monophosphate (8-bromo-cAMP) in patch-clamp recordings. Together, our results suggest that intracellular cAMP- and Ca2+-mediated pathways are involved in umami taste transduction for GMP and its synergistic responses with glutamate.

INTRODUCTION

Humans and animals rely on the sensation of taste to search for nutrients and to avoid potential poisons. “Umami” taste, one of the characteristic taste qualities, is thought to reflect dietary requirements for proteins and nucleotides. Umami taste stimuli include the amino acids L-glutamate and L-aspartate, and the 5′-ribonucleotides guanosine 5′-monophosphate (GMP) and inosine 5′-monophosphate (IMP). These compounds exist naturally as mono- or di-sodium salts in many meats, vegetables, and dairy products (Ikeda 1909; Kodama 1913; Lindemann et al. 2002; Maga 1983). Interestingly, when amino acids and 5′-ribonucleotides are both present in food, the taste intensity of umami is enhanced synergistically and the umami taste threshold is dramatically lowered (Kuninaka et al. 1964; Yamaguchi and Kimizuka 1979). GMP and IMP alone elicit action potentials in gustatory afferent fibers and in central gustatory neurons (Hellekant and Ninomiya 1991; Sako et al. 2000; Scott et al. 1993); however, the transduction mechanisms for ribonucleotides and their synergy with glutamate remain to be determined.

Recently, studies have focused on identification of taste receptors for umami compounds. Two putative G protein-coupled taste receptors for glutamate have been identified, taste-mGluR4 (Chaudhari et al. 1996, 2000) and the amino acid receptor T1R1/T1R3 (Li et al. 2002; Nelson et al. 2002). Both receptors occur in taste buds and, when expressed in heterologous cells, both receptors bind glutamate at concentrations appropriate for umami taste. However, 5′-ribonucleotides presented alone do not activate either of these receptors. Apparently, other receptors yet to be identified may mediate taste transduction for 5′-ribonucleotides.

Although T1R1/T1R3 is not activated by 5′-ribonucleotides, responses to glutamate and other amino acids are greatly potentiated when GMP/IMP are present (Li et al. 2002; Nelson et al. 2002). The mechanism underlying the synergistic reaction has not been determined. Previous studies hypothesize that synergy results from allostERIC interaction of 5′-ribonucleotides with glutamate receptors (Brand et al. 1991; Torii and Cagan 1980). Whether intracellular pathways contribute to synergy is not known. Since both candidate glutamate taste receptors are linked to G protein-mediated pathways, it is possible that synergy involves an amplification or interaction at the level of signaling pathways.

In this study, we used whole-cell patch-clamp and Ca2+ imaging of isolated rat fungiform taste cells to examine responses to GMP alone and in combination with glutamate. Our results provide strong evidence that GMP elicits taste cell responses that are independent of its well-known synergism with glutamate. Further, our data suggest that responses to GMP alone, as well as synergistic responses to GMP and glutamate, are mediated by a decrease in intracellular cAMP, suggesting a convergence of intracellular signaling mecha-

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nisms. Some of these results were presented at a meeting (Lin and Kinnamon 1998).

**METHODS**

**Animals**

Male Sprague-Dawley 4- to 12-wk-old rats were used. Taste buds were isolated enzymatically using a method described previously (Lin and Kinnamon 1999).

**Patch-clamp recordings**

The whole cell patch-clamp technique was used (Hamill et al. 1981). The steady-state current of taste receptor cells of freshly isolated taste buds was recorded with the voltage-clamp configuration. Taste buds were bathed in Tyrode’s solution, containing 140 mM NaCl, 5 mM KCl, 1 mM MgCl₂, 1 mM CaCl₂, 10 mM HEPES, 10 mM glucose, and 10 mM sodium pyruvate (pH 7.4 with NaOH). Glass pipettes for patch recording were pulled from microhematocrit capillaries (Scientific Products, McGaw Park, IL) with a two-stage pipette puller (model PB-7; Narishige, Tokyo). The pipette resistance was 3–6 MΩ when filled with the pipette solution containing 140 mM KCl, 1 mM CaCl₂, 2 mM MgCl₂, 10 mM HEPES, 11 mM EGTA, 1 mM ATP, and 0.4 mM GTP (pH 7.2 with KOH). Membrane currents were low-pass-filtered at 2 KHz and recorded with an Axopatch patch-clamp amplifier (model 200B; Axon Instruments, Foster City, CA). Voltage-gated Na⁺ and K⁺ currents were induced by applying voltage steps from an Indec laboratory computer system (Sunnyvale, CA) and were used to distinguish taste cells from nonsensory epithelial cells which lack these currents. Taste cells were held at −80 mV, and 20 mV hyperpolarizing voltage pulses were used to monitor the membrane conductance.

**Ca²⁺ imaging**

Fura-2 imaging was used to measure intracellular Ca²⁺ levels by a method adapted from our previous papers (Ogura 2002; Ogura et al. 1997). Taste buds were incubated with 2 μM fura-2/AM (Molecular Probes) for 20 min and washed with normal Tyrode’s. The intracellular Ca²⁺ level was obtained as the ratio of fluorescence intensity at excitation wavelengths of 350 and 380 nm. Dual excitation wavelengths were applied by a filter wheel changer (Lambda 10-2; Sutter Instruments) and a xenon lamp (model 770, Optiquip). Fluorescent images were obtained with a 40× oil objective lens (N.A. 1.3) with a >525 nm emission filter (Chroma Technology). Axon Imaging Workbench software (Axon Instruments) was used to capture images and to change the position of the filters. Image pairs were acquired every 2 s during responses and every 5–10 s during control and wash-out periods.

**Chemicals**

Chemicals were bath applied. Monosodium glutamate (MSG), disodium guanosine 5'-monophosphate (GMP), and 8-bromo-adenosine 3',5'-cyclic monophosphate (8-bromo-cAMP) were obtained from Sigma Chemical, St. Louis, MO. All taste stimuli were applied as Na⁺ salts. Since the amount of Na⁺ added was small (<3 mM) compared with the concentration of Na⁺ in the bath, we do not expect that the additional Na⁺ contributed to any responses; thus, responses were considered to result exclusively from GMP and glutamate.

**RESULTS**

**Whole cell current responses to GMP**

GMP (0.1 mM) applied to the bath solution elicited three types of responses in taste cells held at −80 mV: a decrease in holding current and membrane conductance (outward current; type I); an increase in holding current and membrane conductance (inward current; type II); or a biphasic response (type III), characterized by an inward current followed by an outward current (type III; Fig. 1A). In a total of 127 cells tested, 72 cells responded to GMP. Among them, 28 cells showed type I responses, while 19 cells showed type II responses with mean current amplitudes of 15.3 ± 3.8 and 10.4 ± 3.3 pA, respectively. Twenty-five cells showed type III responses (Fig. 1B). In general, the types of responses elicited by GMP were similar to those of glutamate (Bigiani et al. 1997; Lin and Kinnamon 1999), although in any given cell, responses to GMP and glutamate were not always of the same type. Of these 127 cells, 54 cells responded to both GMP and glutamate (61% of 89 responsive cells). Interestingly, 18 cells responded to GMP only (20% of responsive cells), while 17 cells responded to glutamate only (19% of responsive cells; Table 1). Since some cells responded to only one of the stimuli, GMP may activate receptors distinct from those activated by glutamate.

**Whole cell synergistic responses**

Synergy between GMP and glutamate is an important feature of umami taste. A mixture of GMP (0.1 mM) and gluta-

**FIG. 1.** Responses to guanosine 5'-monophosphate (GMP; 0.1 mM) in fungiform taste cells in whole cell patch-clamp recording. Holding potential: −80 mV. A: GMP applied to the bath induced three types of responses: an outward current (type I, top), an inward current (type II, middle), and a biphasic response (type III, bottom). B: number and percentage of taste cells showing each type of response (n = 72).
Glutamate (1 mM) applied to the bath induced synergistic responses in 13 of 48 cells tested. Most synergistic responses occurred in cells that responded to both GMP and glutamate. A few synergistic responses occurred in cells that did not have measurable responses to glutamate. Both inward (n = 5, 10%) and outward (n = 8, 17%) current responses could be potentiated (Table 2). In cells that showed synergistic outward current, individual responses to GMP and glutamate (if measurable) usually were either type I or type III responses that contained an outward component; while in cells that showed synergistic inward current, individual responses to GMP and glutamate usually were type II or type III responses. However, the responses to GMP and glutamate were not always of the same type in the same cells. Figure 2 shows representative responses in a single cell to glutamate, GMP, and a mixture of both; only the outward current was potentiated in this example. We considered a response to the mixture synergistic when current amplitude to the mixture is bigger than the sum of two responses elicited by the two stimuli applied separately. We estimated synergy by calculating the ratio of the response to the mixture versus the sum of separate responses to GMP and glutamate. The mean ratios for these synergistic responses were 1.3 ± 0.1 for inward current and 2.5 ± 0.8 for outward current. That is, synergistic responses involving potentiation of outward current were usually greater than those showing potentiation of inward current.

### Table 1. Percentage of responsive taste cells that responded differently to GMP and glutamate in whole cell patch recording and Ca^2+ imaging

<table>
<thead>
<tr>
<th></th>
<th>GMP+/ Glutamate</th>
<th>GMP+/ Glutamate</th>
<th>GMP−/ Glutamate</th>
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<tbody>
<tr>
<td>Whole cell patch recording</td>
<td>54 (61)</td>
<td>18 (20)</td>
<td>17 (19)</td>
</tr>
<tr>
<td>Ca^2+ imaging</td>
<td>40 (78)</td>
<td>6 (12)</td>
<td>5 (10)</td>
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Values are number of cells with percentages in parentheses; n is number of responsive cells. GMP, guanosine 5′-monophosphate. +, response; −, no response to stimulus.

### Table 2. Percentage of responsive cells showing synergy or nonsynergy in response to the mixture of GMP and glutamate in whole cell patch recording and Ca^2+ imaging

<table>
<thead>
<tr>
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<tr>
<td>Whole cell patch recording</td>
<td></td>
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<tr>
<td>Synergy</td>
<td></td>
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<tr>
<td>With a potentiated inward current</td>
<td>5 (10)</td>
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<tr>
<td>With a potentiated outward current</td>
<td>8 (17)</td>
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<tr>
<td>Nonsynergy</td>
<td>35 (73)</td>
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<tr>
<td>Total</td>
<td>48 (100)</td>
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<tr>
<td>Ca^2+ imaging</td>
<td></td>
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<tr>
<td>Synergy</td>
<td></td>
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<tr>
<td>GMP+glutamate+/ mixture+, GMP+/glutamate−/ mixture+, GMP−/glutamate+/mixture+</td>
<td>6 (10)</td>
</tr>
<tr>
<td>GMP−/glutamate−/mixture+</td>
<td>8 (14)</td>
</tr>
<tr>
<td>Nonsynergy</td>
<td>45 (76)</td>
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<tr>
<td>Total</td>
<td>59 (100)</td>
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Values are number of cells with percentages in parentheses. For symbols and abbreviation, see Table 1.

**Role of cAMP in responses to GMP and mixtures of GMP and glutamate**

Increases in intracellular cAMP antagonize most type I (outward current) responses to glutamate (Lin and Kinnamon 1999). To determine if cAMP is also involved in the response to GMP, a membrane-permeable cAMP analog, 8-bromo-cAMP (1 mM), was added to the bath. In four of five cells tested, cAMP eliminated or reduced responses to GMP (Fig. 3A). Interestingly, 8-bromo-cAMP also eliminated or suppressed the synergistic response to the mixture of GMP and glutamate. In five of seven cells tested, the synergized response was reversibly reduced or diminished by 8-bromo-cAMP (Fig. 3B). These data suggest that the receptors involved in detecting...
GMP and in generating the synergism between GMP and glutamate are negatively coupled to the Ca²⁺ pathway.

**Intracellular Ca²⁺ levels in response to GMP and glutamate**

Because GMP elicited both inward and outward currents, and because synergistic responses usually involved a potentiation of the outward current (which did not result in membrane depolarization), we examined changes in intracellular Ca²⁺ levels using the Ca²⁺-sensitive dye fura-2. GMP (1 mM) applied to the bath solution increased intracellular Ca²⁺ levels in 59 of 364 cells tested. The average Ca²⁺ response to GMP was 10 ± 0.9% above the resting level. In a subset of responsive cells, oscillatory Ca²⁺ responses occurred with a longer application of GMP (Fig. 4, A and B). In addition to GMP (1 mM), two other stimuli, glutamate (2.5 mM) and a mixture of GMP (1 mM) and glutamate (2.5 mM), were applied in 358 cells. Forty cells responded to both glutamate and the mixture (78% of 51 responsive cells). Six cells responded (12% of 51 cells) to GMP only and five cells (10% of 51 cells) responded to glutamate only (Table 1). The observation that 22% of these 51 cells responded to only one or the other of the two stimulants suggests that taste cells may respond to GMP and glutamate using different receptors and/or signal transduction mechanisms.

To examine whether synergistic Ca²⁺ responses occur when a mixture of GMP and glutamate is applied, we compared responses to a mixture of GMP and glutamate with responses to GMP and glutamate individually. The mixture was applied to cells regardless of whether they had responses to individual stimuli; a total 59 of 358 cells responded to the mixture. Most cells did not show synergism; response magnitudes to the mixture were larger than those elicited by either GMP or glutamate alone but less than the summation of the two individual responses (45 of 59 responsive cells; 76%, Fig. 4C and Table 2). However, in a subset of cells that had individual responses to GMP and/or glutamate, synergistic responses were observed (Table 2, 6 of 59 cells, 10%). Interestingly, another subset of cells that had very small or no individual responses to GMP and glutamate displayed significant synergistic responses to the mixture of GMP and glutamate (8 of 59 cells, 14%, Fig. 4D and Table 2). Thus we observed an increase in the number of responsive cells when testing with the mixture compared with either stimulus alone. In summary, stimulation with the mixture of GMP and glutamate led to increases both in the intracellular Ca²⁺ levels and in the number of responsive cells.

All stimuli used in this study, i.e., GMP, glutamate, and a mixture of the two, caused increases in Ca²⁺ levels; no decreases in intracellular Ca²⁺ levels were observed. This result was unexpected given the number of cells where the response was an outward current, which presumably would not produce membrane depolarization. To examine whether extracellular Ca²⁺ is necessary for the increase in intracellular Ca²⁺ in response to GMP, GMP-responding cells were tested in Ca²⁺-free bath solution. The responses to GMP (1 mM) in Ca²⁺-free saline were variable, depending on the cell tested. Some cells displayed a rise in intracellular Ca²⁺, even in Ca²⁺-free solution. Other cells failed to respond when bathed in a Ca²⁺-free solution, but recovered the response when Ca²⁺ was restored. These results suggest that some cells respond to GMP by releasing Ca²⁺ from intracellular stores, whereas others respond to GMP by influx of Ca²⁺ from extracellular sources.

**DISCUSSION**

We examined the response of taste receptor cells in rat fungiform papillae to umami taste stimuli, including GMP, glutamate, and a mixture of the two. Both patch-clamp recording and Ca²⁺ imaging demonstrated that a subset of taste cells responds to GMP applied alone. Many but not all the GMP-responsive cells also were responsive to glutamate. When challenged with a mixture of GMP and glutamate, a subset of responsive cells showed synergistic responses. Further, our data suggest that the cAMP pathway may be involved both in the transduction of GMP and in its synergy with glutamate.

Our results are compatible with previous recordings from the chorda tympani nerve. In those studies, GMP and IMP both elicited measurable responses. Many nerve fibers that responded to glutamate also responded to GMP, while some fibers responded only to glutamate or the 5'-ribonucleotides, and only a subset of fibers showed synergy (Hiji and Sato 1967; Ninomiya et al. 1992; Sato et al. 1970; Ugawa and Kurihara 1994; Yamamoto et al. 1991). These data, together with our results, support the suggestion (Chaudhari 2001, Sako and Yamamoto 1999) that the transduction of GMP and glutamate can occur independently, which would require separate
membrane receptors for transduction. The nature of the GMP receptor is presently unknown. It is unlikely to be T1R1/T1R3, because the expressed receptor did not respond to IMP/GMP independently of amino acids (Li et al. 2002; Nelson et al. 2002). The response of taste-mGluR4 to GMP has not been determined.

Despite apparent separate glutamate and GMP receptors, responses to GMP closely resemble responses to glutamate in isolated taste receptor cells. Both GMP and glutamate elicit similar current response profiles (Lin and Kinnamon 1998, 1999), and both stimuli increase intracellular Ca\(^{2+}\) levels. A possible explanation is that both glutamate receptors and GMP receptors activate the same second messenger pathway. Stimulation of taste buds with glutamate causes decreases in intracellular cAMP levels (Abaffy et al. 2002; Zhou and Chaudhari 1997) and cAMP suppresses responses to glutamate and to the metabotropic glutamate receptor agonist, L-AP4 (Lin and Kinnamon 1999). In the present study, patch-clamp measurements showed that cAMP suppressed GMP responses as well as synergistic responses to the mixture of GMP and glutamate in some cells. Thus it is likely both GMP and glutamate receptors reduce intracellular cAMP levels in some taste cells. Whether the receptors activate phosphodiesterase or inhibit adenylyl cyclase to decrease intracellular cAMP levels has not been determined. Since not all GMP responses were suppressed by cAMP, other transduction mechanisms for GMP also may exist, such as activation of an ionotropic receptor or the IP\(_3\) pathway (Ninomiya et al. 2000).

Synergy between GMP and glutamate is a characteristic feature of the umami taste. Our results from both whole cell patch recordings and Ca\(^{2+}\) imaging showed that the intensity of the responses induced by the mixture of the two could be potentiated synergistically in some cells. Moreover, some synergistic responses were obtained in cells that had only small, or undetectable, responses to glutamate and GMP applied individually. Thus the mixture caused an increase in the apparent number of responsive cells, similar to the responses originating from T1R1/T1R3 in heterologous expression (Li et al. 2002; Nelson et al. 2002). Both taste-mGluR4 and T1R1/T1R3 receptors have been proposed to mediate umami taste elicited by glutamate. Behavioral studies (Delay et al. 2000) have shown that IMP synergistically enhances preference for L-AP4, an agonist for both T1R1/T1R3 and taste-mGluR4. In nature, only amino acids with acidic side chains containing COOH, such as l-glutamate and l-aspartate, elicit umami tastes (Maga 1983). Since cloned T1R1/T1R3 receptors respond to many amino acids with different taste qualities (Li et al. 2002; Nelson et al. 2002), taste receptor cells may employ other mechanisms to differentiate the umami taste of glutamate from the sweet or bitter tastes elicited by other amino acids.

Many taste cells that responded to both glutamate and GMP individually had no synergy when glutamate and GMP were applied in a mixture. Results of single nerve fiber responses (Hellekant et al. 1997; Hellekant and Ninomiya 1991; Ninomiya and Funakoshi 1989) and central gustatory neurons (Adachi and Aoyama 1991) are compatible with our results. Why the mixture of GMP and glutamate elicits synergy in some taste cells but not in others is not clear. It is possible that GMP binds to glutamate receptors as a co-agonist and also binds to distinct receptors independent from glutamate in the same taste cells. Further studies will be required to determine the mechanism of synergy and the differential effects induced by the mixture.

Taste cells in the present study responded to glutamate and GMP with increases in intracellular Ca\(^{2+}\). Similar increases in intracellular Ca\(^{2+}\) were observed when taste cells of C57BL mouse fungiform papillae (Ninomiya et al. 2000) and rat foliate papillae (Caicedo et al. 2000) were challenged with glutamate or the mixture. In contrast, glutamate and the mixture elicited both increases and decreases in intracellular Ca\(^{2+}\) in distinct circumvallate and foliate taste cells from C3H mouse (Hayashi et al. 1996). It is not clear if this difference reflects methodological differences or distinct mechanisms in different papillae or strains of mice.

In comparing patch-clamp and Ca\(^{2+}\) imaging data, considerably more cells responded to umami stimuli in patch-clamp experiments than in Ca\(^{2+}\) imaging experiments. However, when considering only cells that responded to one or more stimuli, the percentage of differentially responsive cells was similar in the two assays (compare Tables 1 and 2). The reason for a lower overall response rate in the Ca\(^{2+}\) imaging experiments is not clear. In patch-clamp recordings, taste cells were dialyzed with pipette solution and were held at −80 mV, which may elevate amplitudes of some responses to detectable levels, thus resulting in more responsive cells.

Since we applied stimuli to taste cells in isolated taste buds, it is possible that some of the responses may not be mediated by receptors located at the apical membrane. Indeed, Caicedo et al. (2000) reported that glutamate activates N-methyl-D-aspartate (NMDA) receptors in taste buds that are preferentially located in the basolateral membrane, and these would have been stimulated in our experiments. Responses to glutamate and its agonists NMDA (NMDA receptor) and L-AP4 (mGluR4) have been characterized under similar experimental conditions (Lin and Kinnamon 1999). NMDA induced inward currents exclusively. However, not all inward currents induced by glutamate result from activation of NMDA receptors, as some cells responded to L-AP4 with an inward current. Since behavioral studies showed the absence of synergy between IMP and NMDA (Delay et al. 2000), the potentiated inward current may be due to activation of mGluR4 or the newly cloned amino acid receptor T1R1/T1R3.

The mechanism of Ca\(^{2+}\) increase induced by GMP is not known. One possibility is that IP\(_3\)-mediated pathways are involved, since IMP and GMP have been shown to increase IP\(_3\) production in taste cells (Ninomiya et al. 2000). In support of this, we found that some responses to GMP and to the mixture were independent of extracellular Ca\(^{2+}\). Similarly, responses to glutamate and a mixture of glutamate and GMP/IMP were independent of extracellular Ca\(^{2+}\) in taste cells of C57BL mouse fungiform papillae (Ninomiya et al. 2000).

Increases in intracellular Ca\(^{2+}\) are not always coupled to membrane depolarization. In bitter taste, denatonium induces both membrane depolarization and hyperpolarization (Ogura et al. 1997; Seto et al. 1999). Bitter stimuli elicit only increases in intracellular Ca\(^{2+}\), and these are mediated via the IP\(_3\) pathway (Ogura et al. 1997, 2002). In bitter transduction, the βγ partners of α-gustducin mediate the increase in intracellular Ca\(^{2+}\) (Huang et al. 1999). A similar mechanism may operate in umami taste. Recent data show that α-gustducin knockout mice have less preference for umami compounds than wild-type mice (He et al. 2002; Ruiz et al. 2002), but further experiments
REFERENCES


