Brain Research, 368 (1986) 79–86
Elsevier

BRE 11522

Sensory-Specific Satiety: Food-Specific Reduction in Responsiveness of Ventral Forebrain Neurons After Feeding in the Monkey

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(Accepted July 23rd, 1985)

Key words: hypothalamus — satiety — sensory-specific satiety — taste — hunger — lateral hypothalamus — substantia innominata

It has been shown previously that some neurons in the lateral hypothalamus and substantia innominata respond to the sight of food, others to the taste of food, and others to the sight or taste of food, in the hungry monkey. It is shown here that feeding to satiety decreases the responses of hypothalamic neurons to the sight and/or taste of a food on which the monkey has been satiated, but leaves the responses of the same neurons to other foods on which the monkey has not been satiated relatively unchanged. This suggests that the responses of these neurons in the ventral forebrain are related to sensory-specific satiety, an important phenomenon which regulates food intake. In sensory-specific satiety, the pleasantness of the sight or taste of a food becomes less after it is eaten to satiety, whereas the pleasantness of the sight or taste of other foods which have not been eaten is much less changed; correspondingly, food intake is greater if foods which have not already been eaten to satiety are offered.

INTRODUCTION

Damage to the lateral hypothalamus can disrupt feeding[1,3,30]. However, it is not clear from this evidence that the lateral hypothalamus is involved in the control of feeding, for systems such as the dopaminergic pathways which course near the lateral hypothalamus are damaged by the effective lesions, and at least contribute to the aphagia[4,13–18] more direct evidence on the role of different brain regions in feeding has been obtained by recording the activity of single neurons during feeding[13–18]. Using this method it has been found that a population of neurons in the lateral hypothalamus and adjoining substantia innominata of the monkey responds to the sight and/or taste of food[19]. Evidence that these neurons may be involved in the elicitation of feeding when food is seen and tasted is that these neurons only respond to food when the monkey is hungry[2], and that the responses of these neurons precede and predict the responses of the hungry monkey to food[22]. Further, it has been shown that through learning these neurons come to respond to the sight of visual stimuli which signify food[6].

While experiments in which the effect of hunger on the responsiveness of this population of basal forebrain neurons to food were being performed, it was observed that if a neuron had ceased responding to a food on which the monkey had been fed to satiety, then this neuron might still respond to another food on which the monkey had not been fed to satiety. These experiments are described here. They have implications for the mechanisms of satiety, and for the effects which the variety of food available have on the amount of food eaten (see Discussion). Preliminary reports of this work have appeared[15,16,21,24].

MATERIALS AND METHODS

The methods used were similar to those described previously[2,19,20,22,31,33], and are presented here as briefly as possible, except where they differ.

Recording

Three male cynomolgus monkeys, *Macaca fascicularis,* weighing 4.0–5.5 kg were implanted under

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thiopentone sodium anesthesia with stainless-steel holders on which an adaptor could be fitted for later daily single-unit recording sessions using glass-coated tungsten microelectrodes (after Merill and Ainsworth, ref. 5, but without the platinum plating). 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. Data were analyzed using an on-line PDP-11 computer. The computer continuously acquired single unit action potentials from the neuron, eye movement data from permanently implanted EOG electrodes, and the behavioral lick responses made by the monkey when he fed or drank. It presented the results of every trial individually as a dot display, and computed online peristimulus time histograms together with statistical analyses of changes in neuronal firing using cumulative sum statistics[32] and *t*-tests, as described below.

Analysis of neuronal responses

The responses of the neurons to food and water were measured while the monkey was hungry and thirsty using the following 3 test situations. First, to determine whether there was any response related to feeding or drinking, the neuronal activity was measured while the monkey was shown and then given food or water to ingest by the experimenter ('clinical testing'). Gustatory responses were defined and measured as described fully elsewhere[28,33]. Second, to test whether the neuron had a response to the sight of food, and if so to measure its latency, food or non-food objects were shown to the monkey when a large-aperture shutter opened. Third, to test whether these neurons responded in relation to the initiation of a feeding response, their activity was measured while the monkey performed a visual discrimination task to obtain food. In this task, the monkey had to decide on each trial whether or not to initiate feeding, on the basis of the shape of a visual stimulus shown on a video screen. Full descriptions of these tests have been given elsewhere[2,19,20,22,31]. The monkey was fed, and given water ad libitum at the end of each daily recording session, so that he was approximately 18 h food- and water-deprived during the recording sessions.

Satiety tests

After a neuron had been found which responded in the above 3 tests to foods, but not to non-food stimuli, the effects of feeding the monkey to satiety with one food on the responses of the neuron to a range of foods was investigated as follows.

First, the responses of the neuron to a range of foods was tested in the 'clinical' testing situation. In these 'clinical' tests a variety of food, non-food and aversive objects, and water was presented and brought towards the monkey, and in the case of foods and water placed in the mouth for ingestion. Measurements of the firing rate of the neuron were taken in consecutive periods according to the following standard protocol: (1) when the monkey was sitting quietly (spontaneous neuronal activity); (2) as the experimenter reached behind a screen to retrieve an object from a tray that was out of the monkey's sight (prepresentation period 1); (3) as the experimenter's arm was gradually brought back into view (prepresentation period 2); (4) as the object was shown to the monkey at a distance of about 1 m; (5) as the object was gradually brought towards the monkey; (6) while the object was held close to the monkey's mouth so that mouth movements were made; (7) as the food or water was in the monkey's mouth and being tasted and ingested; and finally (8) as the object was removed. The objects tested included foods such as banana, peanuts, orange, apple, carrot, and a 2 ml syringe (distinguished by a white circle mounted on it) with which the experimenter fed the monkey fruit juice, banana, or 5% glucose solution, a 2 ml syringe (distinguished by a white triangle mounted on it) with which the experimenter gave the monkey water to drink, neutral stimuli such as gratings and laboratory objects, and aversive stimuli such as a 1 ml syringe from which the monkey was given mildly aversive hypertonic saline to drink. This sequence of counts used in the standard protocol allowed initial assessment of whether neuronal responses were to the sight of food or water, were gustatory or olfactory, or were cue or movement-related[19,31,34]. The tests are referred to as 'clinical', in that after the standard protocol sequence had been completed, further interactive tests could be performed as in a clinical neurological examination to define further the nature of the responsiveness of the neuron.

After the response profile of the neuron had been

determined in this way, the monkey was fed to satiety, usually with 20% (w/v) glucose solution. This was given to the monkey in 50 ml aliquots from a syringe using the standard 'clinical' feeding protocol and firing rate measurement periods just described. On each trial the acceptability of the food for the monkey was measured on a scale on which +2 indicated maximum acceptance (reaching for and opening the mouth for the food), +1 indicated acceptance (opening the mouth for the food), 0 indicated neutrality (swallowing the food if it was placed in the mouth, but without any attempt made to obtain the solution), −1 indicated rejection (attempting to close the mouth to prevent administration of food, and failure to swallow all the food placed in the mouth), and −2 indicated maximum rejection (pursing the lips and closing the teeth, using the tongue to eject delivered food, swallowing little, and using the hands to push away the food). If the behavior was intermediate between these types, then intermediate scores were given. After the monkey showed satiety to the glucose (showing behavioral ratings of −1 or −2), the responsiveness of the neuron to the same wide range of foods used previously was again determined.

Localization of recording sites

The locations of the neurons described in this paper were determined in two ways. First, at the end of every track, X-ray photographs were taken of the frontal and lateral views of the head to determine (to within 0.5 mm) the position of the tip of the recording electrode relative to permanently implanted reference electrodes, whose positions were later determined histologically. Second, at the end of the recording period, lesions were made through the tip of the recording electrode to mark typical units. This was done by passing a cathodal current of 100 μA for 100 s. Following tranquillization with ketamine and then a lethal i.p. dose of pentobarbitone sodium the monkey was perfused with 0.9% saline followed by formal-saline. After equilibration in sucrose-formalin, serial frozen 50 μm brain sections were cut and stained with thionin.

RESULTS

An example of the effects of feeding a monkey to satiety with glucose on the responsiveness of a ventral forebrain neuron to the sight of food is shown in Fig. 1. The spontaneous firing rate of the neuron was approximately 8 spikes/s. At the start of the experiment, when the monkey was hungry, the neuron increased its firing rate to 50–70 spikes/s when 20% glucose solution, or a piece of banana was shown prior to feeding. (The rate increased to 95 spikes/s for a peanut.) The firing rate measurements shown in Fig. 1 were made in count period 4 of the clinical testing protocol, and represent the mean and S.E.M. of 4 or more firing rate samples. Then, on the trials indicated, the monkey was fed 50 ml of the glucose solution. It is shown that after a number of such trials the neuron started to respond less to the sight of the glucose-containing syringe, and that at the same time behavioral satiety started to develop (lower graph). After the monkey was satiated on the glucose, the response of the neuron to the other foods was retested. It was found that the neuron still responded at least partly to the sight of the foods which had not just

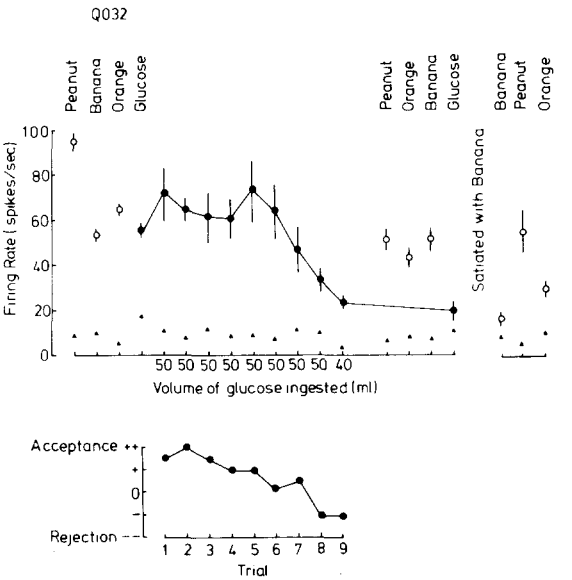

Fig. 1. The effect of feeding the monkey to satiety with 20% glucose solution on the responses of a hypothalamic neuron to the sight of the glucose (filled circles) and to the sight of other foods (open circles). After the monkey had fed to satiety with glucose, the neuron responded much less to the sight of the glucose. Then the monkey was fed to satiety with banana (at the break in the abscissa). The neuron then also stopped responding to the sight of the banana, but continued to respond to the sight of the other foods. The means (± S.E.M.) of the firing rates are shown. The small triangles show the spontaneous activity of the neuron. The lower graph shows the rating of the monkey's acceptance of the glucose solution (see text).

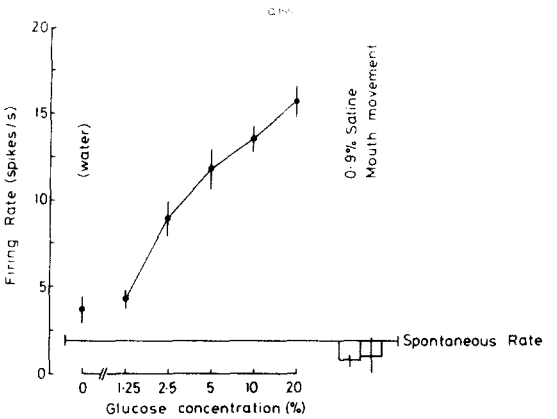

Fig. 2. The effect of the concentration (w/v) of glucose in the mouth on the responses of a hypothalamic neuron with a gustatory response. The neuron did not respond when the monkey drank saline, or when he made mouth movements. The means (± S.E.M.) of the firing rates are shown.

been eaten, namely the peanut, orange and banana, and showed only a small response to the sight of the glucose. It was found at this time that the monkey refused the glucose, but continued to accept the other foods. In a further part of this experiment the monkey was satiated on one of the foods which he still accepted, the banana, and it was found that the responses of the neuron to the banana then decreased (but the responses to other foods remained (see Fig. 1)).

It was notable throughout these experiments that

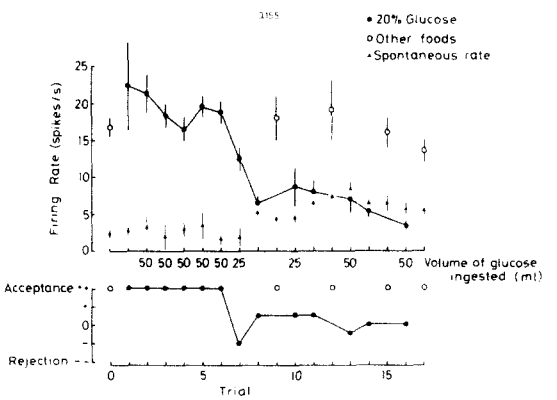

Fig. 3. The effect of feeding the monkey to satiety with 20% glucose solution on the responses of a hypothalamic neuron to the taste of the glucose (filled circles) and to the taste of other foods (open circles). After the monkey had fed to satiety with glucose, the neuron responded much less to the taste of the glucose.

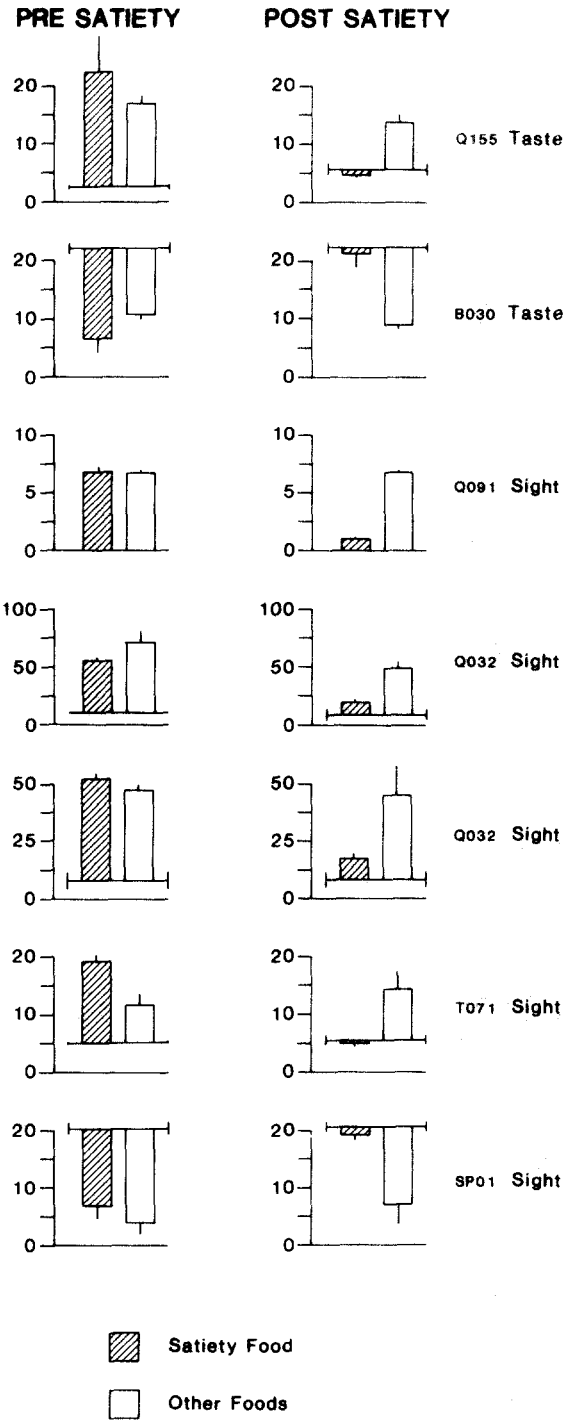

Fig. 4. The firing rate for each neuron tested to the food on which the monkey was satiated (shaded bars) and the foods on which he was not satiated (open bars) before (pre-) and after (post-) satiety was induced. The means (± S.E.M.) of the firing rates are shown, and the spontaneous firing rate is also indicated by the horizontal bar. Whether the neuron responded to the taste or to the sight of food is shown on the right.

the responsiveness of the neurons to food was reduced by the transition from hunger to satiety, but that the spontaneous firing rate of the neurons was little affected by the transition from hunger to satiety, and this is illustrated in Fig. 1, and also in the later figures in this paper.

An example of the effects of satiety on a neuron with responses associated with the taste of food is shown in Figs. 2 and 3. In Fig. 2 it is shown that the firing rate of the neuron increased as a function of the concentration of the glucose in the mouth. There was very little response when the monkey was drinking water (even though he was thirsty), and no response when he was tasting saline or making mouth movements. In Fig. 3 (Q155) it is shown that before feeding to satiety with glucose, the neuron responded to the taste of the glucose and to other foods, which included banana, apple and blackcurrant juice. As the monkey was being satiated with 20% glucose, the response of the neuron to the glucose decreased, but the response to the other foods remained.

It was possible to repeat these experiments for a number of neurons. Fig. 4 shows for each neuron tested in this way the neuronal responses before and after satiety to the food on which the monkey was satiated and to the other foods. In each case, it is clear that there was a significantly larger decrease in the response to the food which had been eaten to satiety

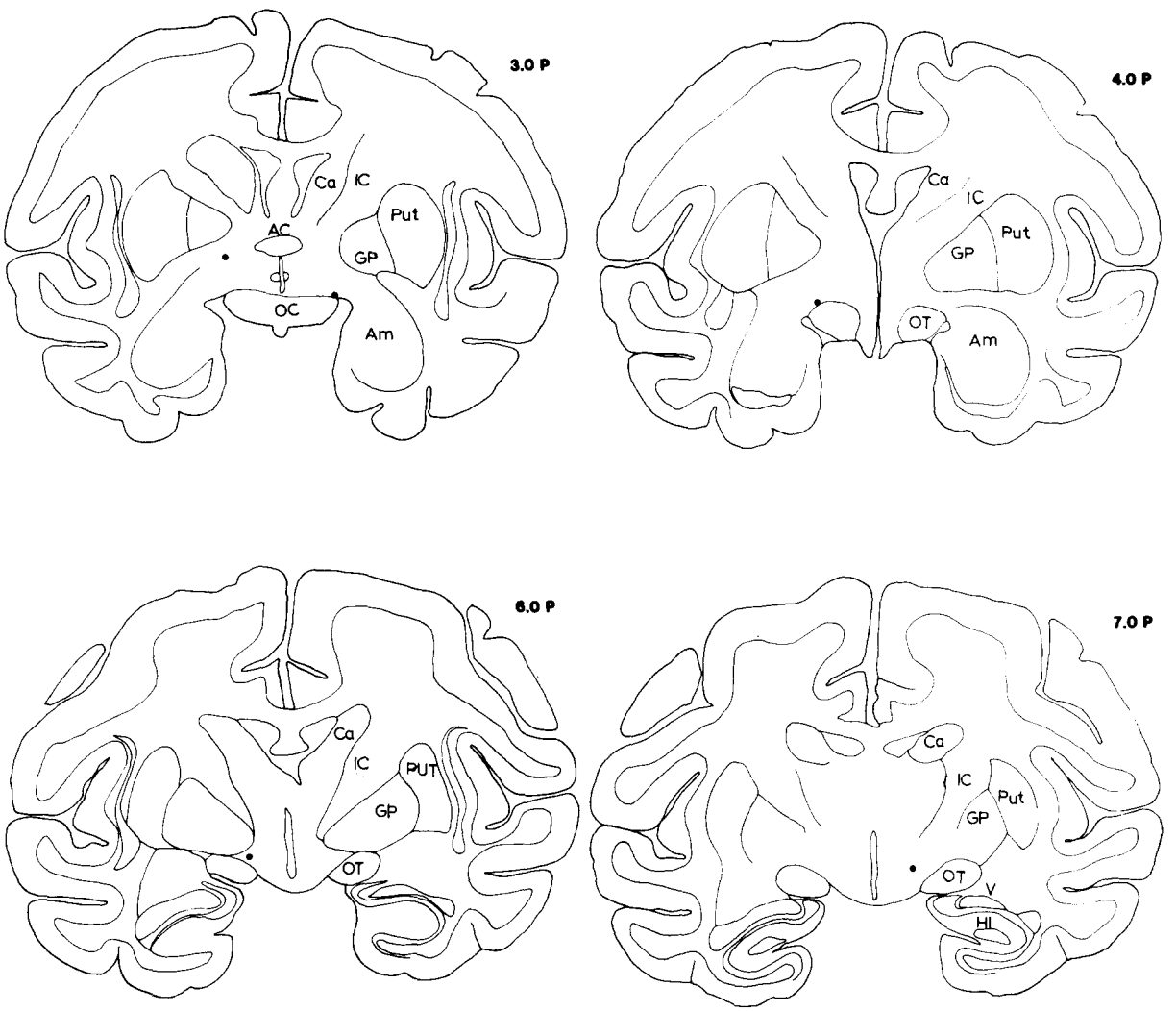

Fig. 5. The sites in the lateral hypothalamus and substantia innominata at which the neurons were recorded. AC, anterior commissure; Am, amygdala; Ca, caudate nucleus; Gp, globus pallidus; HI, Hippocampus; IC, internal capsule; OC, optic chiasm; OT, optic tract; Put, putamen; V, lateral ventricle.

than to the other foods which had not been eaten to satiety. (The response of the neuron is the difference between the spontaneous firing rate of the neuron and its firing rate to the stimulus.) This effect was found for neurons with responses associated with the taste of food, as well as for neurons with responses associated with the sight of food. In addition, in all cases it was found that there was only a relatively minor effect of the transition to satiety on the spontaneous firing rate of the neuron. (The mean change of spontaneous firing rate observed was 0.1 ± 0.6 spikes/s, and the greatest change for any of the neurons in Fig. 4 was 2.8 spikes/s.)

The significance of the sensory-specific satiety effect was tested using an analysis of variance performed on the data shown in Fig. 4. In a two-way ANOVA in which one treatment was presatiety vs postsatiety and the other treatment was the response to the food with which satiety was produced vs the response to the other foods, the interaction between the treatments was $F[1,6] = 33.2$, $P < 0.002$. This shows that satiety had a different effect on the responses to the food with which satiety was produced from the effect it had on the responses to the other foods. It can also be seen from the standard errors shown in Fig. 4 that this same result was found for every neuron tested.

The sites in which these neurons were recorded are shown in Fig. 5. The neurons were found in the lateral hypothalamus and substantia innominata.

DISCUSSION

These results show that neurons in the basal forebrain which respond to the sight or to the taste of food, respond after feeding to satiety less to the particular food on which the monkey has been satiated, but may still respond to other food on which he has not been fed to satiety.

This finding suggested that satiety itself might be at least partly specific to a particular food which has been ingested. This was confirmed by the finding that after these neurons had ceased to respond to a particular food because the monkey had just been fed that food, the monkey while rejecting that food was still willing to accept other foods which he had not just been fed. This finding has been extended in a number of experiments to humans as well as rats. It has been shown that a food which has just been eaten to satiety by humans tastes and looks less pleasant, but that the sight and taste of other foods which have not been eaten to satiety remain relatively pleasant. In line with these ratings, if the humans are then offered a range of foods to eat, they eat little of the food which now tastes less pleasant to them, and relatively more of the foods which they have not just eaten[7–9,21]. Because of this relatively specific decrease in the pleasantness of a food which has just been eaten, offering a variety of foods leads to more eating than offering the same food repeatedly, and this can lead to an increase in the energy consumed in a meal of 33% (ref. 8). In rats, it has been possible to show that this effect can lead in the long-term to obesity[11]. This is thus an important principle which determines the amount of food eaten, the amount of energy ingested, and also perhaps in man, in addition to the rat, may influence long-term body weight control.

Because this decrease in the neuronal response to and pleasantness of a food which has been eaten to satiety is relatively specific to the food which has been eaten, the effect has been termed sensory-specific satiety. Further evidence for this is that the effect can be obtained independently of the nutrients ingested. For example, sensory-specific satiety can be found even for foods which contain no energy[7], and can occur as a reaction to a particular color of food, even when that food is identical in taste and nutrients to foods of different colors[10].

The mechanism of this sensory-specific satiety appears to involve a sensory-specific decrease in the pleasantness of a food, rather than adaptation in the sensory pathways of sensory responses to a particular food which has just been eaten. Evidence for this is that even when basal forebrain neurons no longer respond to the sight of a food because the monkey has been satiated with that food, neurons in the inferior temporal visual cortex are still responding to the sight of the stimulus[20]. The fact that at this high level of the visual system, which through the amygdala could provide inputs to the basal forebrain neurons[14–16,17,18], neurons are not influenced by satiety provides evidence that satiety does not modulate neuronal responses at this stage of visual information processing, nor at the earlier stages of cortical visual processing which project into the inferior temporal visual cortex. There is comparable evidence for the taste system. When monkeys are fed to satiety, with for ex-

ample glucose, there is no reduction in the responsiveness of neurons at the first central relay of the gustatory system, the nucleus of the solitary tract, to the taste of glucose[33]. It is of interest that even in the frontal opercular taste cortex, and in the taste cortex in the rostral insula, satiety does not modulate the responsiveness of gustatory neurons to gustatory stimuli with which the monkeys have been fed to satiety[29,34]. It is only when taste information has reached the orbitofrontal cortex[31], and the lateral hypothalamus as shown here, that satiety, and sensory-specific satiety, are seen to modulate the responsiveness of neurons with gustatory responses. Thus peripheral adaptation or habituation in the taste pathways does not account for sensory-specific satiety in the primate taste system. Further evidence for this view is that when humans rate food as tasting less pleasant after they have just ingested it to satiety, there is little change in the rating of the intensity of the taste of the food[25].

It should be noted that the effects described in this paper are not due to lower initial responsiveness to the particular food which was subsequently fed to satiety, as shown not only by the initial neuronal response to the different foods (see Fig. 4), but also by the acceptability of the different foods to the monkeys. In addition, on some occasions after the monkey had been satiated on one food, and sensory specific satiety had been obtained, it was possible to satiate him on another food, and then obtain sensory specific satiety to that food (e.g. see Fig. 1), even though it was not necessarily his second most preferred food.

The present results show that a sensory-specific reduction in the responsiveness to a food with which satiety has been produced is a property of hypothalamic neurons which respond to food. This close parallel with the similarly partly selective effect which feeding to satiety produces on behavioral responses to food provides further evidence that these neurons are related to behavioral responses made to food, such as feeding, and autonomic and endocrine responses[15–18].

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