

The Responsiveness of Neurons in the Insular Gustatory Cortex of the Macaque Monkey is Independent of Hunger

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Received 19 August 1986

YAXLEY, S., E. T. ROLLS AND Z. J. SIENKIEWICZ. *The responsiveness of neurons in the insular gustatory cortex of the macaque monkey is independent of hunger.* *PHYSIOL BEHAV* 42(3) 223-229, 1988.—(1) In order to determine whether the responsiveness of neurons in the insular gustatory cortex is influenced by hunger, neuronal activity was analysed in it while macaque monkeys (*Macaca fascicularis*) were fed to satiety. The responses of single neurons in the insular gustatory cortex to the prototypical taste stimuli glucose, NaCl, HCl and quinine HCl, and to fruit juice, were measured before, while, and after the monkey was fed to satiety with glucose or fruit juice. (2) While behavior turned from avid acceptance to active rejection upon repletion, the responsiveness of the neurons to the stimulus array, including the satiating solution, was unmodified. (3) It is concluded that in the insular gustatory cortex, neuronal responses to gustatory stimuli are not influenced by the normal transition from hunger to satiety. This is in contrast to the responses of a population of neurons recorded in the hypothalamus, which only respond to the taste of food when the monkey is hungry. Thus the neurons in the insular gustatory cortex are involved in a motivation-independent analysis of gustatory stimuli, whereas the hypothalamic neurons may be more closely related to the influence of motivational state on behavioral responsiveness to gustatory stimuli.

Taste Hunger Satiety Gustatory cortex Primate Sensory-specific satiety

IN order to analyse the neural control of feeding, the activity of single neurons is being recorded during feeding in brain regions implicated in feeding in the monkey [22-34]. It has been found that a population of neurons in the lateral hypothalamus and adjoining substantia innominata of the monkey respond to the sight and/or taste of food [29]. Part of the evidence that these neurons are involved in the control of the responses which are made to food when hungry is that these neurons only respond to food when the monkey is hungry [6,36]. Indeed, Rolls has suggested that the principle whereby the sensory response to a motivationally relevant sensory stimulus such as the taste of food is modulated by the motivational state, for example hunger, is one important way in which motivational behavior is controlled [21,25].

Given that such modulation of sensory input by motivation is seen when recordings are made from hypothalamic neurons, it may be asked whether this is a special property of hypothalamic neurons which they show because they are specially involved in the control of motivational responses, or whether this type of modulation is a general property which is evident throughout sensory systems. In order to investigate the effect of motivational state on taste processing in the gustatory pathways, as well as how information is coded in the gustatory pathways of primates, we have analysed neuronal activity in the first central relay in the

gustatory system, the rostral part of the nucleus of the solitary tract [41]. The caudal half of this nucleus receives visceral afferents, and one possibility is that such visceral information, reflecting for example gastric distension, is used to modulate gustatory processing even at this early stage of the gustatory system. However, in recordings made in the nucleus of the solitary tract, we have found that neuronal responses to gustatory stimuli were not attenuated by feeding the monkey to satiety [44]. Thus, taste processing at this early stage of the gustatory system does not appear to be modulated by hunger.

Anatomical studies have shown that the next projection in the taste system in the primate is from the nucleus of the solitary tract directly to the thalamus, to the parvocellular part of the ventroposteromedial thalamic nucleus (VPMpc) [3,4]. This thalamic region then projects to the primary gustatory cortex, which, defined in this way, is in the monkey in the frontal operculum and in the adjoining rostral part of the insula [2, 5, 17, 40, 43]. One potential route for taste information to reach the basal forebrain and hypothalamus in the primate is via the projections from the rostral insula to the amygdala [1, 12-15], which in turn projects into the basal forebrain and hypothalamus [16,38]. Another potential route is from the frontal opercular taste cortex to the caudolateral orbitofrontal cortex (Wiggins, Baylis, Rolls and Yaxley, in

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preparation), which in turn projects to the hypothalamus and substantia innominata [16,38]. It is in the basal forebrain and hypothalamus that gustatory responses are known to be modulated by hunger [6,36].

In order to determine whether hunger influences processing in the gustatory system at one of the stages beyond the nucleus of the solitary tract, but before the hypothalamus, we decided to record the activity of single neurons in the insular gustatory cortex, and to determine whether feeding to satiety influenced their responsiveness to gustatory stimuli. To ensure that our results were relevant to the normal control of feeding (and were not due for example to abnormally high levels of artificially administered putative satiety signals), we allowed the monkeys to feed until they were satiated, and determined whether this normal and physiological induction of satiety influenced the responsiveness of neurons in the insular gustatory cortex, which were recorded throughout the feeding, until satiety was reached. First we performed a study, described elsewhere, in which we analysed the responses of neurons in the insular gustatory cortex of the monkey [45]. In the study described here, we determined whether hunger influenced the responsiveness of neurons recorded in the part of the rostral insula found to contain neurons with gustatory responses. The recordings were made in the monkey, to make the results as relevant as possible to understanding sensory processing and the control of feeding and its dysfunctions in the human.

METHOD

The methods used were similar to those described previously [6, 29, 31, 37, 39, 41, 42, 44], and are presented here as briefly as possible, except where they differ.

Recording

Two male cynomolgus monkeys, *Macaca fascicularis*, weighing 3.8–4.0 kg were implanted under thiopentone sodium anaesthesia with stainless-steel holders on which a Kopf adaptor could be fitted during recording sessions. After 1 or 2 weeks, daily recording sessions were initiated. Neuronal activity was recorded using glass-coated tungsten microelectrodes (after Merrill and Ainsworth [11]), while the monkey sat in a primate chair with head restraint to provide recording stability. The electrode was protected by a guide tube which ended just below the lignocaine-anaesthetised dura. The signal from the microelectrode was passed through a FET source follower amplifier mounted on the microdrive, amplified by conventional band-pass filtered amplifiers, and displayed on an oscilloscope. The monkey was fed, and given water ad lib, at the end of each daily recording session, so that he was approximately 18 hr food and water deprived during the recording sessions.

Analysis. Single neuron responses were acquired, analysed and displayed on-line by a PDP-11 computer. Mean discharge rates were computed during either control periods or stimulus presentation, with the analysis extending 5 sec from stimulus onset. The computer also calculated and displayed peristimulus time histograms in 50 msec bins.

Stimuli and Stimulus Delivery

Five stimuli plus water were applied to the tongue during a recording session. Four were prototypes of the four basic tastes, each at a concentration determined from intensity-response functions in these same subjects [41,42]. These were 1.0 M glucose, 1.0 M NaCl, 0.01 M HCl and 0.001 M

quinine HCl. The fifth stimulus was 20% blackcurrant juice (Ribena, Beecham Products, Brentford, U.K.). This was chosen as a stimulus which, because of its palatability and complexity of taste, would be readily accepted and which would activate many gustatory neurons.

Stimuli were delivered through a hand-held syringe in quantities of approximately 0.5 ml. Manual delivery was used to ensure replicable gustatory stimulation of a large and nearly constant receptive field throughout a recording session despite different mouth and tongue positions adopted by the monkeys as the palatability of the solutions varied with the stimulus quality and level of satiety.

Neurons in the insular gustatory complex responded differentially, but usually not uniquely, to the four prototypical taste stimuli, and did not respond to somatosensory stimulation (see [45]).

Requirements for Conducting a Satiety Experiment

Seven satiety experiments were performed at different sites within the primary gustatory cortex. Each was separated from the others by at least two days so as to permit the effects of repletion to dissipate. In order to initiate a satiety experiment, three conditions had to be satisfied.

(1) *Gustatory responsiveness to the satiating chemical.* The neuronal response elicited by application of the stimulus which would subsequently be used to satiate the monkey had to be robust. Since satiety was induced in most cases by glucose, most of the neurons studied in the satiety experiments responded well to sweet stimuli.

(2) *Recording stability.* After a neuron had been found in the insular gustatory cortex, the stability of the recording and of the evoked response were tested periodically over the next 30–60 min before a decision was made to begin the experiment.

(3) *Avidness for the satiating chemical.* A series of objective criteria for the avidness of acceptance has been developed [31,44]. A satiety experiment was not initiated unless a monkey's behavior warranted a rating of at least +1.0 on a scale of +2.0 (acceptance) to –2.0 (rejection) (see below). In practice, this required an efficient search for a neuron in the gustatory cortex and the achievement of a stable recording with a minimum of stimulus presentations, so that the monkey was still hungry when the experiment started.

Criteria for Acceptance or Rejection

Scores on the scale of acceptance or rejection were based on the following behavioral criteria:

+2.0: maximal acceptance; reaching for the solution with hands and mouth; avid licking.

+1.0: clear acceptance; opening the mouth, licking and swallowing the solution.

0.0: neutrality; swallowing the solution when placed in the mouth; absence of avidness; no attempt made to obtain the solution.

–1.0: clear rejection: pursing the lips to prevent administration of the solution; failure to swallow all of the solution placed in the mouth.

–2.0: maximum rejection: pursing the lips and closing the teeth; using the tongue to eject delivered solution; swallowing little; using the hands to push away the solution.

If the behavior was intermediate between these types, then intermediate scores were given.

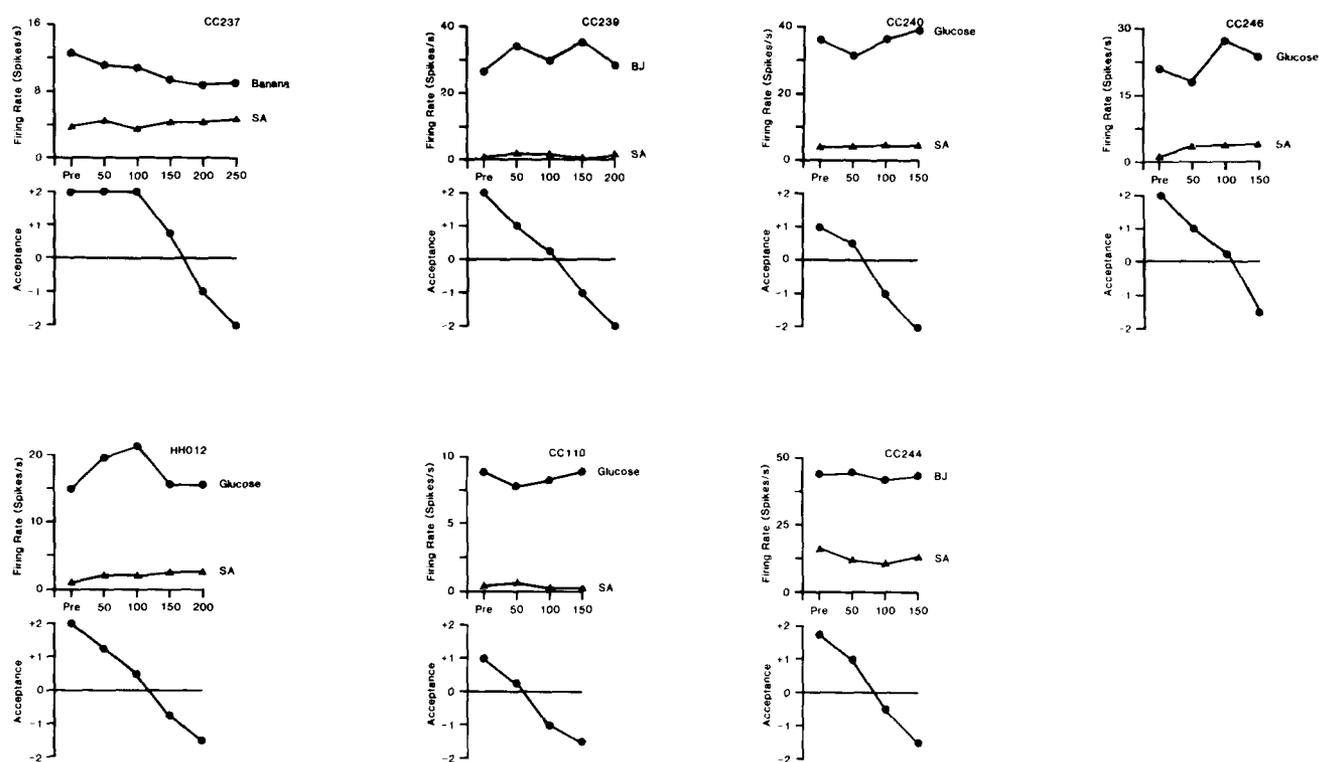


FIG. 1. Effects of feeding to satiety on the neural response (spikes/sec) to the solution on which the monkey was satiated, for the seven separate experimental runs. The spontaneous firing rate is also indicated (SA). Below the neural response data for each experiment, the behavioral measure of the acceptance or rejection of the solution on a scale from +2 to -2 (see text) is shown. The solution used to feed to satiety was 20% glucose, 20% blackcurrant juice (BJ), or mashed banana, as labelled. The monkey was fed 50 ml of the solution at each stage of the experiment as indicated along the abscissa, until he was satiated as shown by whether he accepted or rejected the solution. Pre—the firing rate of the neuron before the satiety experiment started. The standard error of the mean of the firing rate measurements was 1–2 spikes/sec, that is of the order of size of the symbols in the diagram, and so is not indicated separately.

Protocol

If the criteria for conducting a satiety experiment were satisfied, the following protocol was invoked.

(1) The gustatory neural response to each of the five sapid stimuli plus water was determined by application of 0.5 ml of each solution. Each application was followed by a 1.0 ml water rinse, and a minimum period of 30 sec of rest. The stimulus series was then repeated. The total testing time was approximately 12 min, and the volume consumed was a maximum of 16 ml.

(2) The monkey's acceptance-rejection score for the satiating solution was determined by observing his response as 0.5 ml was applied to the tongue.

(3) The monkey was fed a 50 ml aliquot of the satiating solution. In ten cases this was 20% w/v glucose. This was the primary agent for inducing satiety because, insofar as postabsorptive processes are involved, these will be expedited by glucose which needs not be metabolized before absorption. In one case 20% blackcurrant juice was used, so as to provide a wider range of information on satiety. All satiating solutions were delivered by a syringe. The duration of administration was approximately two minutes for the initial aliquot, and as much as four minutes for the last.

(4) The monkey's acceptance-rejection score to the satiating solution was reassessed.

(5) Steps 1 to 4 were repeated through as many cycles as were required to attain a behavioral score of -1.5 to -2.0.

This typically involved five 50 ml aliquots over a period of 60 min. Conventional satiety, defined by the stage at which the subject would stop working to obtain food, would normally correspond to a rating of 0.0 to -0.5. Thus, the feeding used in these experiments was sufficient to produce very complete satiety, to ensure that if there was a modulation of the neuronal responses by satiety, the degree of satiety induced in the experiments was sufficient for the effect to be manifested. Further evidence that normal satiety was induced in these experiments was the large quantity of glucose ingested by the monkeys. The quantity was at least 150 ml of 20% glucose solution (as shown in Fig. 1), i.e., at least 30 g of glucose for a 4 kg monkey. After satiety was reached, and feeding had stopped, multiple further measurements were taken of the neuronal responses to each of the sapid solutions and to water.

Analysis

The responses of single neurons were acquired, analysed and displayed on-line by a PDP-11 computer. Mean discharge rates were computed during either control periods or stimulus presentation, with the analysis extending 5 sec from stimulus onset. Neuronal activity, together with stimulus markers, was also recorded on magnetic tape for subsequent analysis, which included the calculation and display of peristimulus time histograms in 50 msec bins.

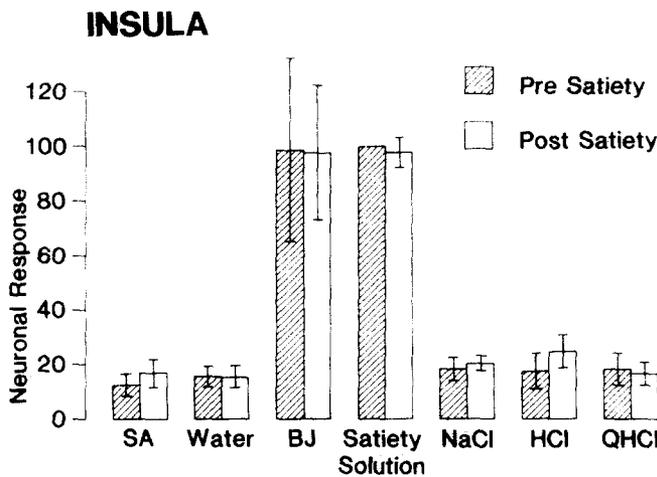


FIG. 2. The neuronal response before and after satiety to each of the gustatory stimuli, and to the solution on which the monkey was satiated. The results are expressed relative to the response before satiety obtained to the solution on which the monkey was satiated (set at 100%), and the data are averaged over the seven experimental runs shown in Fig. 1, with the mean and sem shown. The satiating solution was as shown in Fig. 1. SA—spontaneous activity.

Localisation of Recording Sites

The position of each recording site was determined in two ways. First, following each track, X-ray photographs were taken from frontal and lateral perspectives. Recording sites could then be reconstructed to within 250 μm by reference to deep electrodes permanently implanted at planes close to those of the recording track. The positions of the deep electrodes were subsequently determined histologically. Second, in the final several tracks, microlesions were made through the recording electrode (60 μA for 60 sec, electrode negative). After the final experiment, the tranquilization with ketamine was followed by deep anaesthesia using intravenous sodium pentobarbital. Perfusion was with 0.9 percent saline followed by formal-saline. The brains were placed in sucrose formalin for at least seven days after which 50 μm serial frozen sections were cut and stained with cresyl violet and by the Gallyas [8] method for myelin (for which 25 μm sections were used).

RESULTS

The effects of feeding the monkey to satiety with glucose on the responsiveness of neurons recorded in the insular gustatory cortex are shown in Fig. 1. Each part of the figure shows one experiment in which the effect of satiety on the responsiveness of a single insular gustatory neuron was measured. The responses to the satiating chemical and the spontaneous firing rate of the neuron, are shown at the different stages of each experiment. In four experiments the satiating chemical was glucose, in two it was blackcurrant juice, and in one it was mashed banana, as labelled. It is clear that in no case did satiety abolish, or even produce a major reduction, in the responsiveness of the neurons to the food. In some cases a small decline in the magnitude of the responses was seen, and in other cases the responses increased. In all cases these small changes in the neuronal response to the satiating food were not statistically significant (as shown by a *t*-test which compared the initial with the

post-satiety firing rate). (These *t*-tests were computed from the multiple measurements of the neuronal response to each of the stimuli made before and after satiety).

The results of feeding the monkey to satiety on the neural responses to each of the gustatory stimuli are shown in Fig. 2. The means and standard errors of the firing rates of the neurons before the satiety test was started, that is when the monkey was approximately 18 hr food deprived, and after the monkey had been fed to satiety, are indicated. The results are shown averaged over the seven experiments in order to provide a summary of the effect of satiety on processing in the insular gustatory cortex. It is clear that no consistent changes in the gustatory responses to either the gustatory stimulus with which satiety was produced, or to any other of the gustatory stimuli used, were produced by feeding to satiety. Averaged over the 7 experiments, the effect of satiety was to decrease the response to the food on which the monkey was satiated by 2.1%. This effect was not significant, as shown by a paired *t*-test which compared the response to the food before and after it was eaten to satiety, $t(6)=0.36$, ns. Thus, overall, there was very little effect of the satiety on the responsiveness of these gustatory neurons.

Another way in which the effect of satiating the monkey on the neuronal responsiveness was analysed was by comparing the response to the satiating solution (food) to the responses to 1.0 M NaCl, 0.01 M HCl and 0.001 M quinine HCl (non-foods), before and after satiety. If satiety decreased the response to the food stimulus, but not to other gustatory stimuli, this ratio should decrease. The ratios of food to non-food responses showed no change as a result of satiety [mean before satiety 13.7, after satiety 7.7, $t(20)=1.66$, ns]. (This was the case in addition for each of the non-foods considered separately, as indicated in Fig. 2.) (The reader is reminded that the neuronal response was defined as the firing rate elicited by the stimulus minus the spontaneous firing rate.) Thus this analysis also showed that satiety had little influence on the responsiveness of neurons in the insular gustatory cortex.

The sites of the neurons on which these satiety experiments were performed are shown in Fig. 3. All the neurons were in the insular taste cortex, as defined neurophysiologically by Yaxley, Rolls and Sienkiewicz [45].

DISCUSSION

These results provide evidence that satiety does not modulate the responsiveness of neurons in the insular gustatory cortex of the monkey. It may be emphasized that this result was found under physiological conditions, when the monkey himself determined when he was satiated. Although apparent modulation of responsiveness may be demonstrable under artificial conditions, such findings may not be informative about normal, physiological, satiety.

These results were obtained during normal feeding to satiety, when a comparison was made between the hungry and the satiated condition. The results do not completely eliminate the possibility that at some considerable time into the post-satiety period, some decrease of responsiveness to foods might occur. But even if this does occur, such modulation would not then account for the change in acceptability of food, which of course is seen as the satiety develops, and is used to define satiety. Nor would this modulation be relevant to the decrease in the pleasantness in the taste of a food which occurs when it is eaten to satiety [7, 18–20, 30, 35]. The results also do not eliminate the

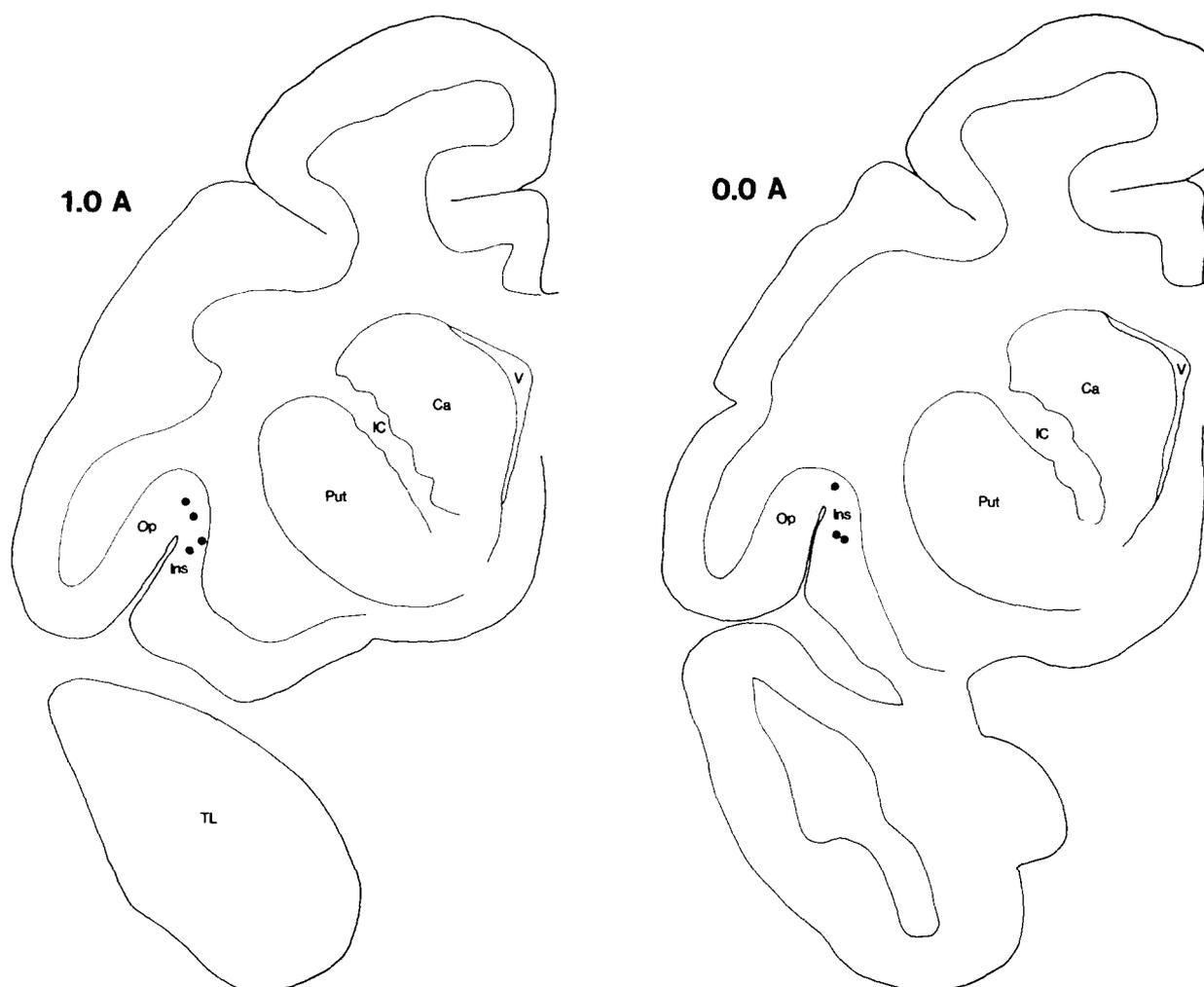


FIG. 3. The recording sites in the insular gustatory cortex at which the seven satiety experiments were performed, shown on coronal sections. The numbers refer to mm anterior to the posterior part of the sphenoid. Ca—caudate nucleus; IC—Internal capsule; Ins—Insular taste cortex; Op—frontal opercular taste cortex; Put—Putamen; TL—tip of the Temporal Lobe; V—ventricle.

possibility that there are some neurons in the insular gustatory cortex in which responsiveness to food is modulated by hunger. However, insofar as our sample of 7 neurons failed to provide evidence for modulation by hunger, such modulation does not appear to be a characteristic property of neurons recorded in the insular gustatory cortex.

Thus, it appears that the reduced acceptance of food as satiety develops, and the reduction in its pleasantness [7, 18–20, 30, 35], are not produced by a reduction in the responses of neurons in the insular gustatory cortex to gustatory stimuli. Similarly, in the opercular frontal gustatory cortex, it has been found that neuronal responsiveness is not modulated by hunger [37]. Sites at which neuronal responsiveness to the taste of food is modulated by satiety include the lateral hypothalamus and substantia innominata [6,36], and neurons in these regions may accordingly be more closely related to motivational control systems. It will be of great interest in the future to determine whether in any of the brain regions which provide possible routes from these primary gustatory cortical areas to the hypothalamus, such as the amygdala and orbitofrontal cortex (see Introduction), gustatory processing is modulated by hunger.

The results described here on the insular gustatory cortex are consistent with those described for the monkey nucleus of the solitary tract (NTS) [44]. In the monkey NTS, neuronal responsiveness to foods was not modulated by satiety. This is consistent, for if modulation had occurred peripherally, then it is not likely that cortical neurons would be able to respond independently of hunger. Indeed, the present result in the insular cortex provides a useful confirmation of the finding in the NTS, in which it was necessary to analyse multiunit responses rather than single unit responses, due to the small size of neurons in the rostral part of the NTS in the monkey.

In one respect it would be inefficient if motivational modulation were present throughout the gustatory system, because this would imply that sensory information was being discarded without the possibility for processing independently of the level of hunger. A subjective correspondent of such a situation might be that it might not be possible to taste food when satiated. It is perhaps more efficient for most of the system to function similarly whether hungry or satiated, and to have a special system (such as the hypothalamus) following sensory processing where motivational state influ-

ences responsiveness. Evidence on the actual state of affairs which exists for visual processing in relation to feeding is that in the inferior temporal visual cortex (a region of visual association cortex which has outputs to limbic structures and thus can potentially influence the hypothalamus), hunger does not influence the responsiveness of single neurons to visual stimuli [31]. The present result indicates that there is a comparable situation in the primate gustatory system, in which taste processing does not appear to be modulated by motivational state in the NTS or in the primary gustatory cortex. The situation may be different from that in the rat, in which there is evidence that gastric distension or administration of glucose can decrease gustatory responsiveness in the NTS [9,10]. It is possible that in the rat, there is relatively more peripheral processing in the gustatory system concerned with feeding, with correspondingly less opportunity for general-purpose cortical gustatory processing (see [27,28]).

The results described were obtained in the monkey. It is of course a possibility that the neural control of feeding is differently organised in the rat. However, the results obtained here compare interestingly with human taste sensations, in that after feeding to satiety humans reported that the taste of the food on which they had been satiated was almost as intense as when they were hungry, though much less

pleasant [35]. This comparison is consistent with the possibility that activity in this gustatory cortical region in the insula does not reflect the pleasantness of the taste of a food, but rather its sensory qualities independently of motivational state.

The present results also provide evidence on the nature of the mechanisms which underlie sensory-specific satiety. Sensory-specific satiety is the phenomenon in which the decrease in the palatability and acceptability of a food which has been eaten to satiety are partly specific to the particular food which has been eaten [18-20, 30, 35]. The present results suggest that such sensory-specific satiety cannot be largely accounted for by adaptation at the receptor level, in the nucleus of the solitary tract, or in the primary gustatory cortex, to the food which has been eaten to satiety, otherwise modulation of neuronal responsiveness should have been apparent in the present study. Indeed, the present finding suggests that sensory-specific satiety is not represented in the primary gustatory cortex. It is thus of particular interest that a decrease in the response of hypothalamic neurons to the sight and/or taste of food occurs which is partly specific to the food which has just been eaten to satiety. The activity of these hypothalamic neurons, but not of the neurons in the primary gustatory cortex, thus parallels sensory-specific satiety [36].

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