Modulation during Learning of the Responses of Neurons in the Lateral Hypothalamus to the Sight of Food[1]

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Recordings were made from single neurons in the lateral hypothalamus and substantia innominata of the rhesus and squirrel monkey during feeding. A population of these neurons which altered their firing rates while the monkeys looked at food but not at nonfood objects was investigated. Because the responses of these neurons must have been affected by the previous experience of the animals, the activity of the neurons was measured during tasks in which the monkeys learned whether or not objects which they saw were associated with food. During visual discrimination tests these neurons came to respond when the monkey saw one stimulus associated with food (e.g., a black syringe from which the animal was fed glucose), but not when the monkey saw a different stimulus which was not associated with food (e.g., a white syringe from which the animal was offered saline). During extinction tests these units ceased to respond when the monkey saw a visual stimulus such as a peanut if the peanut was repeatedly not given to the monkey to eat. The learning or extinction behavior approximately paralleled the response of the neurons.

The findings that the neurons in the lateral hypothalamus and substantia innominata respond when a monkey is shown food only if he is hungry, and as shown here, if as a result of learning the visual stimulus signifies food, provide information on a part of the brain which may be involved in feeding. The findings are consistent with other data which suggest that the responses of these neurons are involved in the autonomic and/or behavioral reactions of the animal to the sight of food.

INTRODUCTION

It has been reported that neurons in the lateral hypothalamus and substantia innominata change their firing rate when a hungry monkey looks

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at food but not at nonfood objects (9), and/or when some solutions (e.g., 5% glucose) but not others (isotonic saline or quinine) are in the mouth of the monkey (8). In these studies it was found that approximately 13% of the neurons recorded in this region had responses associated with the sight and/or taste of food. It has also been found that the responses of these neurons are diminished when the animal is fed to satiety (2). These findings, together with the evidence that lesions in this region disrupt feeding and electrical stimulation produces eating (3), are consistent with the possibility that these neurons are involved in some way in feeding (8).

Because the responses of these neurons occurred when the monkeys saw foods such as peanuts, oranges, and bananas, and also when they saw a black syringe from which they had been previously fed glucose, it seemed that the responses of these neurons were affected by the previous experience of the animals. To test the possibility that the responses of these units were affected by learning, formal learning tests were conducted as described here. The monkeys were put into a situation in which they learned to discriminate between two differently colored visual stimuli, only one of which was associated in the experiments with food. In another set of experiments the extinction of a previously learned association was investigated. A visual stimulus which had been previously associated with food was repeatedly presented to the monkey without food reinforcement. During these procedures both the behavior of the monkey and the responses of units described above were measured.

METHOD

Recording Method. Single units were recorded extracellularly with tungsten microelectrodes from the lateral hypothalamus and substantia innominata in two unanesthetized squirrel monkeys (*Saimiri sciureus*) and one unanesthetized rhesus monkey (*Macaca mulatta*) using the techniques, apparatus, and general procedure described elsewhere (9). Because the neurons described in this paper were held for many hours, care was taken to ensure that recordings were made from single cells, by continuously monitoring the waveform of the action potentials and by showing that the spikes were never coincident in time. At the conclusion of every recording session anterior and lateral X-ray photographs were taken. The position of the unit could then be calculated by reference to the X ray which showed both the microelectrode, and the nearby chronically implanted stimulation electrodes the sites of which were determined when histology was performed. In addition, lesions were made through the recording microelectrode to mark selected units. This was done by passing an anodal current of 30 to 60 μA for 30 to 100 sec.

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 (8–10). 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 (9). The units analyzed here were in some cases the same units as those for which response characteristics have been described elsewhere (8–10). The learning experiments described here were performed after the response characteristics had been determined.

In previous studies in a total sample of 764 units in the lateral hypothalamus and substantia innominata, 71 were classed as responding in association with the sight of food, and 19 as responding in association with the taste of food (8–10). The experiments described here each lasted for several hours and were completed on 12 of these 71 neurons.

General Test Procedure. At the start of an experiment on a single unit the monkey was hungry, as the previous meal had been eaten at 1800 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 throughout the experiment on an ultraviolet polygraph recorder and the single-unit spikes and a voice channel were recorded on magnetic tape. The monkeys were sitting in a primate chair in the test situation described fully elsewhere (2, 9).

Visual Discrimination Test. When a neuron had been found which responded in association with the sight of food and not in association with the sight of nonfood stimuli or with touch, movement, or arousal, the visual discrimination test started. The monkey was presented with 2-ml syringes of different colors: one was black and contained 20% glucose or sucrose solution, and the other was white and contained 0.9% saline or 0.025% quinine hydrochloride solution. The visual stimulus, which was presentation of the syringe, 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 response of the neuron was measured by averaging the firing rate of the cell during this 10-sec period. During the following 5-sec period, 0.5 ml glucose or saline was delivered into the animal's mouth for the animal to drink. These tests were repeated every 2 min for a number of trials until at least ten trials after behavioral discrimination was evident (see Results). The baseline firing rate of these units was determined in this interstimulus interval.

The visual stimuli for other cells were a real peanut contrasted with a blue one made of modeling clay. The general procedure of this test was identical to that used with syringes. In some experiments the only difference was that during the 5-sec period of ingestion the monkey was allowed to eat the real peanut but not the blue one. These tests were repeated every 2 min.

Extinction Test. The general procedure was as for the previous test. The stimuli used were in all cases peanuts. For the first few trials a peanut was presented to the monkey as described above, the response of the unit was measured during the 10-sec period in which the peanut was seen by
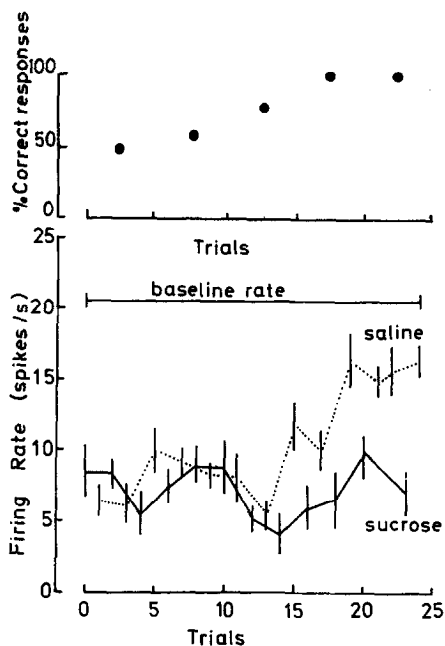

FIG. 1. Firing rate of a lateral hypothalamic unit during the learning of a visual discrimination. On alternate trials the monkey saw and was then fed from a black syringe containing 25% sucrose, or a white syringe containing 0.9% saline (which was aversive). The firing rate of the unit ($\pm$ the standard error) over the 10 sec during which the monkey saw a syringe is shown on the ordinate. Between Trials 0 and 14 the firing rate of the unit was decreased from its baseline spontaneous rate (see below) and the monkey accepted either syringe, so that his performance was approximately 50% correct (see above). After Trial 15 the unit continued to fire at less than its baseline rate when the monkey saw the black syringe containing sucrose, but gradually during the next few trials the sight of the white syringe containing saline had less and less effect on the unit. At the same time the monkey learned the visual discrimination, that is, it refused to accept fluid from the white saline-containing syringe but continued to accept the glucose-containing syringe.
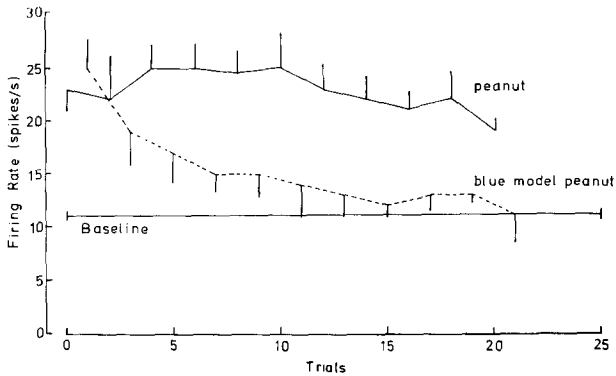
FIG. 2. Firing rate of a lateral hypothalamic unit during the learning of a visual discrimination. On alternate trials the monkey saw for 10 sec and was then fed a real peanut, or he saw for 10 sec an artificial peanut made of blue modeling clay ("blue model peanut"). The firing rate of the unit ($\pm$ the standard error) for the 10 sec during which the monkey saw the stimulus is shown on the ordinate. Initially the response to both stimuli was an increase of the firing rate from the baseline spontaneous rate of 11 spikes per second. During the next few trials the response to the blue model peanut became smaller and the response to the real peanut remained approximately constant.

the monkey as the peanut approached the monkey's mouth from a distance of 1 m, and then the monkey was allowed to eat the peanut. Then extinction was started. On each succeeding trial the monkey was shown the peanut as before, but the peanut was not placed in the monkey's mouth at the end of the 10-sec period in which the peanut was shown to the monkey. After a number of extinction trials, acquisition was reinstated and the monkey was fed the peanut on every trial.

RESULTS

The results of a standard visual discrimination test are shown in Fig. 1. At the beginning of the test the squirrel monkey accepted both the black (glucose) and the white (saline) syringes, as he had previously been fed glucose from a syringe. The presentation of either syringe (or foods such as peanuts) produced a decrease of the spontaneous firing rate from 20 spikes per second to approximately 8 spikes per second. After a number of trials in which the animal continued to accept both the black glucose-containing and the white saline-containing syringe, the animal came to reject the white syringe on every trial on which it was presented, but continued to reach for and accept the glucose-containing syringe. Rejection was measured by failure to reach for the syringe or active rejection of the

syringe with the hand, and if the syringe was then placed in the monkey's mouth, by turning of the head and failure to drink the solution. As shown in Fig. 1, performance was at approximately 50% correct (i.e., the animal accepted the black syringe correctly but failed to reject the white syringe) for the first two blocks of five trials each, after which the animal started to perform the visual discrimination. As the discrimination was learned, the firing rate of the unit continued to decrease when the animal saw the black glucose-containing syringe, but ceased to respond when the animal saw the white saline-containing syringe (see Fig. 1). The spontaneous baseline firing rate in the intertrial interval did not change during the experiment.
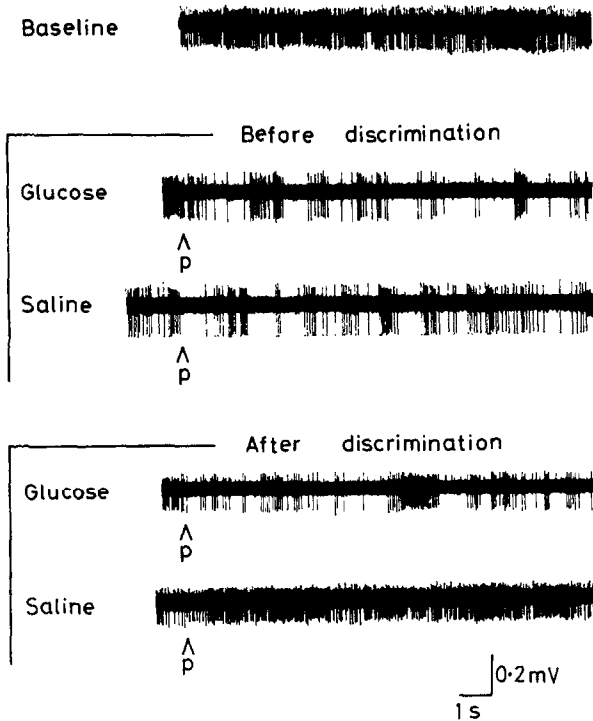

FIG. 3. Photographs of spike activity of a lateral hypothalamic unit during the learning of a visual discrimination similar to that in Fig. 1 between a black syringe containing 20% glucose, and a white syringe containing 0.9% saline. First trace—baseline firing rate (photographed at the end of the experiment in which the spike amplitude showed a small decrease). Second and third traces—similar responses, of a decrease of firing rate, before discrimination on Trials 2 and 3 during the presentation starting at p of the black glucose-containing and white saline-containing syringes. Fourth and fifth traces—after discrimination on Trials 20 and 21 the unit still responded during presentation of the glucose-containing but not during presentation of the saline-containing syringe.

Figure 2 shows another visual discrimination test in a rhesus monkey. The cell responded with an increase from its spontaneous firing rate of 11 spikes per second to 22–25 spikes per second when a peanut was shown to the monkey. The discrimination task was between a real peanut and an artificial one made of blue modeling clay. In this experiment the monkey was not given the artificial peanuts to eat but in other experiments the animal was allowed to eat the artificial peanuts. After three to four trials, the monkey started to learn the discrimination, as shown by reaching for
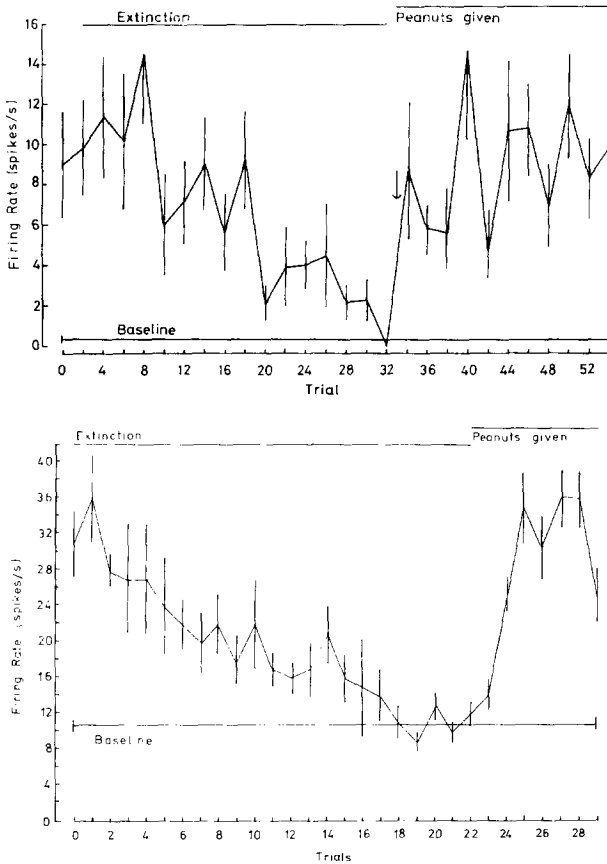

FIG. 4. Firing rate of two lateral hypothalamic neurons during extinction. Before the start of extinction at Trial O, both units increased their firing rates above the spontaneous baseline rate during the 10-sec period prior to being fed the peanut in which the monkey was shown the peanut (ordinate). During extinction the monkey was shown but not fed the peanut. The response of the neurons in the 10-sec period during which the monkey saw the peanut gradually became smaller throughout extinction. When acquisition was reinstated by allowing the monkey to eat the peanuts after being shown them, the responses of the unit returned.
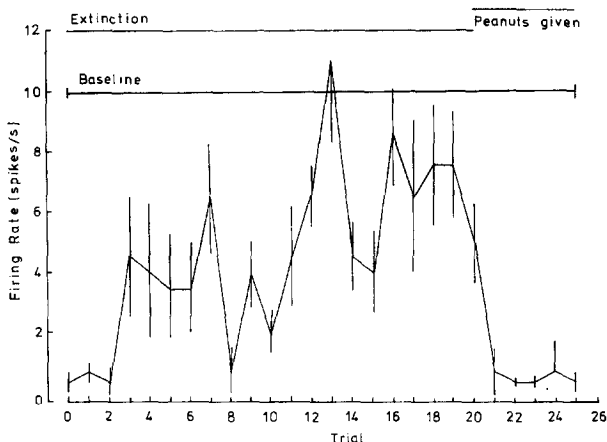
FIG. 5. The firing rate of a lateral hypothalamic unit during extinction. The response of this unit was to decrease its firing rate below the spontaneous baseline rate when the monkey looked at the peanut. Explanation as for Fig. 4.

the real peanuts but failing to reach for the artificial ones. After three to four trials the unit stopped responding to the artificial peanut but still responded on each trial with an increase of its firing rate to the real peanut. Discrimination tests of the type shown in Figs. 1 and 2 were completed on four units in two squirrel monkeys, and three units in one rhesus monkey. In all cases, while the animals learned the visual discrimination, the units altered the responses they showed.

Figure 3 shows photographs of the spikes of a single unit on which a visual discrimination experiment was performed.

Figure 4 shows the results of two extinction experiments performed on two different cells in the rhesus monkey which responded with an increase of their spontaneous firing rates when food was shown to the monkey. Both cells had low spontaneous firing rates (one and 11 spikes per second, respectively) and the cells increased their firing rate to approximately ten and 30 spikes per second, respectively, when the monkey looked at the peanut. Trial 1 in the figures was the first trial on which the peanut was not given to the monkey, although the peanut was still shown in the standard way and approached the monkey's mouth from a distance of 1 m. During the next 25 trials the response of the cells to the peanut became small. After a number of trials on which no response of the cell to the peanut was detectable, acquisition was reinstated. On the presentation of the peanut following that on which the monkey was allowed to eat the peanut, the response of the cell to the sight of the peanut was reinstated to the preextinction level. The spontaneous baseline rate of the units remained constant throughout the experiments.

Fig. 6. Example of a lesion (arrow) made to mark the recording site in a rhesus monkey brain of a unit which responded when the hungry monkey looked at food. Further sites are shown in (9). Hyp—hypothalamus, SI—substantia innominata, Am—amygdala, Gp—globus pallidus, Put—putamen, Ca—caudate nucleus, IC—internal capsule, OT—position of optic tract, V—ventricle.

Figure 5 shows the results of an extinction experiment performed in the rhesus monkey on a unit which decreased its firing rate when food was shown to the animal. Results comparable with those shown in Fig. 3 were obtained. Results on extinction comparable with those shown in Figs. 3 and 4 were found in the five units tested.

Location of the Recorded Units. The units described here were recorded in the lateral hypothalamus and substantia innominata. An example of a lesion made to mark a recording site is shown in Fig. 6, and further examples are shown elsewhere (9).

DISCUSSION

The experiments described here indicate that the responses of neurons in the lateral hypothalamus and substantia innominata which are associated with the sight of food in the hungry monkey are modulated by learning during the discrimination and extinction tests. The neurons only responded to the visual stimulus if the stimulus was associated with feeding. In other tests (9) it was found that these units did not respond to visual stimuli such as a squeeze bulb which the monkeys had learned was aversive and which produced arousal. It was also observed that major responses of these neurons were not found to nonfood visual stimuli for which the animal would work.

As the responses of the units occurred when the monkey subsequently ate food, the question arises of whether the responsiveness of the neurons could be accounted for by a failure to look at stimuli which the monkey had learned were not associated with food. Two types of evidence show that this was not the case. First, after extinction had occurred, the visual stimulus still approached the monkey's face from a distance of 1 m so that it was a salient visual stimulus which, it was observed, the monkeys continued to inspect. Second, in experiments performed under the same experimental conditions on units recorded in the visual inferotemporal cortex, the units continued to respond to stimuli which the monkey had learned were not associated with feeding. This finding indicates that the monkey must still have been looking at the visual stimulus after learning had occurred. Another possibility is that the neuronal responses found occurred because of altered motor responses occurring during the tests. There was certainly a good correlation between whether these neurons responded to the visual stimulus and whether the monkey subsequently accepted it. However, as noted elsewhere (9), the responses of these neurons were not clearly associated with gross movements, and in this respect are different from other neurons in the same and other brain areas recorded in the same

test situations (8, 9). Nevertheless we would not exclude the possibility that these neurons are involved in the initiation of motor behavior.

The alteration of responsiveness of the hypothalamic units described here, when a monkey learns to associate the sight of some visual stimuli with food and other visual stimuli with nonfood objects, is consistent with the view that these units are involved in the reaction of the monkeys to the food. In learning experiments in the rat it has been found that hypothalamic units alter their responsiveness to a tone while the animal learns that the tone is associated with food (4–6). In those studies on the basis of the latency and the rapidity of the effect during learning it was suggested that this modulation of responsiveness could be involved in the animal's learned reaction to the tone (5, 6). The neurons described here, in the monkey, could be involved in the rapid autonomic and endocrine responses which occur when a hungry animal sees and recognizes a food object, and/or they could be involved in the initiation and maintenance of feeding when the hungry animal recognizes food. The following evidence is consistent with all these possibilities. First, these neurons respond when the animal looks at food but not at nonfood objects, or when he tastes food, or both. Second, they respond to food only if the animal is hungry (2, 9). Third, lesions in this region produce aphagia (3, 8). Fourth, electrical stimulation in this region can lead to feeding. 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 [see (8)]. Although these points are consistent with the view that the neurons in the lateral hypothalamus and substantia innominata described here are involved in the control of 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 damage to sensory and motor pathways which are damaged by the lateral hypothalamic lesions (3, 8). Some further evidence to suggest that the neurons described here are involved in motivated behavior is that they are activated by brain-stimulation reward of some sites (1, 7, 8, 10) and that self-stimulation occurs through the microelectrode when it is in this region and may be enhanced by hunger and attenuated by satiety. In this context it is of interest that as described here these neurons respond when the monkey sees what he interprets as food objects. The experiments with brain-stimulation reward provide some evidence that these neurons are involved in the rewarding properties which food has for a hungry animal (1, 7) but confirmation of this view will depend on knowledge of the input and output connections of these cells [see (8)].

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