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Effects of Hunger on the Responses of Neurons in the Lateral Hypothalamus to the Sight and Taste of Food[1]

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Recordings were made from single neurons in the monkey lateral hypothalamus and substantia innominata which had previously been shown to respond with an increase or decrease of their firing rates when the hungry monkey tasted food, and/or when he looked at food. It was found that the responsiveness of these neurons to food decreased over the course of a meal of glucose as satiety increased. When satiety, measured by whether the monkey rejected the glucose, was complete, there was no response of the neurons to the taste and/or to the sight of glucose. The spontaneous firing rates of these cells were not affected by the transitions from hunger to satiety. This modulation of responsiveness to food of hypothalamic cells was specific to them in that it was not seen in cells in the globus pallidus which responded in relation to swallowing and mouth movements, or in cells in the visual inferotemporal cortex which responded when the monkey looked at the glucose-containing syringe. On the basis of this and other evidence it is suggested that the hypothalamic cells described here could be involved in the autonomic, the endocrine, and/or the feeding responses which occur when an animal sees or tastes food.

INTRODUCTION

Some neurons in the monkey and rat lateral hypothalamus and substantia innominata respond in association with the taste of food, in that the firing rates of the neurons change when one solution (e.g., glucose) is tasted, but not when other solutions (e.g., saline or water) are tasted (11, 13). Other neurons in the same region respond when a monkey looks at food but not at nonfood objects (12). As these neurons respond to food, and are in the region where lesions disrupt food intake and where stimulation can lead to feeding (5, 1), it seemed possible that the neurons were involved in the control of feeding. We therefore recorded from these units

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before feeding when the animal was hungry, during feeding as hunger diminished, and after feeding when satiety was complete, to determine whether these units altered their activity in any way which was related to the control of food intake. The plan of the experiments was to find in a hungry monkey a single unit in the lateral hypothalamus or substantia innominata which responded to the sight and/or taste of food, and to record its activity while the monkey ate to satiation. It was sometimes possible to hold the unit over the next few hours until the monkey became hungry again, and thus to confirm that the changes seen during the transition from hunger to satiety could be reversed by allowing the animal to become hungry again. Control experiments were performed in which recordings were made from single units in the globus pallidus which did not fire to the taste and/or sight of food, but did respond to motor movements such as swallowing, to determine whether or not the effects of satiation on hypothalamic units were specific to them. A preliminary report of this work has appeared (3).

METHOD

Recording Method. Single units in the lateral hypothalamus and substantia innominata were recorded with tungsten microelectrodes driven by a hydraulic microdrive in three unanesthetized squirrel monkeys (*Saimiri sciureus*) and one unanesthetized rhesus monkey (*Macaca mulatta*) using the techniques and general methods described previously (12). As the single-unit recordings described here usually lasted for several hours, particular care was taken to ensure that a recording was being made only from a single unit, by continuously monitoring the waveform of the action potentials [see e.g., (12) Fig. 1] and by showing that the spikes were never coincident in time. Recording sites were located by taking X-ray photographs during an experiment, and by making micro-lesions through the recording electrode for subsequent histological verification (12).

Characteristics of Single Units. In the initial phase of the experiment single-unit responses in the lateral hypothalamus and substantia innominata were characterized as described in more detail elsewhere (11–13). Units classed as responding in association with the taste of food increased or decreased their firing rates during the ingestion of one food (e.g., 5% glucose solution) but not during the ingestion of other foods or fluids (e.g., water and isotonic saline). If the response was specific in this way it suggested that the firing of the unit was not related to general changes in behavior such as mouth movements and swallowing, which accompanied the ingestion of all the fluids. Units classed as responding in association with the sight of food altered their firing rates when a monkey saw a preferred food such as a peanut, but not when a monkey saw nonfood

objects, ate in the dark, or when motor behavior such as reaching or swallowing occurred, when food was smelled, when the monkey became aroused by the sight of a squeeze-bulb from which air was puffed on to his face, or in other control tests (12). On some tracks as the microelectrode was lowered at an angle toward the substantia innominata and lateral hypothalamus, it passed through the globus pallidus, and single units were recorded which fired in relation to sensory–motor events such as reaching with the arm, touch to the face and mouth region, and swallowing (12, 13). As noted in the Introduction, recordings were also made from these neurons while the animal was fed to satiety to determine the specificity of the effects of satiety on the responses of hypothalamic neurons which respond to food.

In previous studies in a total sample of 764 hypothalamic units, 71 were classed as responding in association with the sight of food, and 19 as responding in association with the taste of food (11–13). The experiments described here were performed on some of these units after the analysis of their responsiveness to food had been completed.

Effects of Satiety. At the start of an experiment on a single unit the monkey was hungry, as the previous meal had been eaten at 18.00 hr the day before and initial testing of the characteristics of a unit was usually completed by approximately noon. The firing rate of the unit was plotted out throughout the experiment on an ultraviolet polygraph recorder and the single-unit spikes and a voice channel were recorded on magnetic tape. The effect on the firing rate of the unit of presenting food to the animal was then determined, and repeated determinations were made while the animal was fed to satiety. The usual method used for these experiments was to present the animal, who was sitting in a primate chair, on each trial with a black 2-ml syringe which contained 20% glucose or sucrose and which had previously been used to feed the animal the glucose or sucrose. This provided a standard visual and a standard taste stimulus. Other food-associated visual stimuli, such as peanuts, were presented similarly. The visual stimulus occurred during a 10-sec period before ingestion during which the animal could see the syringe gradually approaching its mouth in the center of its visual field from a distance of 1 m. The visual response of the unit was measured by the firing rate of the unit during this 10-sec period. The taste stimulus occurred during a following 5-sec period during which the 2-ml syringe of glucose was steadily emptied into the animal's mouth. The taste response of the unit was measured by the firing rate of the unit during this period in which the monkey drank the solution. These tests were repeated every 2 min until the monkey became satiated. Thus it was possible to measure the response of a unit to the sight and/or taste of food while the animal was hungry,

during the transition from hunger to satiety, and during satiety. It was also possible to relate the response of the unit to the degree of hunger of the animal. At the start of the experiment the animal reached for the glucose syringe as soon as it was presented, and accepted the glucose to drink very readily. After a number of trials, on each of which 2 ml of 20% glucose had been ingested, the monkey showed a longer latency to reach for the glucose syringe, until it stopped reaching for the syringe, but continued to accept the glucose readily when it was emptied into the mouth. On later trials the monkey attempted to reject the syringe by averting its head (although the 2 ml of solution was still given so that the response of the unit to the stimulus given during satiety could be measured). Then feeding was discontinued. One measure of satiety, taken to compare with the response of the unit, was whether the animal accepted, or tried to reject, the syringe when it was placed in the mouth. The preceding description of the behavior of the animal during the testing shows that some satiety (as seen by lack of reaching for the syringe) had started to occur before the animal ceased to accept the syringe when it was placed in its mouth. Whenever possible, the unit was held for the next several hours until the monkey became hungry and was willing to reach for the glucose syringe again.

RESULTS

The results of a typical experiment are shown in Fig. 1. Initial testing had indicated that the hypothalamic unit decreased its firing rate when the hungry monkey looked at the black syringe from which it was fed glucose or at a peanut, both of which were food-associated visual stimuli, and that the response was not due to olfactory, auditory, somatosensory, or gustatory stimuli, or to reaching or arousal. The effects of satiety on the firing rate of a hypothalamic unit which responded to the sight of the glucose syringe are shown in Fig. 1. The spontaneous firing rate of the unit at the start of the experiment was 21 spikes/sec. The response of the unit when the hungry monkey looked at the glucose syringe at the start of the experiment (Trial 0) was a decrease of the firing rate to approximately eight spikes/sec. At the end of the experiment (Trial 35), when satiety was complete (see below), the unit no longer showed a decrease of its firing rate from its spontaneous baseline firing rate when the syringe was shown. It should be emphasized that the satiated monkey was still fed glucose from the black syringe, so that he fixated the glucose-containing syringe when it was presented on each trial throughout the experiment, and did not become drowsy toward the end of the experiment. It was possible to show that 2 hr later, when the animal was hungry again and accepted the glucose, the response of the unit to the sight of the glucose

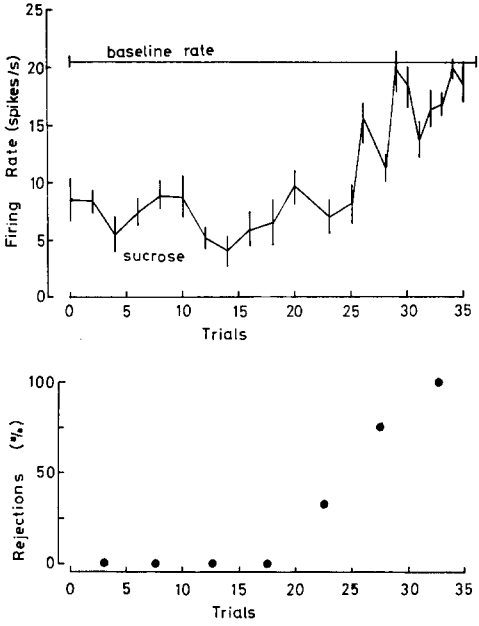

FIG. 1. (Above) Effect of the sight of a syringe (from which the squirrel monkey was fed 2 ml of 20% sucrose solution) on the firing rate of a hypothalamic single unit. The rate decreased below the spontaneous baseline rate (mean and S.E.M.) at the start of the experiment when the monkey was hungry, but not at the end of the experiment when the monkey was satiated. The firing rate and its standard error were measured over a 5-sec period during which the monkey was looking at the syringe. Immediately afterwards the monkey drank the glucose. On some trials (left blank) different stimuli were shown, and the monkey was not fed. (Below) The time-course of satiety of the monkey in the same experiment. For each block of trials, the percentage of trials on which the monkey rejected the sucrose solution is shown.

syringe returned. Thus the unit only responded to the sight of the glucose syringe if the animal was hungry. Satiety did not affect the spontaneous baseline firing rate of the unit which remained at 21 spikes/sec throughout the experiment.

The hunger of the animal, measured by whether or not the animal accepted the glucose solution, is also shown in Fig. 1. The monkey accepted the glucose readily over the first few blocks of trials, started to reject it between Trials 20 and 25, and always rejected the glucose at the end of the experiment (Trials 30 to 35). Thus the monkey started to accept the food less readily at about the same time as the unit started to show a smaller response to the food.

Filmed responses of another similar unit which only responded to food when the monkey was hungry are shown in Fig. 2.

The effects of satiety on the firing rate of a hypothalamic unit which responded in the hungry monkey to the taste of glucose and to the sight of the glucose-containing syringe are shown in Fig. 3. (The unit did not respond when the monkey drank water or isotonic saline.) The monkey was hungry on Trial 0 (see Method), 2 ml of 20% glucose solution were fed on every trial, and satiety was complete (as measured by consistent rejection of the glucose) by Trial 12. The spontaneous firing rate of the unit was approximately 4 spikes/sec, and remained approximately constant (the regression line is shown) throughout the experiment. At the start of the experiment, the unit increased its firing rate during the 5-sec period in which the monkey drank the glucose, as well as during the immediately preceding 5-sec period in which the monkey looked at the glucose syringe. By the end of the experiment, when satiety was complete, the firing rate of the unit when the glucose was seen or tasted did not increase above the spontaneous level. Thus the responses of this unit which were associated with the taste of glucose and the sight of the glucose-containing syringe occurred only when the monkey was hungry.

It was possible to complete this type of experiment which involved recording for several hours from a single unit during feeding for ten different units in the lateral hypothalamus or substantia innominata in three squirrel monkeys and one rhesus monkey. All ten units showed the effect

FIG. 2. Effect of hunger on the responsiveness to food of a lateral hypothalamic unit in the squirrel monkey. Upper trace: spontaneous baseline firing rate. Middle trace: the firing rate of the unit decreased while the hungry monkey looked at a black glucose-containing syringe (period after "glucose shown") and while the monkey drank the glucose (period after "drinking glucose"). Lower trace: after the monkey had been fed until he was satiated the firing rate of the unit did not change from the spontaneous firing rate while the monkey looked at the black glucose-containing syringe (period after "glucose shown"), nor did the firing rate change while the monkey drank the glucose (period after "drinking glucose").

described here. That is, the response of the units to food was modulated by hunger, so that the units responded to the sight and/or taste of food only if the monkey was hungry. The response measured was either a decrease or an increase of the firing rate away from the spontaneous baseline firing rate. The baseline firing rate was relatively unaffected by the transition from hunger to satiety. Three of the units responded to the taste and to the sight of food, one responded only to taste, and six responded only to the sight of food. The sites of these units in the lateral hypothalamus and substantia innominata, and further details of the way in which this type of unit responds to food, have been described elsewhere (11–13).

For comparison with these results, recordings were made from a number of units in the globus pallidus which fired in relation to feeding (e.g., during swallowing), and which did not respond to the taste or the sight of food. An example of a unit which responded in relation to swallowing is shown in Fig. 4. Previous tests on the unit (13) had shown that the unit responded equally when the squirrel monkey drank 20% glucose, isotonic saline, and water. In Fig. 4 it is shown that the unit increased its firing rate from the spontaneous rate of 21 spikes/sec to approximately 70 spikes/sec when the animal drank 2 ml of 20% glucose. The experiment was performed in the same way as for the hypothalamic units, until by Trials 12 to 14 behavioral satiety was reached, and the animal rejected the glucose. At this stage the unit still responded when the animal was made to drink the glucose by emptying the syringe into its mouth, as in the previous experiments. Thus the degree of hunger or satiety did not modulate the changes in the firing rate which occurred in relation to feeding in this

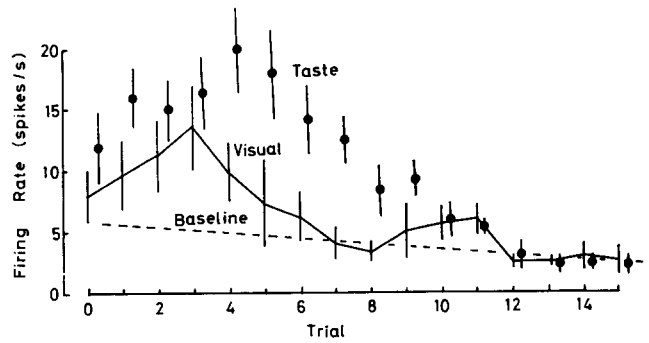

FIG. 3. This hypothalamic unit recorded in the squirrel monkey increased its firing rate when the monkey tasted glucose (Taste response) and when the monkey saw the glucose syringe (Visual response) if the animal was hungry (Trials 0–6) but not when the monkey was satiated (Trials 12–14). Conventions as in Fig. 1. The taste response (mean and SEM of firing rate) was measured over the 5-sec period during which the monkey drank 2 ml of 20% glucose on each trial. The baseline spontaneous firing rate is indicated by its regression line.

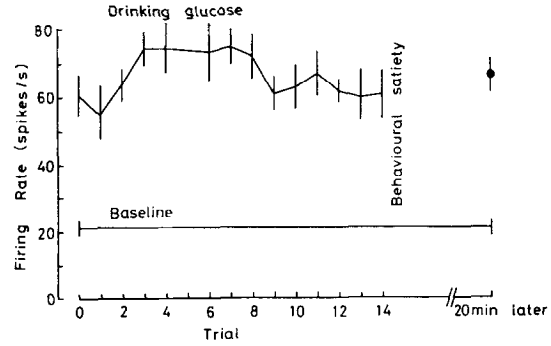

FIG. 4. Lack of effect of the transition from hunger (Trial 0) to satiety (Trials 12–14) on the increase of firing rate produced by swallowing in a control unit in the globus pallidus.

type of unit. This finding was replicated in the four different pallidal units tested of the 24 which had altered their firing rates during the feeding tests. (The total sample of pallidal units was 185.)

DISCUSSION

These experiments show that the responsiveness of units in the lateral hypothalamus and substantia innominata which appear to respond to the sight or taste of food (11–13) is modulated by hunger. The units respond to food only if the animal is hungry. There is evidence that this type of control also occurs in the rat, for in the food-deprived rat some hypothalamic neurons were found which responded to the taste of sucrose, and in the water-deprived rat some hypothalamic neurons were found which responded to the taste of water (7).

The modulation of responsiveness to food appears to be an effect specific to those hypothalamic neurons which respond to food, in that a modulation of response by hunger was not found in sensory–motor neurons in the globus pallidus which fired in relation to swallowing or to mouth movements associated with feeding. The same observations show that the modulation by hunger of the responsiveness of the taste neurons was not an artifact due to failure to ingest the taste solution when the animal was satiated.

A comparison can also be made with the characteristics of neurons in the visual inferotemporal cortex of the rhesus monkey analyzed under the same experimental conditions, some of which can be shown to respond when the monkey looks at a range of objects which includes the syringe used to feed the monkey in the satiety experiments described above. These inferotemporal neurons still respond to the sight of the glucose-containing

syringe when the monkey has been satiated in the type of experiment described here (observation of E. T. Rolls and S. J. Judge). This observation shows that the monkey still looks at the syringe when he is satiated. (The syringe is still salient to the animal when he is satiated, because he is still given glucose from it.) This observation also shows that the modulation of responsiveness to food is a characteristic of the hypothalamic neurons which respond to food, in that it does not occur in neurons in the visual inferotemporal cortex which respond in the same test situation.

These hypothalamic neurons could be involved in the rapid autonomic and endocrine responses which occur when a hungry animal is given food (6), and they could be involved in the control of feeding behavior. The following evidence is consistent with all these possibilities. First, the neurons respond when the animal looks at food but not at nonfood objects, or when he tastes food, or both (11–13). Second, as shown here, they respond to food only if the animal is hungry. A response in these neurons could thus act as a signal that the animal should eat food which he saw or tasted. Third, lesions in this region produce aphagia (5, 1). Fourth, electrical stimulation in this region can lead to feeding [(5), personal observations]. Fifth, there are other neurons in the hypothalamus which may indicate hunger and which could thus modulate the responsiveness of the hypothalamic neurons described above. Examples of other neurons which have so far been described include those which may respond to glucose utilization (4, 8) and to stomach distension (2). The modulation of responsiveness may occur in the hypothalamus, because neurons which could indicate hunger are present there, but in the olfactory system the effects of this modulation are seen as far peripherally as the olfactory bulb, where neurons respond to food odors only if a rat is hungry (9). While these points are consistent with the view that the neurons in the lateral hypothalamus and substantia innominata described here are involved in feeding behavior as well as in endocrine and autonomic responses, further evidence on this is required, especially as at least some aspects of the lateral hypothalamic syndrome may be accounted for by changes to sensory and motor pathways which are damaged by the lateral hypothalamic lesions (5, 11). Some further evidence is that the animal will work to obtain electrical stimulation through the microelectrode while it is in the region of these neurons. Furthermore, this brain-stimulation reward is enhanced by hunger (10, 11, 13). In addition, the neurons described here are activated by brain-stimulation reward of some sites (10, 11, 13). Taken together, these findings are consistent with the possibility that there are cells in the lateral hypothalamus and substantia innominata which maintain feeding behavior if they are activated by food in a hungry animal. In this sense these neurons would be food-reward neurons (10,

11, 13). The experiments with brain-stimulation reward provide some evidence that these neurons are involved in feeding. However, understanding of the precise role of these cells in feeding behavior will depend on knowledge of their input and output connections and also on a comparison of the activity of these cells with others in areas with known motor and sensory functions.

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