

Responsiveness of Monkey Preoptic Thermosensitive Neurons to Non-Thermal Emotional Stimuli

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HORI, T., T. KIYOHARA, M. SHIBATA, Y. OOMURA, H. NISHINO, S. AOU AND I. FUJITA. *Responsiveness of monkey preoptic thermosensitive neurons to non-thermal emotional stimuli*. BRAIN RES BULL 17(1) 75-82, 1986.— Responsiveness of 143 preoptic neurons to changes in hypothalamic temperature and to non-thermal emotional stimuli were investigated while rewarding (foods) and aversive objects (hypertonic saline, a toy snake, an air puffer) were given. About 71% of thermosensitive neurons and 32% of thermally insensitive neurons changed the activity when emotional stimuli were shown to and/or tasted by the monkey. Such responses were modulated by satiety/hunger state and were dependent on the degree of perturbation of emotional state. About half of the neurons tested responded when the monkey opened the mouth and protruded the tongue or moved fingers in trying to obtain foods with strong motivation, but did not when the animal made such movements less readily or reluctantly with the progress of satiation. This response was most frequently found among warm-units. The results raise a possibility that preoptic thermosensitive neurons, besides their postulated thermoregulatory functions, might be involved in the response of coordination with thermal and non-thermal emotional behaviors controlled in the hypothalamus.

Monkey thermosensitive neurons Preoptic area Emotion Thermoregulation Feeding Drinking

THE preoptic area has been demonstrated to contain thermosensitive neurons which respond to small changes in hypothalamic temperature in both homeothermic and poikilothermic animals [3, 11, 12, 21]. These neurons have been generally assumed to play a principal role in the central control of thermoregulation, based on the findings of whole body thermoregulatory responses and the corresponding responses of thermosensitive neurons during ablation, thermal stimulation and pharmacological stimulation [1,8]. Quite recently we have found that a considerable number of preoptic thermosensitive neurons recorded in freely behaving rats changed the activity consistently in association with non-thermal behaviors [15] and some neurons responding to ambient temperature in the conscious monkey altered the activity during a food-seeking operant behavior as well as a thermoregulatory operant behavior [9,10]. Since the thermoregulatory behaviors have been closely related to the affective and emotional aspects of thermal sensation [4], it is interesting to see whether non-thermal emotional stimuli may affect the activity of preoptic thermosensitive neurons. In the present study, we have investigated the responsiveness

of preoptic thermosensitive neurons in the alert monkey during presentation of non-thermal objects which may affect the emotional state.

METHOD

Experimental Animals and Operations

Two monkeys (*Macaca mulatta* and *Macaca fuscata*, 4-6 kg) were stereotaxically implanted under pentobarbital anesthesia with an acrylic plate on the skull, which restrained the head of the monkey and thus allowed chronic single neuron recording during the daily experimental sessions. In the same operation three stainless-steel re-entrant tubes (two for thermodes and one for a thermocouple) were also stereotaxically and radiographically implanted to bracket the left medial preoptic area. After a recovery period of two weeks or more, the animals were re-operated under ketamine hydrochloride anesthesia to make a stereotaxically oriented small hole (2 mm in diameter) in the skull and to incise the dura mater through which the recording electrodes were later inserted. All the operations and insertion of elec-

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TABLE 1
CHANGES IN FIRING RATE OF WARM-SENSITIVE, COLD-SENSITIVE AND THERMALLY
INSENSITIVE NEURONS IN THE MEDIAL PREOPTIC NUCLEUS OF MONKEYS DURING
PRESENTATION OF JUICE AND SALINE

	Total No. of Neurons	Firing rate Changed at least one			Total No. of responsive neurons
		Stage 1	Stage 2	Stage 3	
Warm-sensitive Neurons	28	12 (42.9%)	19 (67.9%)	11 (39.3%)	25 (89.3%)
		3	18	3	
Cold-sensitive Neurons	24	10 (41.7%)	12 (50%)	13 (54.1%)	20 (83.3%)
		8	3	8	
Thermally insensitive Neurons	91	16 (17.5%)	40 (44%)	25 (27.5%)	51 (56.0%)
		4	30	11	
Total	143	38 (26.6%)	71 (49.7%)	49 (34.2%)	96 (67.1%)
		9	57	19	

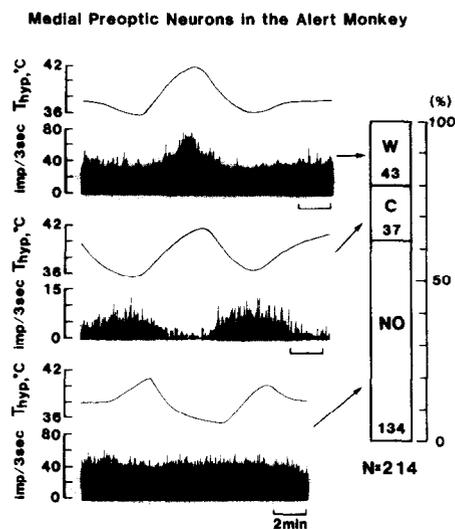


FIG. 1. Firing rate responses of a warm-sensitive neuron (upper), a cold-sensitive neuron (middle) and a thermally insensitive neuron (lower) in the medial preoptic area to changes in hypothalamic temperature (T_{hyp}). Shown on the right are numbers of warm-sensitive neurons (W), cold-sensitive neurons (C) and thermally insensitive neurons (NO) and their percentage in a total population of medial preoptic neurons.

trodes were aseptically carried out and antibiotics were administered topically and subcutaneously after each experiment.

Recording

Single neuron activity was recorded using glass-coated tungsten microelectrodes while the monkey sat in the primate chair with head restraint to provide recording stability. At the end of each electrode track, an x-ray photo of the frontal and lateral aspects of the head were taken to determine the electrode placement. All the recordings were made in the medial preoptic area and its vicinity at the co-ordinates of A 20.5–22.5, L 1.0–3.0 and H +1.5–+5.0 in the *Macaca fuscata* (the atlas of Kusama and Mabuchi) and A 15.5–17.0, L 0.5–1.5 and H +2.0–+4.0 in the *Macaca mulatta* (the atlas of Snider and Lee). The signal from the microelectrode was passed through a FET preamplifier, amplified by a conventional band-pass filtered amplifier and displayed on an oscilloscope. The single unit spikes and firing rate were also displayed on a polygraph, together with hypothalamic temperature and event marks for visual presentation of various stimuli and consumption of food. All the signals were also recorded in the magnetic tape.

Thermal Responsiveness of Neurons

After successful recording of single neuron activity was made, thermal stimulation of preoptic area was given in the range of 34–42°C by changing slowly the temperature of water which perfused through the implanted thermode tubes. The hypothalamic temperature was measured with a thermocouple inserted in the implanted tube which was in a symmetrical position to the microelectrode with respect to the thermodes. Neurons having a thermal coefficient of more than 0.7 impulses/sec°C in absolute value or a Q_{10} of more

than 2.0 were defined as thermosensitive neurons. There was no conflict between these two criteria.

Presentation of Stimuli and Analysis

After the thermal responsiveness of neurons was studied, a 'clinical' type of testing was performed at normal hypothalamic temperature (37–38°C) to allow analysis of neuronal responses to the presentation of rewarding and aversive objects. As the rewarding stimuli, various foods (juice filled in a red syringe, raisin and small ball of bread) or water in a yellow syringe were shown and then given. As the aversive objects, a toy snake, an air puffer and hypertonic (5%) saline in a white syringe (in descending order of aversiveness), were shown and then the animal received an air puff in the face or was forced to lick saline. Hypertonic saline was mildly aversive stimuli, and our monkeys licked it, though reluctantly, in 60% of trials when the saline-containing syringe was held close to the mouth. The 'neutral' objects tested were familiar and harmless laboratory objects such as paper and pencil. The firing rate of the neuron was measured in the consecutive periods according to the following protocol: (1) observation of spontaneous firing rate while the monkey was sitting quietly, (2) the experimenter reached behind the screen to take an object which was out of the animal's sight, (3) the object was introduced rapidly into the animal's field of view at a distance of about 1 m, (4) the object was gradually brought toward the animal, (5) the object was held close to the animal's mouth, (6) the animal was fed (if it was food, water or saline) or puffed on the face (if it was an air puffer), and finally (7) the object was removed out of the animal's sight. In some trials of presentation of non-liquid food, the animal was allowed to reach, pick up and eat it.

To determine to what events the neuronal activity changes are related, different procedures were used such as by extending the time for each stage described above or by changing the objects at random or by observing the response after satiation. Neurons were considered to be responsive if the average firing rate over the entire period of a particular event exceeded by more than 30% above or below the spontaneous baseline firing rates during interstimulus intervals. To ensure the results, neuronal response had to be repeated at least three times.

The strength of motivation to obtain foods or water was measured behaviorally by the monkey's willingness to work for them. At least four grades of the willingness could be detected, (1) the animal opened the mouth and protruded the tongue as soon as the objects were held close to the mouth, or (2) less readily (after a longer latency), or (3) the animal did not open the mouth voluntarily but accepted readily when the objects were placed into its mouth, or (4) the animal showed the complete rejection even when they were placed into the mouth.

RESULTS

Responsiveness of Neurons to Hypothalamic Temperature

Analyses were made in 214 neurons recorded in the medial preoptic area. Of these, 43 (20.1%) neurons were warm-sensitive neurons which increased the firing rate to a rise in hypothalamic temperature and 37 (17.3%) neurons were cold-sensitive neurons which showed the opposite type of response to temperature changes. The remaining 134 (62.6%) neurons were thermally insensitive in the range between 34 and 42°C (Fig. 1). Thermal coefficients of warm-cells ranged

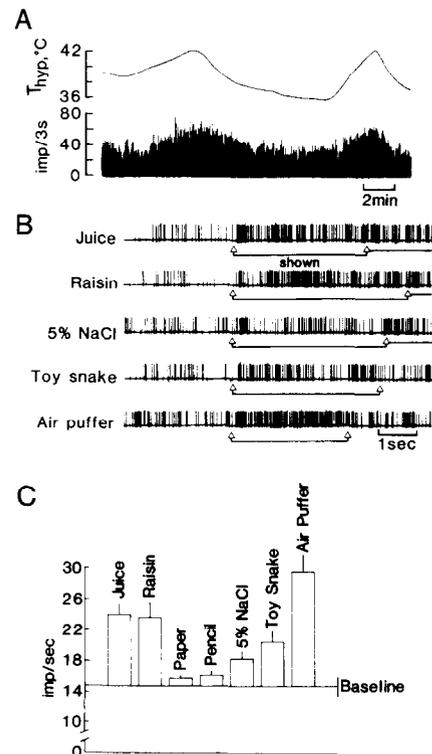


FIG. 2. Firing rate responses of a preoptic warm-sensitive neuron to changes in hypothalamic temperature (A) and to the sight of different objects (B and C, stage 1 response). Objects were shown to the monkey at a distance of 1 m from the animal (between two open triangles) and then moved gradually towards the animal's face. In C, average rate of firing when visual stimuli were given to the animal, compared with the spontaneous baseline firing rate before visual stimulation.

from 0.7 to 6.3 imp/sec°C (mean, 2.3) and those of cold-cells were in the range between -0.8 and -4.5 imp/sec°C (mean, -2.0).

Responsiveness to Non-Thermal Stimuli

Out of 143 preoptic neurons tested, 96 (67.1%) neurons changed the firing rate in at least one phase of presentation of non-thermal stimuli (Table 1). The responses were tentatively categorized into three types according to the phase in which the neuronal activity changed, i.e. (1) when the animal looked at the objects (stage 1), (2) when the objects were held close to the animal's face (stage 2) and (3) when the animal was fed with food or puffed on the face and thereafter (stage 3). Shown in Table 1 is the summarized data for non-thermal responsiveness of preoptic neurons. The occurrence of responsiveness to non-thermal stimuli was higher among thermosensitive neurons (45 of 52 neurons) than it was among thermally insensitive neurons (51 of 91) ($\chi^2(1)=13.9$, $p<0.0002$). The details of neuronal responses will be described in the following.

The Neuronal Activity During the Stages 1 and 3

The neuronal activity changed in 38 of the 143 neurons (22 of 52 thermosensitive neurons and 16 of 91 thermally insensitive neurons) when the objects were introduced into the

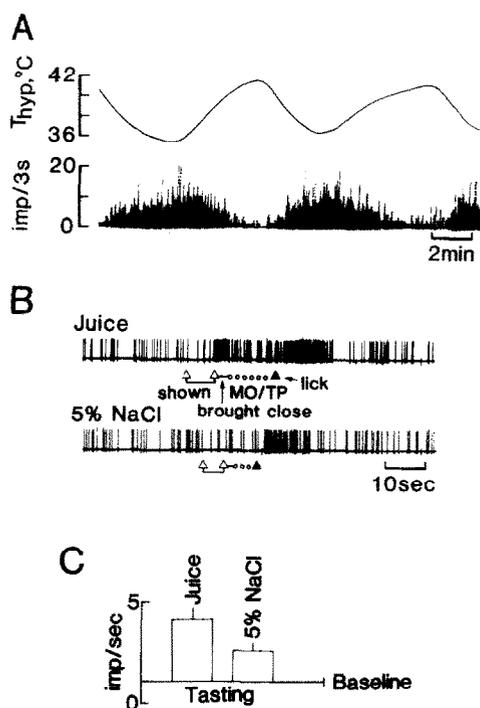


FIG. 3. Firing rate responses of a preoptic cold-sensitive neuron when juice and hypertonic saline were shown and then presented (stage 3 response) to the monkey. A, firing rate responses to changes in hypothalamic temperature. B, increases in firing rate after the animal licked juice and saline. C, average rate of firing after licking (5 trials). Juice in a red syringe or saline in a white syringe was shown at a distance of 1 m from the animal (between open triangles), brought close to the animal's mouth (between an open triangle and an open circle), then held to the animal's mouth but not touched by the animal who opened the mouth and protruded the tongue (MO/TP, a row of open circles), and licked by the animal (a filled triangle).

field of view at a distance of 1 m from the monkey and then was slowly moved toward the monkey. An example of such responses is shown in Fig. 2. The neuronal activity increased while the monkey looked at juice or saline-containing syringes with different colors, a piece of raisin, toy snake or an air puffer. The direction of changes in firing rate of this type of response to different objects was the same in all the 38 neurons tested, regardless of whether the object was rewarding (juice, raisin) or aversive (saline, toy snake, air puffer). However, the magnitude of changes in the firing rate was different among the objects presented. There was a less pronounced increase in the firing rate when saline or a toy snake was shown (Fig. 2B and C), and these were less aversive objects than an air puffer for this monkey as judged from the behaviors. Virtually no response was observed to the 'indifferent' objects such as paper or pencil which did not arouse the animal's interest significantly. The stage 1 response decreased or disappeared when the objects, whether they were rewarding or aversive, were shown at the distance of 2 m or more from the animal. In addition, the response to the sight of juice diminished after the monkey was satiated with it. These observations negate the idea that such activity of neurons is associated with simple visual stimulation or with the smell of objects or with eye movements of monkeys. Rather, the neuronal changes at the sight of objects appeared

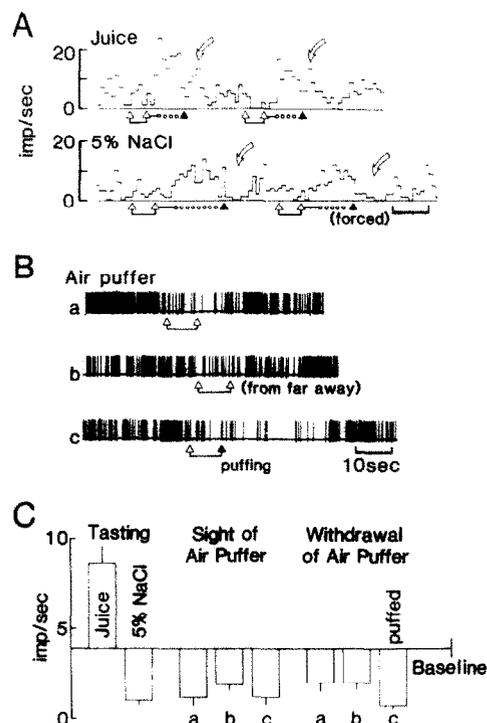


FIG. 4. Firing rate responses of a preoptic neuron to presentation of different objects (stage 3 response). Shown in A are an increase and a decrease in firing rate after licking juice and saline respectively. In addition, this neuron increased the activity when the monkey opened the mouth and protruded the tongue in trying to lick (stage 2 response). The same conventions as in Fig. 3. B shows the neuronal response when an air puffer was shown at a distance of 1 m (a and c) or 3 m (b) and then was withdrawn from the visual field (a and b) or the animal was puffed on the face (c). C shows the average rate of firing in the responses shown in A and B (4 trials each).

to be dependent upon the animal's concern about the objects presented.

Forty-nine of the 143 neurons (24 of 52 thermosensitive neurons and 25 of 91 thermally insensitive neurons) changed the activity when the monkey received foods, water or air puff (the stage 3). This stage included the period from tasting liquid or non-liquid foods to ingestion or the period from being puffed on the face to the withdrawal of the air puffer from the monkey's field of view. Eighteen of 22 neurons which responded to both juice and saline exhibited the same direction of changes in the firing rate when received both rewarding and aversive stimuli (Fig. 3). The remaining 4 neurons changed the firing rate in an opposite direction to rewarding and aversive stimuli (Fig. 4A and C). This neuron increased the firing rate after the animal's licking of juice, but decreased it after tasting with hypertonic saline. The decreased activity in this neuron was observed also when an air puffer, a more aversive object, was shown at a distance of 1 or 3 m from the monkey (Fig. 4B and C). The responses continued for 5–30 sec after the air puffer was removed out of the visual field. The magnitude and the duration of the responses when the air puffer was shown and then withdrawn depended upon the degree of perturbation of the emotional state. The greatest response with longest duration was observed after the animal was puffed (Fig. 4B-c) and the

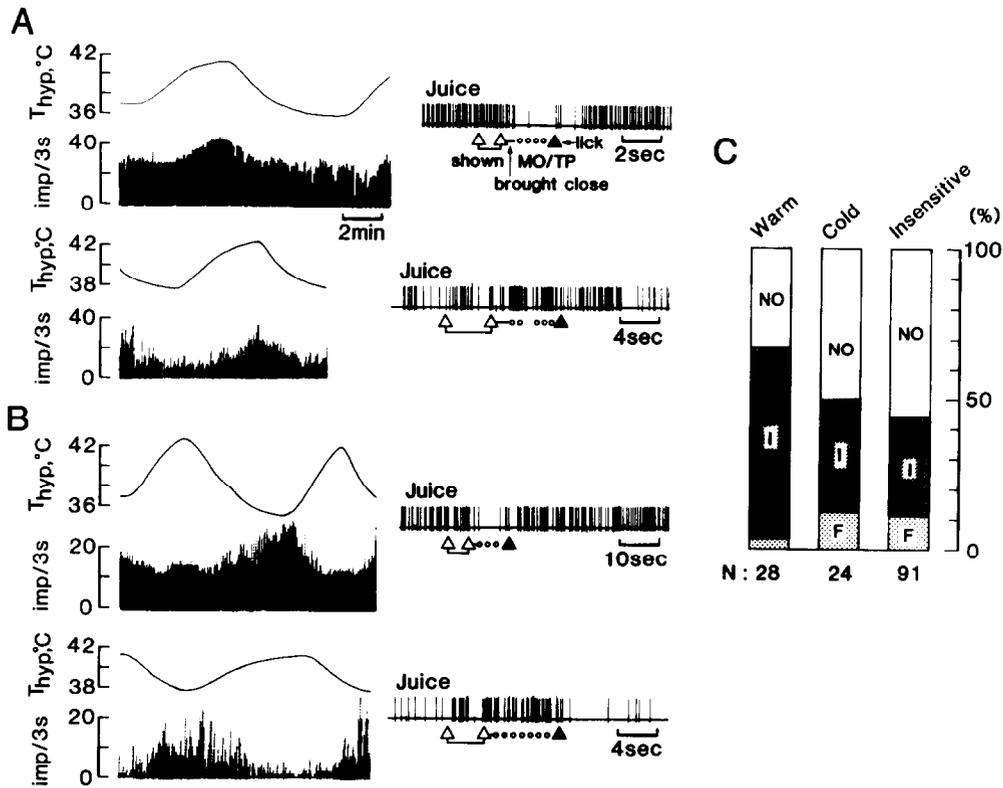


FIG. 5. The stage 2 responses of two warm-sensitive neurons (A) and two cold-sensitive neurons (B) observed when the monkey opened the mouth and protruded the tongue in trying to lick juice. The same conventions as Fig. 3. Neurons shown in upper panels of A and B decreased the activity and neurons shown in lower panels increased the activity. In C, percentage of populations of the stage 2 responses of warm-sensitive, cold-sensitive and thermally insensitive neurons. F, neurons which responded with increased firing rate. I, neurons which responded with decreased firing rate. NO, no response.

least pronounced response was found when the air puffer was shown from far away (distance 3 m) and then withdrawn without puffing (Fig. 4B-b). Eleven of 39 neurons showing the stage 3 responses exhibited the same direction of changes in firing rate to the sight of juice or saline (the stage 1 response), while five neurons showed the opposite type of response at the stage 1. Thus, the neuronal changes observed during the stages 1 and 3 seem to be associated with the degree of changes in emotional states aroused by presentation of objects. It is also noted that both stage 1 response and stage 3 response were more frequently found among thermosensitive neurons than among thermally insensitive neurons ($\chi^2=10.4, p<0.002$ for the stage 1 response; $\chi^2=5.1, p<0.05$ for the stage 3 response).

The Neuronal Responses at the Stage 2

Seventy-one (47.9%) of the 143 neurons increased (14 of 71) or decreased (57 of 71) the firing rate when the monkey took voluntary motor actions to obtain food or non-food objects (Fig. 5). This stage 2 response was not related to a specific movement, but it was observed during movement of the mouth and tongue as well as finger movements in trying to pick up the food (Fig. 6) or the non-food objects in which the animal was interested. It was not correlated with individual movements of mouth opening, tongue protrusion or

finger movements. The response was not seen when the animal opened the mouth during yawning or moved the hands without any apparent intention.

This stage 2 response was modulated by the changes in animal's motivation for taking foods. The response decreased when the animal accepted objects less readily. When a saline-containing syringe was held close to the mouth for a relatively long time, the monkey sometimes opened the mouth, though not readily, and in association with the oral movement the neuronal activity changed but less conspicuously than it did when the animal took juice or raisin (Fig. 6B). Furthermore, the response was found to decrease after satiation with objects. The effects of satiety on a warm-sensitive neuron which exhibited the stage 2 response in a thirsty monkey are shown in Fig. 7. The spontaneous firing rate at the start of the experiment was 14.8 ± 2.5 (SD) imp/sec (baseline rate). The mean firing rates of the cell during the stage 2 at the start of the experiment (trial 1) was 5.6 imp/sec and 5.2 imp/sec in the case of water and juice respectively. The response to water was gradually diminished with the repeated trials (animal drank 10 ml water in each trial), and it disappeared after the 6th trial although the animal opened the mouth and took water. After the 8th trial, the animal rejected the water and did not open the mouth voluntarily and the neuronal response was not seen although the monkey drank water which was put into mouth by the experimenter. How-

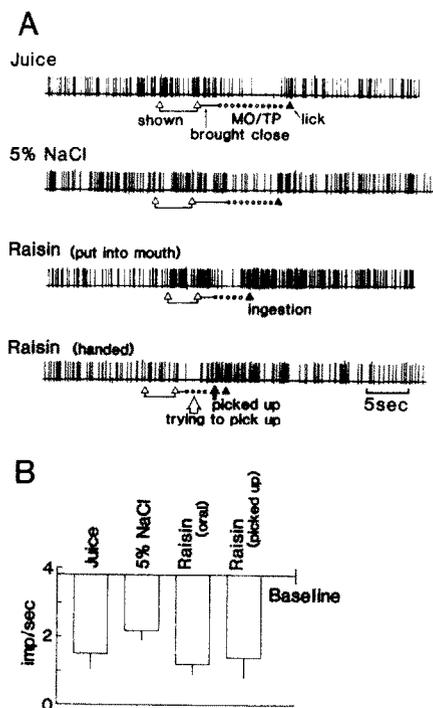


FIG. 6. The stage 2 responses of a preoptic neuron. In three upper panels of A, the neuron decreased the activity when different objects were held close to the monkey's mouth and the monkey opened the mouth and protruded the tongue in trying to lick or eat them. In the bottom panel of A, the neuron showed a similar decrease in activity when the monkey was trying to pick up a piece of raisin through a small hole on a front panel of restraint chair. B shows the average rate of firing in the response shown in A (5 trials each).

ever, the neuronal response to juice was still observed after the behavioral satiation with water was established. Thus the movement-related response occurred only when the monkey was motivated to take the objects.

Of the 71 neurons exhibiting the stage 2 response, 57 (80.3%) neurons decreased the activity and 14 (19.7%) neurons increased it. There was a higher incidence of neurons which decreased the activity at the stage 2 among warm-sensitive neurons (18 of 28, 64.3%) than among cold-sensitive neurons (9 of 24, 37.5%) and thermally insensitive neurons (30 of 91, 33.0%) ($\chi^2=8.83$, $p<0.02$, Fig. 5C). Thirty-eight of the 71 neurons showing the stage 2 response exhibited the stage 1 and/or 3 responses, like the neuron shown in Fig. 4A.

DISCUSSION

The present study has shown that (1) the preoptic thermosensitive neurons found in the alert monkey have essentially the same characteristics as those recorded in the other mammals in the anesthetized condition, and (2) the preoptic neurons, the thermosensitive neurons in particular, respond to the presentation of non-thermal emotional stimuli.

Since this is the first report on the thermosensitive neurons in the medial preoptic area in the unanesthetized monkey, it seems appropriate to compare the properties of these neurons with those of preoptic thermosensitive neurons in the other species of animals. In the present study, 20.1% and 17.3% of 214 medial preoptic neurons were

warm-sensitive and cold-sensitive respectively. Similar results have been observed in the studies on a similar number (more than 200) of preoptic neurons in anesthetized animals of non-primate species, e.g., 21.6% and 6.5% in the rat [7] and 25.0% and 13.2% in the rabbit [2], and 28.9% and 6.3% in the tissue slice of preoptic area of the rat [12]. Previous analysis of preoptic neurons in unanesthetized animals, however, have revealed somewhat different percentages of distributions; 16.9% (warm-cells) and 3.8% (cold-cells) in 53 preoptic neurons of goats [17], 43.3% and 26.6% in 30 preoptic neurons of kangaroo rats [6] and 52.3% and 23.8% in 21 neurons of ducks [25]. Due to the small numbers of neurons investigated in these reports, exact comparison of their distributions with that of the present result is not possible. As to the thermosensitivity of preoptic neurons, the present result is in agreement with those reported previously. While thermal coefficients of warm-cells and cold-cells in alert monkeys are 0.7–6.3 imp/sec°C and -0.8–4.5 imp/sec°C respectively, the corresponding values in the previous reports are 0.49–2.76 imp/sec°C and -0.29–3.72 imp/sec°C in awake kangaroo rats [6], 1.68 and -1.68 in anesthetized rabbits [13] and 1.21 ± 0.45 and -1.65 ± 1.70 in anesthetized rats [7].

The magnitude of neuronal responses observed when the monkey saw aversive and rewarding objects (the stage 1 response) and when the animal tasted food or was puffed by an air puffer (the stage 3 response) were found to be related to changes in emotional state aroused by these visual and non-visual experiences in the present study. All the stage 1 responses observed in 38 neurons and the stage 3 responses in 45 of 49 neurons were found that the neurons showed the same direction of changes to both rewarding and aversive stimuli. In this regard, the stage 1 response is not the same as the responses of lateral hypothalamic neurons to the sight of rewarding objects like foods, since such hypothalamic neurons did not show any changes to the sight of aversive objects [23]. In view of the properties of stage 1 and 3 responses, it may be inferred that these responses might reflect some general emotional 'arousal' state produced by visual and non-visual stimuli, which is not discriminatory between pleasant and unpleasant experiences. It has been demonstrated that many PO/AH neurons alter the firing rate in association with cortical EEG changes from synchronization to desynchronization and with sleep and wakefulness [6]. Histological and electrophysiological studies have revealed that PO/AH receives inputs from brainstem reticular formation [17]. Local warming and cooling of preoptic area produce synchronized and desynchronized cortical EEG patterns in anesthetized animals [5]. Thermal responsiveness of many preoptic thermosensitive neurons changes during slow wave sleep and REM sleep [6]. These observations, taken together, indicate that the stage 1 and 3 responses of preoptic neurons in the present study may reflect the changes in arousal state of animal.

The movement-related response (the stage 2 response) were observed during oral or finger movements to obtain food or non-food objects, whatever the animal was interested in. The response was not correlated with individual movements of mouth, tongue or fingers. It was dependent on the degree of animal's preference to objects and it decreased when the animal accepted the objects less readily. The responses were demonstrated to decrease progressively over the course of ingestion of water or food as satiety increased, and eventually disappeared when satiety was complete and the animal rejected it, even though the animal opened the

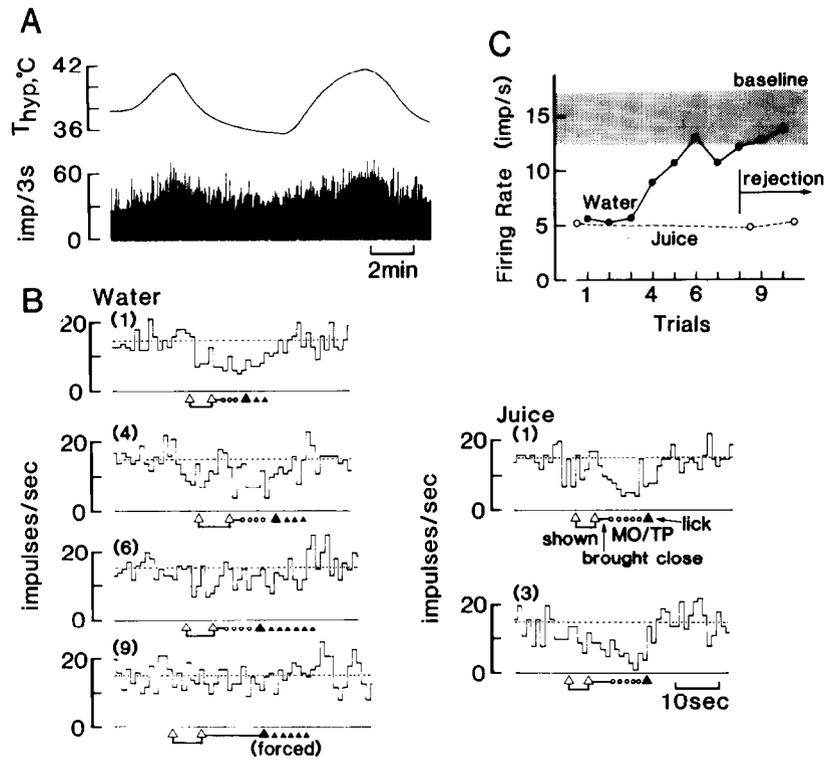


FIG. 7. Effects of satiation on the stage 2 responses of a warm-sensitive neuron. A: a response to changes in hypothalamic temperature. In B, a progressive decrease in the stage 2 response with repeated ingestions of water (10 ml in each trial) from a yellow syringe was observed, but the response to the presentation of juice from a red syringe was still observed. Numbers in parentheses indicate the numbers of trials. At the 9th trial the animal rejected water and 10 ml of water was introduced into the mouth by an experimenter. The same conventions as in Fig. 3. C: the time course of the changes in the stage 2 responses to water and juice. After 70 ml of water was taken, the animal rejected the water (from 8th trial and thereafter).

mouth, though less readily. Thus, the stage 2 response is apparently not a pure motor-coupled response, but might reflect some internal drive state to obtain the objects to which animals are concerned.

Forty-five (86.5%) of 52 thermosensitive neurons changed the activity at least one phase of non-thermal events in the present study. It is difficult to believe that preoptic thermosensitive neurons responding to non-thermal stimuli have no role in thermoregulation and only the thermosensitive neurons unresponsive to non-thermal stimuli are involved in thermoregulation, since it was demonstrated that the reduced number of preoptic thermosensitive neurons by half in the capsaicin-desensitized rat were apparently related to severe deficits of thermoregulatory ability of these animals [7,8]. There are several examples showing responsiveness of preoptic thermosensitive neurons to non-thermal stimuli, such as noxious stimuli to skin [14] and changes in blood pressure [16] in anesthetized rats and such as local changes in osmolality [20] and glucose [24] in rat's hypothalamic slices. Preoptic thermosensitive neurons have been shown to change the activity during different non-thermal behaviors such as feeding, drinking, grooming and exploratory behavior in the rat [15] and a bar-pressing food-seeking behavior in the monkey [9]. Occurrence of such non-thermal responsiveness of preoptic neurons in these studies were again

higher among thermosensitive neurons than they were among thermally insensitive neurons. The overlapping of thermal and osmotic sensitivity has been found also in the neurons of supraoptic and paraventricular nuclei [18]. The overlapping of sensitivity to different classes of stimuli in hypothalamic neurons described above would suggest that these 'multimodal' neurons may have some roles in interactions between different control systems such as thermoregulation, osmoregulation and food intake/energy balance, all of which involved some emotional processes leading to appropriate goal-directed behaviors. It has been recognized that non-thermal emotional stimuli influence thermoregulation. For example, thermal sweating on non-palmar general body skin in men decreases transiently during mental arithmetic and increases in response to pain, noise and other emotional stimuli [22]. Inhibition of ongoing thermoregulation occurs in conscious rabbits during sustained arousal which was evoked by stimulation of hypothalamic 'defense' area and by intraventricular injection of noradrenaline [26]. The present results on the high incidence of non-thermal responsiveness of preoptic thermosensitive neurons suggest that such neurons, besides their postulated thermoregulatory functions, may be involved in the process of coordination with thermal and non-thermal emotional behaviors as well as autonomic responses controlled in the hypothalamus.

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