The Neurophysiology of Taste and Olfaction in Primates, and Umami Flavor[a]

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ABSTRACT: To investigate the neural encoding of glutamate (umami) taste in the primate, recordings were made from taste responsive neurons in the cortical taste areas in macaques. Most of the neurons were in the orbitofrontal cortex (secondary) taste area. First, it was shown that there is a representation of the taste of glutamate which is separate from the representation of the other prototypical tastants sweet (glucose), salt (NaCl), bitter (quinine) and sour (HCl). Second, it was shown that single neurons that had their best responses to sodium glutamate also had good responses to glutamic acid. Third, it was shown that the responses of these neurons to the nucleotide umami tastant inosine 5′-monophosphate were more correlated with their responses to monosodium glutamate than to any prototypical tastant. Fourth, concentration response curves showed that concentrations of monosodium glutamate as low as 0.001 M were just above threshold for some of these neurons. Fifth, some neurons in the orbitofrontal region, which responded to monosodium glutamate and other food tastes, decreased their responses after feeding with monosodium glutamate to behavioral satiety, revealing a mechanism of satiety. In some cases this reduction was sensory-specific. Sixth, it was shown in psychophysical experiments in humans that the flavor of umami is strongest with a combination of corresponding taste and olfactory stimuli (*e.g.*, monosodium glutamate and garlic odor). The hypothesis is proposed that part of the way in which glutamate works as a flavor enhancer is by acting in combination with corresponding food odors. The appropriate associations between the odor and the glutamate taste may be learned at least in part by olfactory to taste association learning in the primate orbitofrontal cortex.

INTRODUCTION

In order to understand how appetite and food intake are controlled by the human brain, and disorders in appetite and feeding, the neural mechanisms involved are being analyzed in primates.[14] A reason for performing these experiments with primates is that the primate taste system may be organized even anatomically differently to the taste system of nonprimates.[8,4,9,13,15] For example, unlike rodents, there is in macaques no subcortical set of pathways from the brainstem, and instead there is an obligatory relay from the nucleus of the solitary tract via the taste thalamus to the taste cortex.

It has been shown that in the orbitofrontal cortex of primates, there is a region of

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secondary taste cortex in which neurons are activated by the taste of food.[19,13,15,16,3] These orbitofrontal taste neurons can be tuned quite finely to gustatory stimuli.[19] Moreover, their activity is related to food reward, in that those that respond to the taste of food do so only if the monkey is hungry.[18] These neurons show effects of sensory-specific satiety, an important mechanism in the control of feeding.[13–16,18,24] This region is implicated in the control of feeding, for it is the first part of the taste system of primates in which neuronal responses to the taste of food occur while hungry, but not after satiation.[18,13,15,16]

The orbitofrontal cortex also contains neurons with multimodal representations, for example, neurons that respond to olfactory and taste stimuli, or to visual and taste stimuli.[13,15,16,20] A neuronal representation of flavor appears to be formed in the orbitofrontal cortex. Approximately 40% of the olfactory neurons in the orbitofrontal cortex have activity that depends on the association with taste reward of the olfactory input, in that some categorize odors depending on whether they are associated with glucose or saline in an olfactory discrimination task.[5,23] Moreover these olfactory responses may modify during the reversal of this olfactory discrimination task.[22] The responses of some of these orbitofrontal cortex olfactory and visual neurons are also modulated by hunger, and contribute to sensory-specific satiety[6] (see also Ref. 24).

The orbitofrontal cortex is thus a region which is involved in taste, olfactory, and flavor information processing in primates. Moreover, we have demonstrated using functional magnetic resonance imaging that there are corresponding taste and olfactory regions in the human orbitofrontal cortex.[25]

An important food taste which appears to be different from that produced by sweet, salt, bitter or sour is the taste of protein. At least part of this taste is captured by the Japanese word 'umami,' which is a taste common to a diversity of food sources including fish, meats, mushrooms, cheese and some vegetables including tomatoes. Within these food sources, it is the synergistic combination of glutamates and 5′-nucleotides that creates the umami taste.[7,27,28] Monosodium L-glutamate (MSG), guanosine 5′-monophosphate (GMP) and inosine 5′-monophosphate (IMP) are examples of umami stimuli.

Umami does not act by enhancing the tastes of sweetness, saltiness, bitterness or sourness in foods, but instead may be a flavor in its own right, at least in humans. For example, Yamaguchi[27] found that the presence of MSG or IMP did not lower the thresholds for the prototypical tastes (produced by sucrose, NaCl, quinine sulphate and tartaric acid), suggesting that umami did not improve the detection sensitivity for the four basic taste qualities. Also, the detection thresholds for MSG were not lowered in the presence of the prototypical taste stimuli. This suggests that the receptor sites for umami substances are different from those for other prototypical stimuli.[28] (A synergistic effect was found when IMP was added to MSG in that the detection threshold for MSG was dramatically lowered.) Yamaguchi and Kimizuka[28] tested the 'singularity' of umami by presenting human subjects with 21 taste stimuli including single and mixture solutions of MSG and sucrose, NaCl, tartaric acid and quinine sulphate. The subjects sorted the stimuli based on taste quality similarity. These scores were placed into a similarity matrix and analyzed using multidimensional scaling procedures. The results revealed that, within a three-dimensional tetrahedron, the four prototypical stimuli were located at the vertices of a tetrahedron. The mixtures containing 2, 3 or 4 prototypical stimuli were located on the edges or surfaces of the tetrahedron. However, MSG was located outside of the tetrahedron, implying that the taste of umami is qualitatively different from the four prototypical stimuli used. In spite of this perceptual distinctiveness, traditional taste-quality descriptors are frequently used in describing the quality evoked by monosodium glutamate, particularly saltiness.[10,30]

NEURONS RESPONSIVE TO THE TASTE OF MONOSODIUM GLUTAMATE

These findings raise the question of whether umami taste operates through information channels in the primate taste system which are separable from those for the 'prototypical' tastes sweet, salt, bitter, and sour. To investigate the neural encoding of glutamate in the primate, Baylis and Rolls[2] made recordings from 190 taste responsive neurons in the primary taste cortex and adjoining orbitofrontal cortex taste area in alert macaques. Single neurons were found that were tuned to respond best to monosodium glutamate (umami taste), just as other cells were found with best responses to glucose (sweet), sodium chloride (salty), HCl (sour), and quinine HCl (bitter). Examples of single neurons tuned to glutamate taste are shown in FIGURE 1.

Across the population of neurons recorded by Rolls and Baylis,[20] the responsiveness

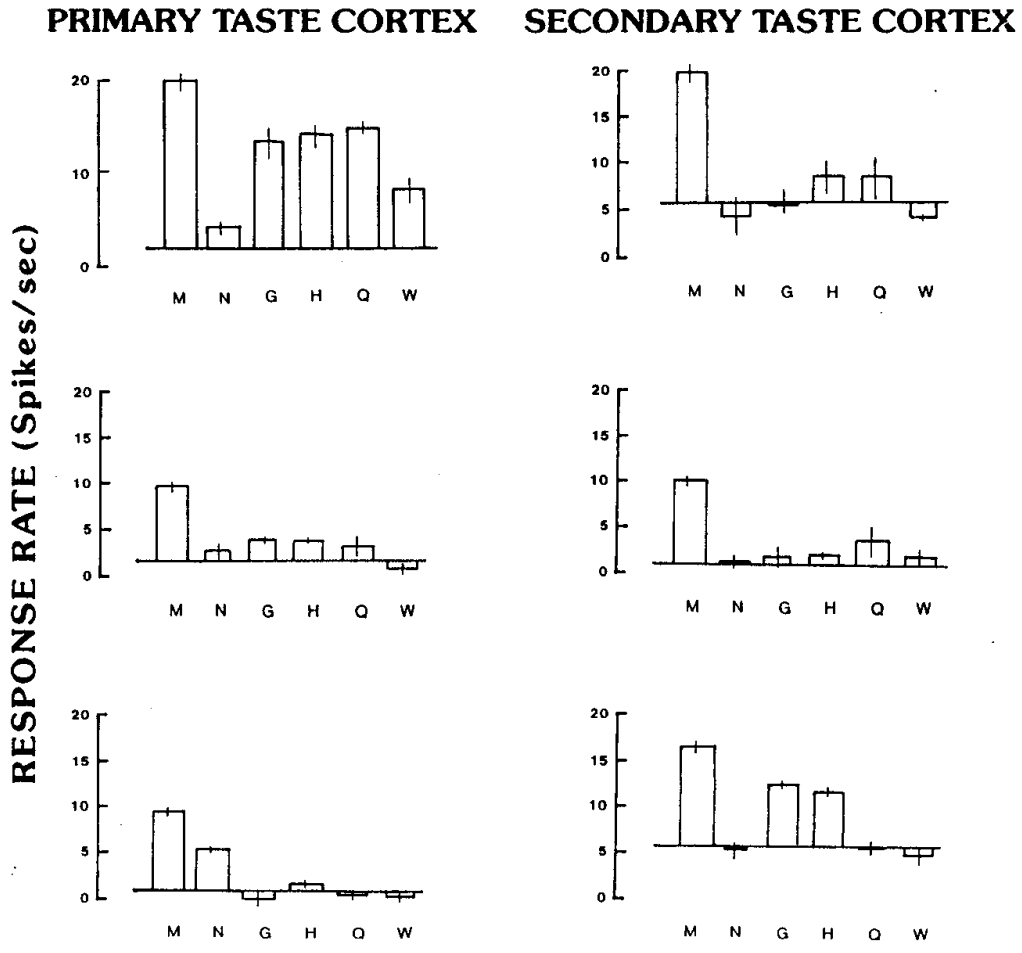

FIGURE 1. MSG—best cells: examples of the responses of three cells in the primary taste cortex, and of three cells in the secondary taste cortex, to monosodium glutamate and other taste stimuli. The firing rate is shown in spikes/sec, relative to the spontaneous baseline firing rate. The means and the standard errors of the responses calculated over 4–6 presentations of each tastant in random sequence are shown. The set of tastants was 1.0 M glucose (G), 0.1 M NaCl (N), 0.01 M HCl (H), 0.001 M QHCl (Q), distilled water (W), and 0.1 M monosodium glutamate (M).

to glutamate was poorly correlated with the responsiveness to NaCl, so that the representation of glutamate was clearly different from that of NaCl. Further, the representation of glutamate was shown to be approximately as different from each of the other four tastants as they are from each other, as shown by multidimensional scaling and cluster analysis. Moreover, it was found that glutamate is approximately as well represented in terms of mean evoked neural activity and the number of cells with best responses to it as the other four stimuli: glucose, NaCl, HCl and quinine. Baylis and Rolls[2] concluded that in primate taste cortical areas, glutamate, which produces umami taste in humans, is approximately as well represented as are the tastes produced by: glucose (sweet), NaCl (salty), HCl (sour) and quinine HCl (bitter).[2]

GLUTAMIC ACID

These studies indicated that a separate mechanism from that for other tastes operates for the neurophysiological processing and for the perception of umami. However, it is still an interesting issue about the role played by the sodium cation in the MSG molecule, and the degree to which this contributes to umami taste quality has not been completely clarified. We therefore performed a neurophysiological investigation in which glutamic acid was used, and its effects on a population of neurons in the orbitofrontal cortex was compared to that of the prototypical tastants as well as monosodium glutamate.[21] It was possible to complete the testing for 70 taste-responsive cells. (The population of neurons analyzed for taste responsiveness included more than 1000 cells. Of the 70 cells analyzed in this experiment, the great majority, 63, were in the orbitofrontal cortex, and the remaining cells were in nearby regions.) Examples of the response profiles of the cells to the set of tastants are shown for 3 cells in FIGURE 2. This shows that some of the cells had large responses to 0.05 M glutamic acid. It also shows that some of the cells that responded to glutamic acid also responded to monosodium glutamate, and did not necessarily have large responses to 0.01 M HCl. (The pH of the glutamic acid was 2.1).

To test how similarly the whole population of 70 cells respond to the two umami tastants monosodium glutamate and glutamic acid compared to other stimuli, the corre-

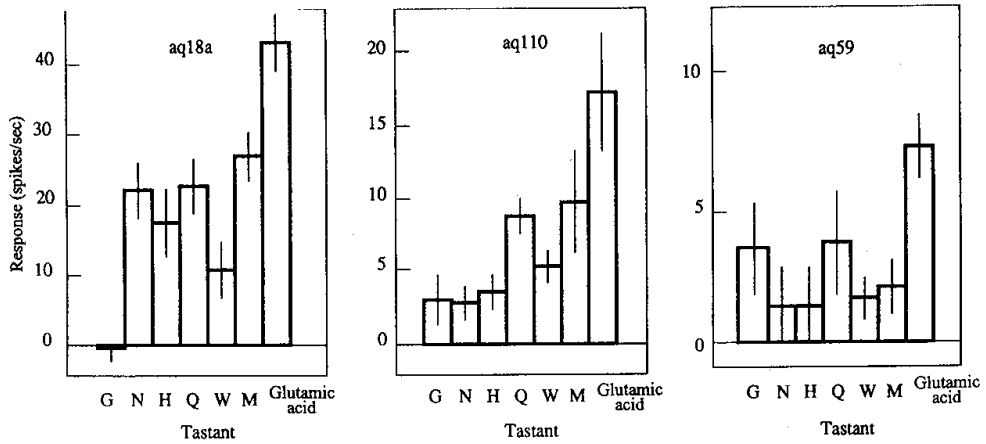

FIGURE 2. Examples for three cells of the response profiles of cells in the taste cortex which responded best to glutamic acid. Conventions and stimuli as in FIGURE 1. The glutamic acid was 0.05 M.

lations of the responses of all 70 cells to each pair of stimuli out of monosodium glutamate (M), glutamic acid (GLA), glucose (G), sodium chloride (N), acid (H) and Quinine (Q) were computed. The Pearson correlation coefficients are shown in TABLE 1. These correlations were based on the response of the 70 neurons to these tastants, that is, they were calculated with the spontaneous firing rate subtracted. It can be seen from TABLE 1 that the correlation between the responses of this population of neurons to M and GLA was 0.75, and that this similarity was greater than most other correlations between stimuli shown in TABLE 1, and was higher than the correlation of glutamic acid with any other stimulus. (The other somewhat high correlation of glutamic acid with another tastant was 0.71 with HCl, which is consistent with the fact that both are acidic, and that some neurons in the population reflect the acidity of tastants.)

In summary, glutamic acid produced responses in this population of neurons that were more similar to those produced by monosodium glutamate than to those produced by any other tastant. This strengthens the evidence that umami taste is represented in the primate brain separately from the representations of the other tastants.

INOSINE MONOPHOSPHATE

Although inosine 5′-monophosphate in the mouth can produce umami taste in humans, and can synergize with monosodium glutamate, its neurophysiological effects in primates have only recently been investigated.[21]

The set of tastants 1.0 M glucose (G), 0.1 M NaCl (N), 0.01 M HCl (H), 0.001 M QHCl (Q), 0.1 M monosodium glutamate (M), and 0.0001 M inosine 5′-monophosphate (IMP) was tested in random sequence, as described above. This is a low concentration of IMP, but was chosen as it was found in our preliminary studies to be effective in producing neuronal responses in macaques. This concentration is just below the human detection threshold for IMP alone,[27] but is a concentration which appears to be able to affect the human taste system, in that in humans this is in the concentration range that has a synergistic effect with monosodium glutamate.

It was possible to complete the testing for 18 cells.[21] Examples of the response profiles of the cells to the set of tastants are shown for 3 cells in FIGURE 3. This shows that some of the cells had responses to 0.0001 M inosine 5′-monophosphate. It also shows that some of the cells that responded to IMP also responded to monosodium glutamate.

TABLE 1. Correlation Coefficients between the Profiles of Responses Generated by Each Stimulus across the Population of 70 Cells

	G	N	H	Q	W	M	GLA
G	—						
N	0.43	—					
H	0.46	0.70	—				
Q	0.35	0.61	0.66	—			
W	0.47	0.72	0.79	0.66	—		
M	0.60	0.69	0.73	0.57	0.65	—	
GLA	0.34	0.62	0.71	0.61	0.62	0.75	—

Abbreviations: G, glucose; N, NaCl; H, HCl; Q, QHCl; W, distilled water; M, monosodium glutamate; GLA, glutamic acid.

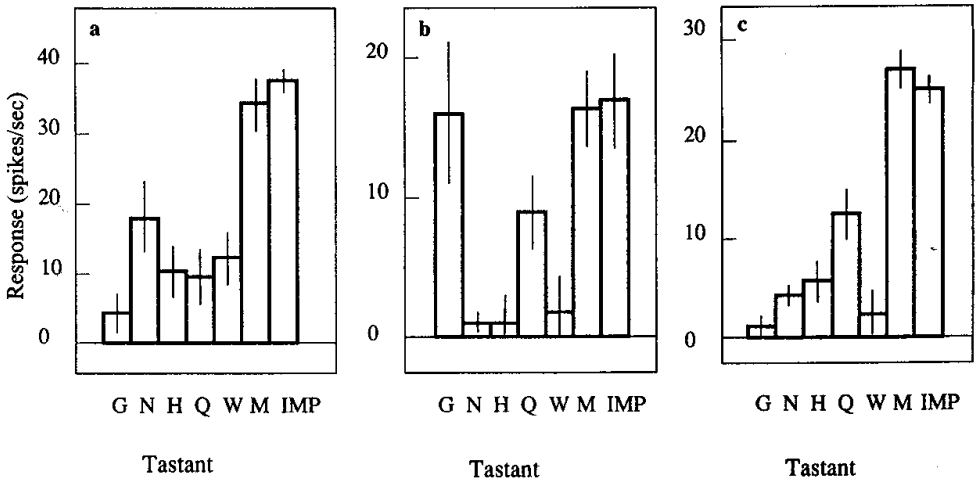

FIGURE 3. Examples for three cells of the response profiles of cells in the taste cortex which responded to inosine 5′-monophosphate (IMP, 0.0001 M). The mean and the standard errors of the responses calculated over 4–6 presentations of each tastant in random sequence are shown. The set of tastants was 1.0 M glucose (G), 0.1 M NaCl (N), 0.01 M HCl (H), 0.001 M QHCl (Q), distilled water (W), 0.1 M monosodium glutamate (M).

Across this set of 18 cells, the correlations between IMP and the other stimuli calculated from the response profiles are shown in TABLE 2. This shows that across the population of cells, IMP produced responses that were much more similar to M than to any of the other tastants (Pearson correlation coefficient of 0.80).

These findings[21] provided further evidence that the representation of umami taste is separate from that of other tastants, in that inosine 5′-monophosphate and monosodium glutamate produced similar activations of the orbitofrontal cortex taste neurons. Inosine 5′-monophosphate and monosodium glutamate may potentiate each other in humans. Neurophysiologically in the macaque we did not find synergism, but this may be related to the fact that even very low concentrations of IMP (0.0001 M) produced quite large neuronal responses in macaques. Macaques are in any case also quite sensitive to the taste of monosodium glutamate, with neurophysiological effects apparent with concentrations as low as 0.001 M.[21]

SATIETY

It has been shown that feeding to satiety decreases the responses of orbitofrontal taste cortex neurons to a food with which a monkey has been fed to satiety.[18] Such a

TABLE 2. Correlation Coefficients between the Profiles of Activity of 18 Cells Generated between Inosine 5′-Monophosphate and Each of the Other Stimuli

	G	N	H	Q	M	W
IMP	0.15	0.55	0.32	0.44	0.80	0.37

Abbreviations: IMP, inosine 5′-monophosphate; G, glucose; N, NaCl; H, HCl; Q, QHCl; M, monosodium glutamate; W, distilled water.

modulation of taste responses by hunger has not been found in the primary taste cortex.[17,29] Moreover, the reduction in neuronal responsiveness in the secondary taste cortex is at least partly specific to the food with which the monkey has been fed to satiety. This is thus a sensory-specific reduction in responsiveness.[18] We investigated whether satiety induced by feeding with monosodium glutamate solution would affect the responses of orbitofrontal cortex cells, and if so, whether the response would be sensory-specific. A modulation of responsiveness by hunger would implicate the neurons in a system involved in motivational responses to food. A demonstration of sensory-specific satiety would add further evidence for a separate neural mechanism for the perception of umami taste.

Cells which responded to the taste of monosodium glutamate, or which responded to the sight of food (see Refs. 26, 20), were tested before, during, and after feeding a monkey with 0.1 M monosodium glutamate until behavioral satiety was achieved. Satiety was induced by feeding the monkey 0.1 M monosodium glutamate rapidly while recording the behavioral acceptance as a function of volume consumed. The response of cells were measured at varying stages in the delivery of the satiating solution, and after the monkey was satiated.

It was possible to perform experiments studying the effect of satiety on taste responses to glutamate on 5 neurons.[21] The responses of one of these neurons during feeding to satiety are shown in FIGURE 4. The response to the taste of glutamate decreased from a value of 19.5 spikes/sec when the monkey was hungry to a value of 9.1 spikes/sec when the monkey was satiated. A similar reduction was not found for the other tastants, and indeed the response to the taste of glucose increased (see FIG. 4). There was a significant interaction between the responses to the different tastants and feeding to satiety (2-way analysis of variance (ANOVA), $p < 0.01$, $F(1,46) = 9.8$). In 2 of the other 4 taste neurons also tested in this way, there was a generalized decrease in the response to monosodium glutamate and to the other tastants. A larger volume of satiating fluid was used in both cases (125 ml and 200 ml), and this may account for the non sensory-specific modulation of responsiveness in these cells.

Satiety experiments using monosodium glutamate were also performed on three cells responsive to the sight of food. The response to the sight of an MSG-containing syringe was decreased after satiety in two of the three food responsive visual neurons. In one case this was a sensory-specific effect, where the response to the MSG-containing syringe was significantly decreased ($p < 0.02$) (to the level of the spontaneous activity) during behavioral satiation, whereas the cell remained unchanged in its responses to foods such as banana, or a blackcurrant juice–containing syringe.[21]

UMAMI FLAVOR PRODUCED BY A COMBINATION OF TASTE AND OLFACTORY INPUTS

It has been shown that taste and olfactory inputs converge onto single neurons in the primate orbitofrontal cortex.[20] It is probably this convergence that produces flavor, which can be defined as the sensation produced by a combination of taste and olfactory stimuli. It is suggested here that this convergence may underlie at least partly how the taste of monosodium glutamate or inosine 5′-monophosphate can produce the flavor of umami. In particular, the hypothesis suggested is that umami flavor can be produced especially when monosodium glutamate or IMP facilitate the effect produced by an appropriate olfactory input.

The fact that the taste of glutamate and the smell of a savory food can activate the same orbitofrontal cortex neuron is documented in FIGURE 5. This neuron responded well to both the taste of 0.1 M monosodium glutamate (M) and to the odor of salmon

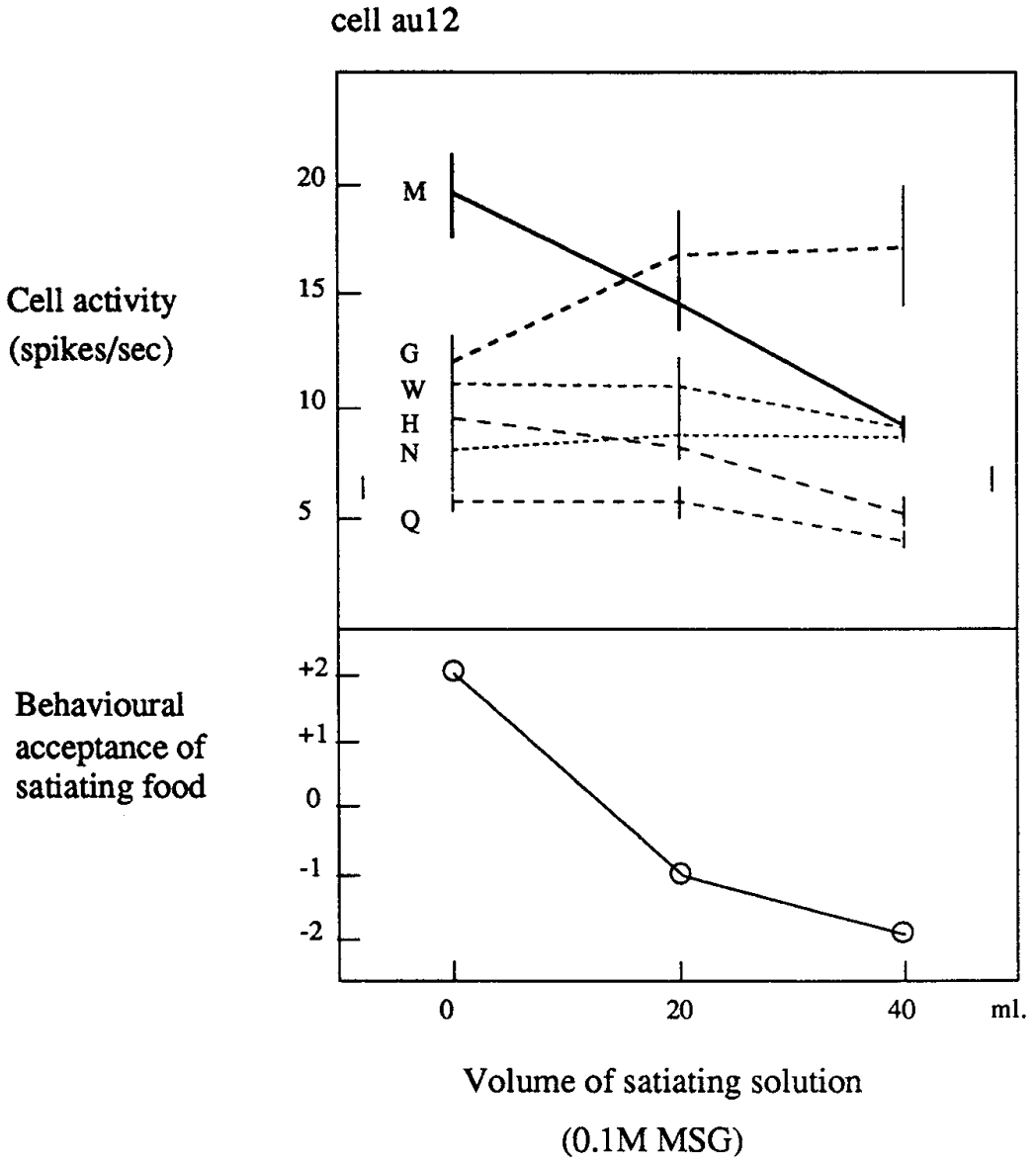

FIGURE 4. The effect of satiation induced with 0.1M monosodium glutamate on the response of a cell to the tastes of 1.0 M glucose (G), 0.1 M NaCl (N), 0.01 M HCl (H), 0.001 M QHCl (Q), distilled water (W) and 0.1 M monosodium glutamate (M). The behavioral acceptance of the satiating fluid is illustrated below the neuronal response. The scale runs from keen avid acceptance (+2), through neutral (0), to firm rejection (−2).

or onion.[20] This type of convergence was found in a number of cases onto different orbitofrontal cortex neurons.[20,5] Such corresponding olfactory and taste responses are likely to be built in the brain by at least in part olfactory to taste association learning, as demonstrated by Rolls *et al.*[22]

To investigate how taste and olfactory stimuli related to umami flavor combine, we (Rolls, Hernadi and Browning) performed a psychophysical experiment in humans. The subjects rated the intensity of the flavor of umami using a visual analog rating

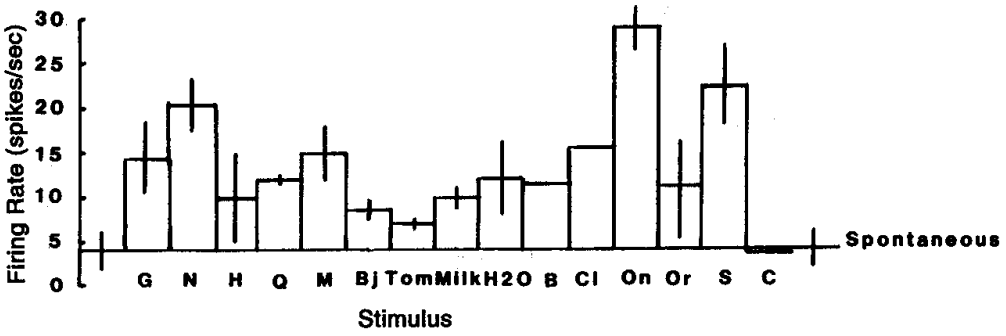

FIGURE 5. The responses of a bimodal neuron (cell 084.1) recorded in the caudolateral orbitofrontal cortex. G, 1 M glucose; N, 0.1 M NaCl; H, 0.01 M HCl; Q, 0.001 M QHCl; M, 0.1 M monosodium glutamate; Bj, 20% blackcurrant juice; Tom, tomato juice; B, banana odor; Cl, clove oil odor; On, onion odor; Or, orange odor; S, salmon odor; C, control no-odor presentation. The mean responses ± SE are shown. The neuron responded best to the tastes of NaCl and monosodium glutamate and to the odors of onion and salmon.

scale. This was a 100-mm line marked at one end very weak and at the other end very intense (see, *e.g.,* Rolls and Rolls[24]). The values obtained from a rating were thus in the range 0–100, obtained by measurement of the distance along the line marked by the subject as representing the intensity of the umami flavor. The taste part of the stimuli were monosodium glutamate in concentrations of 0.005 M, 0.01 M and 0.05 M, as well as distilled water. To each of these solutions was added 0, 1, 5 or 10 ppm (μl/l) of methyl furyl disulfide ($C_{10}H_{10}S_2$), which has the odor of garlic/meaty/savory and which dissolved in the solution. On each trial, the subject was given in random sequence and with no knowledge of which sample was selected for that trial one of the 16 samples to rate for the intensity of umami flavor. The subject placed 0.5 ml of the sample in the mouth, and rated the intensity while the substance was in the mouth. After the rating, the sample was expectorated into a sink, and the mouth was rinsed with 15 ml of water, which was also expectorated. There was then a waiting time to produce a constant intersample interval of 45 sec. After a practice session, new sequences were repeated until the subject had provided 3 ratings of each sample.

The results of this experiment on four experienced subjects are shown in FIGURE 6. For clarity, the results with no odor and with 10 ppm methyl furyl disulfide are shown on the graph. It can be seen that there is an approximately additive effect of the 10 ppm methyl furyl disulfide odor and the monosodium glutamate in producing the flavor of umami. A two-way ANOVA showed highly significant effects of both MSG ($F_{3,176}$ = 119, p <<0.001) and methyl furyl disulfide ($F_{3,176}$ = 11.3, p <0.001), and no significant interaction term (p = 0.3).

The findings of this psychophysical experiment suggest that one way in which monosodium glutamate and the 5′-nucleotide tastants work is in combination with appropriate, savory, odorants, to produce a full umami flavor.

DISCUSSION

The neurophysiological experiments reviewed here provide evidence that there is a neural system involved in representing protein (or umami) taste, by showing that the representation of monosodium glutamate is different to that of other prototypical tas-

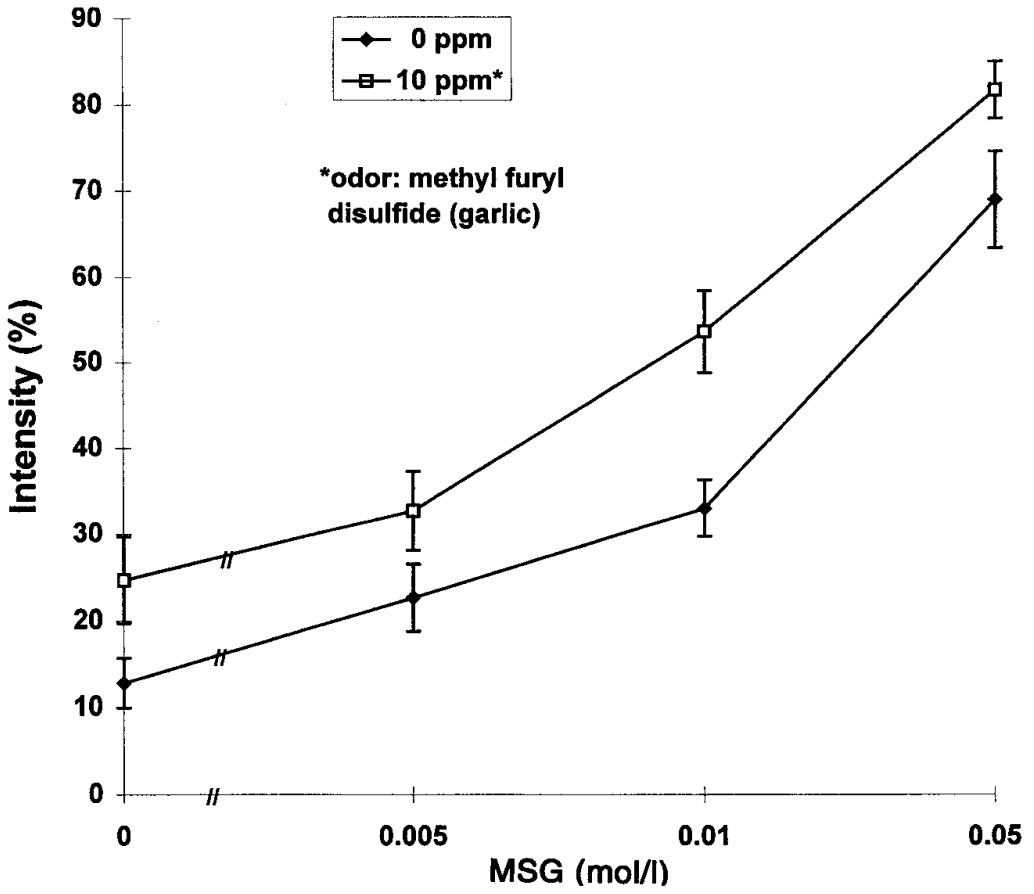

FIGURE 6. The intensity of the flavor of umami produced by combinations of the tastant monosodium glutamate in concentrations of 0.005 M, 0.01 M and 0.05 M, and 0 or 10 ppm of methyl furyl disulfuride, which has the odor of garlic and which was dissolved in the solution. The ratings were made by four experienced human subjects. The means ± SEM of the ratings made using a 100-mm visual analog rating scale are shown.

tants sweet, salt, bitter and sour; and by showing that the neurons in this system respond not only to monosodium glutamate, but also to other umami taste stimuli such as glutamic acid and inosine 5′-monophosphate. In other investigations, gustatory responses of single neurons selective to monosodium glutamate have also been reported from the primary taste cortex and lateral hypothalamic areas of macaques.[12,11] Given the role of the orbitofrontal cortex in food selection and the control of motivational behavior to food,[1,18,13,15] the independent encoding of motivationally and ethologically significant foods such as the taste of umami becomes more important than earlier in the taste system (cf. Ref. 12). The clear separation of the representation of umami from other tastants in the secondary orbitofrontal cortex would enable processes such as sensory-specific satiety to remain specific to individual foods, thereby allowing a finer control of nutrient intake.

The results of the psychophysical experiment described here suggest that part of the way in which monosodium glutamate is effective is that it in combination with appropriate odorants produces a full umami flavor.

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