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Responses of Neurons in the Primate Taste Cortex to Glutamate

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BAYLIS, L. L. AND E. T. ROLLS. *Responses of neurons in the primate taste cortex to glutamate*. PHYSIOL BEHAV **49**(5) 973–979, 1991.—In order to investigate the neural encoding of glutamate in the primate, recordings were made from 190 taste responsive neurons in the primary taste cortex and adjoining orbitofrontal cortex taste area in macaques. Single neurons were found that were tuned to respond best to glutamate (umami taste), just as other cells were found with best responses to glucose (sweet), sodium chloride (salty), HCl (sour), and quinine HCl (bitter). Across the population of neurons, the responsiveness 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. It is 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 (sour).

Taste cortex Orbitofrontal cortex Insular cortex Glutamate Umami Primate

JAPANESE cooks have long used sea tangles to enhance the flavor of foods. However, it was not until 1908 that Ikeda discovered that it was the glutamate in sea tangles that was responsible for the flavor enhancing effect (3). Umami, meaning "deliciousness" in Japanese, was the name that Ikeda gave the distinctive flavor arising from the glutamate salts.

Umami is a taste common to a diversity of food sources including fish, meats, mushrooms, cheese and some vegetables. Within these food sources, it is the synergistic combination of glutamates and 5′-nucleotides that creates the umami taste (19,20). Monosodium L-glutamate (MSG), guanosine 5′-monophosphate (GMP) and inosine 5′-monophosphate (IMP) are examples of umami stimuli and are now widely available as food additives.

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 (20) 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 (20). (A synergistic effect was found when IMP was added to MSG in that the detection threshold for MSG was dramatically lowered.) Further, Yamaguchi and Kimizuka (20) 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 analysed 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.

These findings raise the question of whether umami taste operates through channels in the primate taste system which are separable from those for the "prototypical" tastes sweet, salt, bitter, and sour. [Although the concept of four prototypical tastes has been used by tradition, there is increasing discussion about the utility of the concept, and increasing evidence that the taste system is more diverse than this: (4)]. To investigate the coding of information about umami taste in the primate nervous system, the experiments described here were performed with neurons recorded in the taste cortex of monkeys. The umami stimulus used was MSG. We attempted to answer the following questions. 1) Do cells respond preferentially to umami? Particular attention was paid to whether cells responded differently to MSG and sodium

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chloride, as sodium ions are present in both. 2) Are umami cells as common as cells that respond best to other (known) prototypical stimuli? 3) Do cells, on average, respond as vigorously to umami as to prototypical stimuli? 4) Is umami as different from prototypical stimuli as prototypical stimuli are from each other? If MSG *shares the properties* of the other prototypical stimuli in all these experiments, this is strong evidence that MSG *is* a fifth prototypical taste stimulus in primates.

We know of no previous neurophysiological investigations of umami encoding in the primate central nervous system. Although some neurophysiological investigations on umami have been performed in nonprimates (e.g., mice and rats), in at least some studies no clear evidence for processing of MSG differently from NaCl has been found (21), and in any case there is evidence that some nonprimate species do not respond behaviorally to umami in the same way as humans (4).

Another reason for performing these experiments with primates is that the primate taste system may be organised even anatomically differently to the taste system of nonprimates (7,10). In primates, the three taste nerves terminate in the rostral part of the nucleus of the solitary tract, which projects monosynaptically to the thalamic taste nucleus, the parvicellular division of the ventralposteromedial thalamic nucleus (VPMpc) (7). A remarkable difference from the taste system of rodents is this direct projection from the NTS to the taste thalamus. In rodents, there is an obligatory relay from the NTS to the pontine parabrachial taste nuclei (the "pontine taste area"), which in turn projects to the thalamus (7). The pontine taste nuclei also project to the hypothalamus and amygdala in rodents (6), providing direct subcortical access to these subcortical structures important in motivational behavior (e.g., feeding) and learning (9). In contrast, in primates there may well be no such direct pathway from the brainstem taste areas to the hypothalamus and amygdala (7). The thalamic taste area, VPMpc, then projects to the cortex which in primates forms the rostral part of the frontal operculum and adjoining insula, so that this is by definition the primary taste cortex (8). The responses of neurons in these primary cortical in monkeys have been analysed by Scott, Yaxley, Sienkiewicz and Rolls (14) and by Yaxley, Rolls and Sienkiewicz (22). A secondary cortical taste area has recently been discovered by Rolls, Yaxley and Sienkiewicz (13) in the caudolateral orbitofrontal cortex, extending several mm in front of the primary taste cortex. This region has been shown to receive projections from the primary taste cortex (18). Taste cells are also found more medial to this in the orbitofrontal cortex [(17), Baylis and Rolls, in preparation]. In the study described here, the responses of neurons to glutamate were analyzed in the primary taste cortical areas in the frontal operculum and insula, and more anteriorly in the orbitofrontal cortex, in the area known to be secondary taste cortex (13), and also more medial to this. The overall aim of the investigation was to advance our understanding of the mechanisms which underly the control of food intake and its disorders (9).

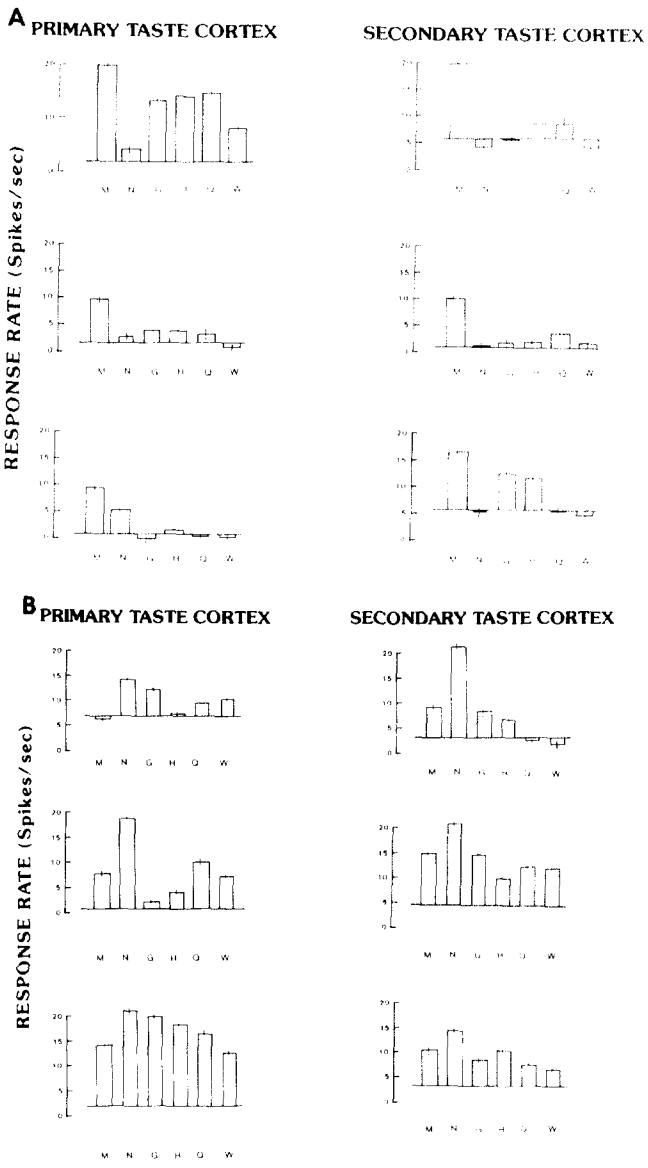

FIG. 1. (A) MSG-best cells. Response profiles of cells in the primary and secondary (orbitofrontal) taste cortex which respond best to glutamate (M). The means and the standard errors of the responses calculated over 4–6 presentations of each tastant in random sequence are shown. (B) NaCl-best cells. Response profiles of cells in the primary and secondary (orbitofrontal) taste cortex which respond best to sodium chloride (N).

METHOD

The methods were the same as those described in detail elsewhere (11, 13, 14, 15, 22), and are described here only briefly or where they differ.

Recordings

Recordings were made from single neurons in the primary taste cortex in the frontal operculum (14) and rostral insula (22) and in the secondary taste cortex and adjoining region in the orbitofrontal cortex (13) of three behaving cynomolgus macaques (*Macaca fascicularis*) weighing between 3.0 and 4.2 kg during testing. Monkeys were fed upon their return to their home cages, and were given access to water ad lib. Glass-insulated tungsten microelectrodes were constructed in the manner of Merrill and Ainsworth (5), but without platinum plating. A computer (Microvax II: Digital Equipment Corporation) collected the spike arrival times and displayed summary statistics or a peristimulus time histogram and rastergram on line.

Localization of Recording Sites

X-radiographs were used to locate the position of the microelectrode after each recording track relative to permanent refer-

TABLE 1

CORRELATION COEFFICIENTS BETWEEN THE PROFILES OF ACTIVITY GENERATED BY EACH STIMULUS

	G	N	H	Q	M
G	—				
N	.29	—			
H	.49	.40	—		
Q	.48	.44	.71	—	
M	.49	.59	.60	.62	—

G—glucose; N—NaCl; H—HCl; Q—quinine HCl; M—monosodium glutamate.

ence electrodes and to the anterior sphenoidal process. Sphenoid was used as a reference due to its visibility on X-radiographs and because it is a bony landmark which has a relatively invariant position with respect to brain structures (1,2). The mean position of the tip of the sphenoid process is 11 mm dorsal and 20 mm anterior to ear-bar zero in this species. During the final recording tracks in each monkey, microlesions were made through the tip of the recording electrode to mark the location of typical units. These lesions allowed the positions of all cells which were known with respect to bony landmarks to be reconstructed in the 50-μ brain sections.

Stimulus Presentation

Broadly two forms of stimulus presentation were used—manual and automated. The manual methods allowed for the screening of a larger number of stimuli whereas the automated method allowed in depth analysis of the time course of neural responses. Due to the nature of the gustatory receptors, and the large size of the oral cavity, the automated method was not appropriate for gustatory testing.

Gustatory Stimuli

The gustatory stimuli used were 1.0 M glucose (G), 0.1 M NaCl (N), 0.01 M HCl (H), 0.001 M QHCl (Q) and 0.1 M monosodium glutamate (M). For additional comparisons, the neuronal responses were also tested to a range of foods including tomato juice, apple juice, milk, and 20% blackcurrant juice. The monkey's mouth was rinsed with distilled water during the intertrial interval (which lasted at least 30 seconds, or until neuronal activity returned to baseline levels) between taste stimuli. The stimuli were delivered in quantities of 0.5 ml with a hand-held 2-ml syringe. For chronic recording in monkeys, this manual method for stimulus delivery is used because it allows for repeated stimulation of a large receptive surface despite different mouth and tongue positions adopted by the monkeys (14).

Treatment of Results

Analyses of variance were performed on the responses of each cell to the different stimuli, measured in a 3-s period following the onset of stimulus delivery. The one-way ANOVA for each cell was performed over the entire range of taste and other stimuli and the spontaneous firing rate in order to determine whether a neuron responded differently to chemosensory stimulation compared to nonchemosensory activity. If a significant difference between the responses to the different stimuli was indicated ($p<0.05$ was the criterion, although for most cells described here p was $<<0.001$), then subsequent post hoc Newman-Keuls' analyses were performed in order to assess and compare the individual efficacies of the different stimuli. The multidimensional scaling and cluster analyses described later were performed with the statistical package Systat (Systat Inc., Evanston, IL).

RESULTS

The response to umami stimulation of the tongue using mono-

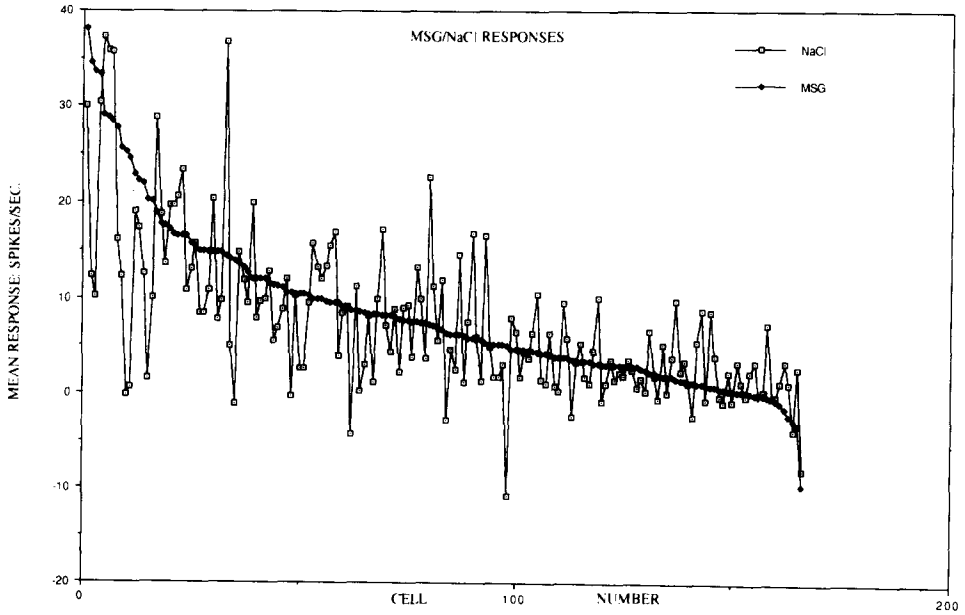

FIG. 2. Across-neuron response patterns for M (◆) and N ⊡. Each cell (indicated along the abscissa) is represented by two points, one showing its response to M, and the other its response to N. The neuronal responses are shown as changes (in spikes/s) from the spontaneous rate.

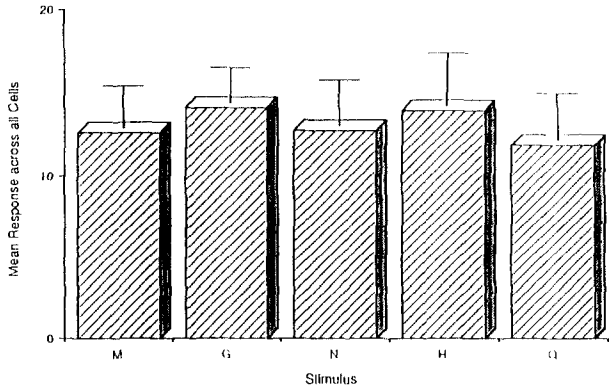

FIG. 3. The mean and standard deviation of the neuronal responses (in spikes/s) to umami (M) and the four other prototypical stimuli (G, N, H, Q) across the total of 190 gustatory cells tested.

sodium glutamate was recorded for a total of 190 neurons.

Examples of the response profiles of individual cells with best responses to M and to N in the primary taste cortex and in the orbitofrontal (secondary and related) taste areas are shown in Fig. 1. It can be seen that both cells responding best to M (Fig. 1A) and to N (Fig. 1B) show a spectrum of selectivity between stimuli, with some cells being highly selective (e.g., the top right profile in Fig. 1A, and the middle left profile in Fig. 1B) and others being very broadly responsive (upper left profile of Fig. 1A, and lower left of Fig. 1B). No qualitative difference in the response profiles of cells in primary and orbitofrontal cortex to umami was seen, and the analysis for these taste areas is combined for the rest of the results. (A further quantitative comparison is made below using a breadth of tuning index.) Nine M-best and 11 N-best cells were found in the "primary" cortex, i.e., in the insular-opercular area, and 15 M-best and 17 N-best in the orbitofrontal cortex. (The anatomical location of these cells is shown in more detail below.)

The data shown in Fig. 1A show that cells are present with best responses to M, and indicate that many of these cells responded better to M than to any other stimulus, including sodium. The data shown in Fig. 1B show that there are different cells tuned to respond better to N than to M. To provide further evidence on this indication of separate tuning within this popula-

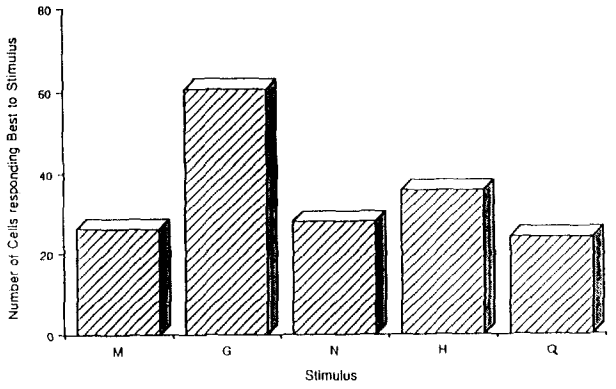

FIG. 4. The number of cells responding best to M and the four prototypical stimuli.

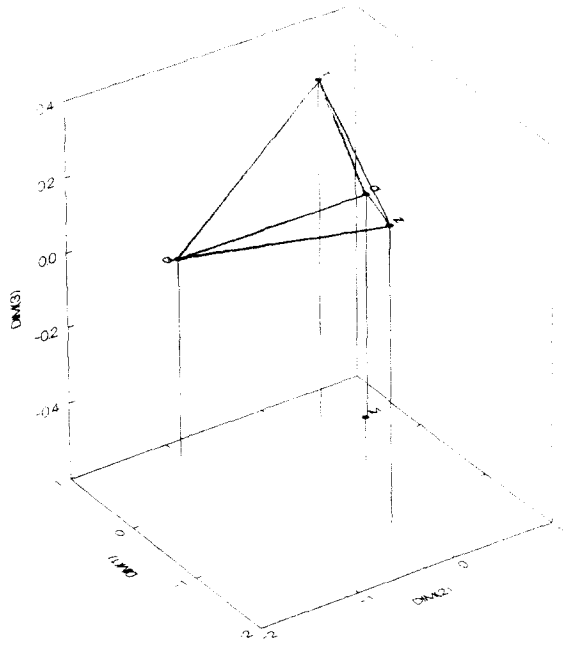

FIG. 5. A three-dimensional scaling of the matrix of correlations between the responses to umami (M) and the other four prototypical stimuli (G, N, H and Q). The tetrahedron formed by G, N, H and Q is indicated.

tion of cells to M and to N, an across neuron comparison of the sensitivity of these neurons to M and to N is shown in Fig. 2. The response rates to M and to N are shown for each cell recorded. It can be seen that across the population of neurons analysed, the responses to M and to N are not always correlated. Thus the

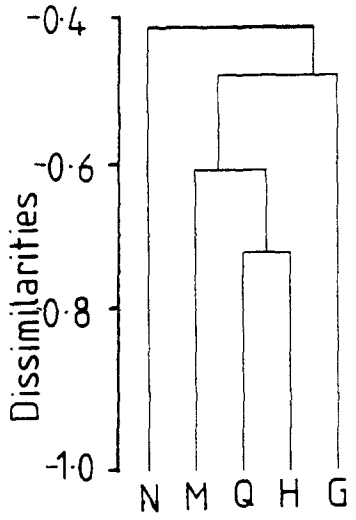

FIG. 6. A dendrogram showing the degree of clustering between the responses to umami (M) and the other prototypical stimuli. A dissimilarity of −1.0 indicates close similarity. This cluster analysis shows that M is not very similar to any of the prototypical stimuli, and indeed is more different from some of them than they (e.g., Q and H) are from each other.

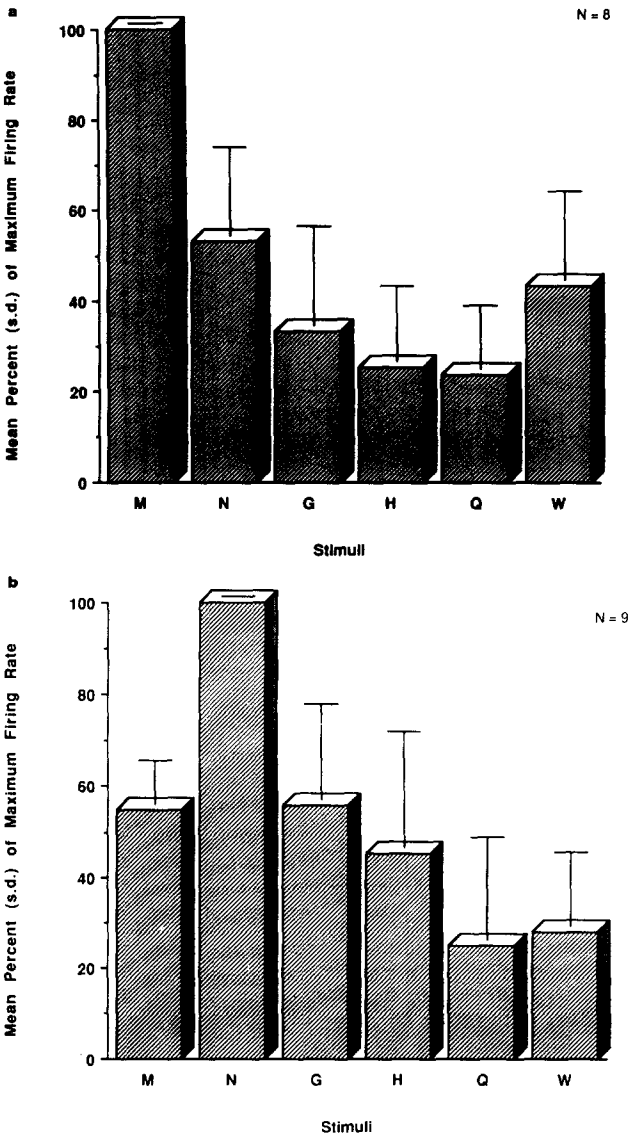

FIG. 7. The mean response profiles (expressed as a proportion of the maximal) across all cells responding best to (a) M (MSG-best) and (b) NaCl (NaCl-best).

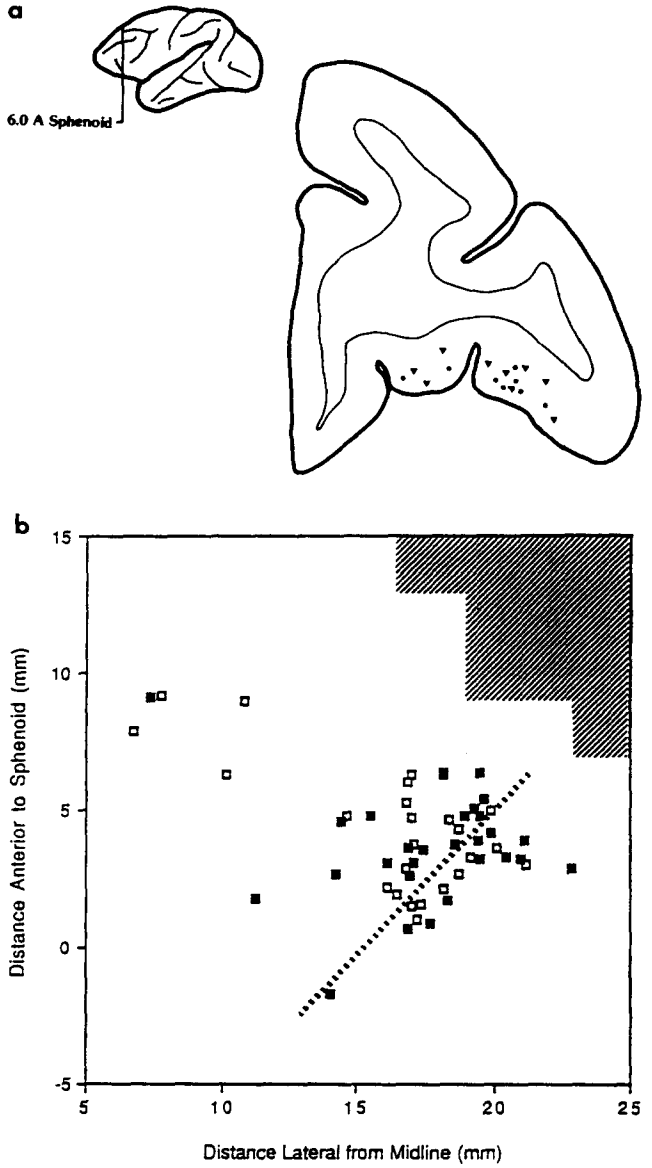

FIG. 8. (a) Examples of the recording sites in the orbitofrontal cortex taste area of neurons which responded best to glutamate (circles) and sodium chloride (triangles). The coronal section shown is 6 mm anterior to the sphenoid reference. (b) The location of cells that respond best to umami (open symbols) and sodium chloride (filled symbols) is shown in this plan view of the primate taste areas. The shaded area represents the edge of the cortex, and the broken line represents the anteromedial boundary of primary taste cortex. (That is, cells posterior and lateral to this line are in the primary taste cortex in the frontal operculum and rostral insula, whereas cells anterior and medial to this line are in the secondary and related taste areas in the orbitofrontal cortex.)

population of neurons has differential sensitivity to M and to N, with some neurons responding better to M, and others to N. Thus sensitivity to sodium ions cannot account for the responses of this population of cells to monosodium glutamate. The correlation coefficient across this population of M-best and N-best cells to M and N was .59.

The mean response to umami (M) and to the other four prototypical stimuli (G, N, H and Q) are shown in Fig. 3. It can be seen that the mean response across all 190 cells to each of the stimuli was approximately 15 spikes per second, and that in this respect responses to M resemble those to the other four prototypical stimuli.

For all cells, the optimal stimulus from amongst the four prototypical stimuli and M was determined. The number of cells responding best to umami and the other 4 prototypical stimuli are shown in Fig. 4. It can be seen from this figure that approximately 16% of cells respond best to all of the stimuli except for glucose. The number of cells for which G was the best stimulus was approximately twice that for all other stimuli, perhaps reflecting the high hedonic value of glucose. However, umami (M) was the optimal stimulus for approximately the same number of cells as H, N, and Q.

To test how similarly cells respond to umami compared to

other stimuli, the correlations of the responses of all cells to each pair of stimuli out of umami (M), 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 167 neurons to these tastants, that is they were calculated with the spontaneous firing rate subtracted. It can be seen from Table 1 that the responses of this population of neurons separates M from the prototypical stimuli (G, N, H and Q) almost as well as they separate the prototypical stimuli from each other. That is, the correlations between umami and other stimuli fall entirely within the range of correlations amongst the other stimuli. In particular, the correlations between the responses to M and the responses to G, N, H, and Q were in the range of approximately 0.5–0.6, in comparison to correlations between the responses to the prototypical stimuli which were in the range 0.3–0.7. The data in Table 1 also show that the response of the population of neurons to M does not correlate highly with the response to that of any of the other tastants, so that M does appear to be represented separately from the other tastants G, N, H and Q.

To present these data in a more readily interpretable form, multidimensional scaling (MDS) was performed on the correlation matrix computed for Table 1. The correlation matrix shows the similarity among stimuli by comparing the profiles of activity that each stimulus evokes across the 167 neuron sample (13). Such a multidimensional space represents the positions of stimuli relative to one another (13). The results of this are shown in Fig. 5. This figure shows the five stimuli spread well apart in a three-dimensional space, with M clearly outside a tetrahedron formed from the responses to G, N, H and Q.

The correlation matrix was also used as the basis for a cluster analysis of the responses of the neurons to the five stimuli, the results of which are shown in Fig. 6. This hierarchical clustering was produced using the average linkage method on the correlation coefficients. It can be seen from this figure that no stimuli cluster much more closely than any other, and in particular, that sodium chloride and M are not closely linked. This is a further way of showing that the responsiveness of this population of taste neurons is different for each of the five stimuli M, G, N, H and Q, and that the responses to M are as well separated from those to the other stimuli as they are from each other.

To provide further evidence on the relation between the processing of salt (N) and umami (M) the mean response profiles across the different stimuli of the cells which responded best to M and N were compared. It can be seen from Fig. 7 that with N-best cells the response to umami (M) is not significantly higher than the responses to other prototypical stimuli. Conversely, with M-best cells, the response to N is not significantly higher than that to other stimuli. This therefore provides converging evidence that umami and sodium chloride are indeed coded separately.

To investigate whether processing of M and N take place in the same areas of the cortex, the location of all cells responding best to sodium chloride and those responding best to umami were plotted in Fig. 8. The location of the putative boundary between primary and orbitofrontal taste cortex has been superimposed on this plot, with the primary cortex lying posterolaterally. It can be seen from this figure that cells responding best to these two stimuli are intermingled and approximately evenly distributed. In particular, there were 9 M-best and 11 N-best cells in the "primary" cortex, i.e., in the insular-opercular area, and 15 M-best and 17 N-best in the orbitofrontal cortex areas. The breadth of tuning metric developed by Smith and Travers (16) was used to compare the sharpness of tuning of the neurons in the primary and orbitofrontal cortex taste areas with best responses to M and N. The proportion of a neuron's total response that is devoted to each of the four basic stimuli can be used to calculate its coefficient of entropy (H). The measure of entropy is derived from information theory, and is calculated as:

$$H = -k\sum_{i=1}^{n} p_i \log p_i$$

where H = breadth of responsiveness, k = scaling constant (set so that H = 1.0 when the neuron responds equally well to all stimuli in the set of size n), p_i = the response to stimulus i expressed as a proportion of the total response to all the stimuli in the set. The coefficient ranges from 0.0, representing total specificity to one of the stimuli, to 1.0, which indicates an equal response to all of the stimuli. There was no difference in the breadth of tuning between cells responding best to M versus cells responding best to M, nor was there any difference between the two areas of cortex [for primary cortex: H(N) = 0.84, H(M) = 0.87; for orbitofrontal cortex: H(N) = 0.86, H(M) = 0.82].

DISCUSSION

This study was designed to investigate the encoding of glutamate (M) in the primate taste cortex, and whether there is a separate representation for glutamate from that for other stimuli such as G, N, H and Q. Many types of evidence were found that glutamate activates the taste cortex differently to the "prototypical" stimuli G, N, H and Q, and that glutamate acts like a prototypical stimulus.

First, glutamate acts on different cells to those activated by the other four stimuli. This is shown for example by the responses of individual cells with best responses to glutamate (Fig. 1A), and the responses of individual cells with best responses to N (Fig. 1B). The difference of cell responses to M and N (even though they have in common the sodium ion) is further made clear by the fact that across the whole population of cells tested, the correlation between the cells' responses to M and N was not high (see Fig. 2).

Second, the representation of glutamate is approximately as different from each of the other tastants as they are from each other, as shown by the between stimuli correlation matrix shown in Table 1, and the multidimensional stimulus space (Fig. 5) and the stimulus cluster analysis (Fig. 6) based on the correlation matrix.

The results shown in Figs. 3 and 4 show that M leads to a very similar mean level of response across cells as the other four stimuli, and that the number of cells responding best to umami is similar to the number responding best to N, H and Q (with rather more cells responding to G). That is, M 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 G, N, H and Q.

It was also found that cells that responded best to M were found in the primary and orbitofrontal taste cortical areas intermingled with cells with best responses to other stimuli (see Fig. 8), so that it is unlikely that the neuronal responses found to glutamate were the result of prior processing of other stimuli within the cortex.

The cortical representation of glutamate thus appears to be analogous to that for the stimuli G, N, H and Q, in that cells are specialised for M, the representation across cells of M is as different from that of G, N, H and Q as they are from each other, and there is no evidence in the cortex that the neuronal responses to M depend on prior processing of the other stimuli. This leads to the suggestion that M (umami) is approximately as well represented in the primate taste cortex as are G (sweet), N (salt), H (sour) and Q (bitter), so that on these criteria M could be considered prototypical to the same extent that G, N, H and Q are. It is

in fact possible that the space is much larger than can be spanned by 5 prototypical tastants, but at this stage there is evidence to conclude that the cortical representation of glutamate is as distinct and efficacious as is that of G, N, H and Q.

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