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EFFECTS OF BIOGENIC AMINES ON CENTRAL THERMO-RESPONSIVE NEURONES IN THE RABBIT

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SUMMARY

1. Single unit activities were recorded with five-barrelled micropipettes from the thermo-responsive neurones in the preoptic area and the mid-brain reticular formation in urethanized rabbits. 5-hydroxytryptamine (5-HT), noradrenaline (NA) and acetylcholine (ACh) were applied micro-iontophoretically to the immediate vicinity of the recording cells.

2. Out of seventeen warm-responsive neurones recorded in the preoptic area, fifteen neurones responded to 5-HT with the increase in firing rate and two showed no response. Thirteen out of seventeen warm-units decreased their firing rate in response to application of NA and four were not affected. ACh had no effect on any of the warm-units examined.

3. Six out of seven cold-units in the preoptic area were depressed by 5-HT, while NA excited five of six units studied. None of the cold-units were influenced by ACh.

4. These results are in good agreement with the changes in rectal temperature produced by 5-HT and NA micro-injected into the hypothalamus in rabbits.

5. In the mid-brain reticular formation, 5-HT excited all of fourteen cold-responsive neurones. Of these, eight cold-units were depressed and six were unaffected by NA, while ACh excited six units and had no effect on eight units. All of the five warm-responsive units were inhibited by 5-HT and none were influenced by NA. Thus, the responses of reticular thermo-responsive neurones to 5-HT and NA were opposite to those of the preoptic thermo-responsive neurones.

INTRODUCTION

Based on the changes in rectal temperature produced by noradrenaline (NA) and 5-hydroxytryptamine (5-HT) when injected into the cerebral ventricles and hypothalamus, Feldberg & Myers (1963, 1964, 1965) suggested that the body temperature regulation may be mediated by controlled release of endogenous monoamines. Although there is much supporting evidence for this hypothesis (Feldberg, 1970; Myers & Beleslin, 1971), a species difference exists in the body temperature responses to injected amines. In studies in cats (Feldberg & Myers, 1963), dogs and monkeys (Feldberg, Hellon & Lotti, 1967; Myers & Yaksh, 1969), 5-HT raised the body temperature whereas NA lowered the body temperature. On the other hand, in rabbits (Cooper, Cranston & Honour, 1965) and sheep (Bligh, 1966), NA produced the hyperthermia and 5-HT hypothermia. In addition, cholinergic influences on the central mechanism of thermoregulation have been suggested in the rat and the monkey (Beckman & Carlisle, 1969; Lomax, Foster & Kirkpatrick, 1969; Myers & Yaksh, 1969). These observations raise the question as to whether the amines and acetylcholine (ACh) produce thermoregulatory responses by the actions on the thermo-responsive neurones in the preoptic area and anterior hypothalamus. These temperature changes could be due to secondary actions of administered drugs at the neuronal structures which are not specific to thermoregulation, or to haemodynamic changes in the brain (Hassler & McCook, 1971). Therefore, we conducted a direct, micropharmacological investigation of the effects of these substances on the hypothalamic thermo-responsive neurones in the rabbit.

The mid-brain reticular formation in the rabbit has been reported to contain many cold-responsive neurones with high negative thermal coefficients (Nakayama & Hardy, 1969), but their physiological role in the central control of thermoregulation is as yet unknown. The microiontophoretic study was also conducted on the thermo-responsive neurones in the mid-brain to see the functional differences between various types of central thermo-responsive cells.

METHODS

Preparation. Forty-three rabbits weighing 2·5–3·5 kg were used in this study. Animals were anaesthetized with urethane at a dose of 1·2 g/kg given I.P. Urethane was chosen as the anaesthetic because it has been suggested that it does not interfere with the activities of hypothalamic thermoregulatory structures significantly (Magoun, Harrison, Brobeck & Ranson, 1938). Following anaesthesia, the animal was placed on a stereotaxic instrument with the head fixed according to Sawyer's stereotaxic co-ordinate system (Sawyer, Everett & Green, 1954). Conductive heating and cooling of the hypothalamus were made by means of a water-perfused thermode

system (Nakayama, Hammel, Hardy & Eisenman, 1963). A tubular thermode was implanted 2 mm lateral from the mid line at the rostral co-ordinate of 3 mm (A3) and to the depth of 15 mm from the surface of the skull. In the experiments on the mid-brain reticular formation, a thermode was similarly placed 1·5 mm lateral, at the caudal co-ordinate of 7 mm (P7) and to the depth of 16 mm. Micro-electrode explorations were made in the preoptic area and the mid-brain reticular formation on the opposite side of the brain to that containing the thermode. The local brain temperature was recorded by a thermistor probe placed in a contralateral position symmetrical to that of micro-electrode with respect to the thermode. Rectal temperature was monitored continuously with a thermistor thermometer and kept between 37 and 39 °C by intermittent radiation from an infra-red lamp.

Micropipettes. Five-barrelled micropipettes were prepared by a method similar to that described by Bradley, Dhawan & Wolstencroft (1966). Extracellular recordings were made through the central barrel filled with 4 M-NaCl. The second barrel contained 1 M-NaCl solution and was used to test the possible effects of current flow on the activity of neurones. In the experiments at the later stage of this study, a 'neutralizing current' (i.e. of equal magnitude and opposite polarity) was passed through this barrel to eliminate the current effects during the application of a test substance (Bloom, Oliver & Salmoiraghi, 1963). The remaining barrels were filled with three of the following drugs in aqueous solution: 0·5 M noradrenaline bitartrate, 0·05 M 5-hydroxytryptamine creatinine sulphate, 1–2 M acetylcholine chloride and 2 M monosodium L-glutamate. Glutamate was used for the activation of silent cells, although the data presented here were obtained from the studies of spontaneously active neurones. The pH of all drug solutions was between 4 and 8. Glutamate was expelled iontophoretically as anion, while all other drugs were ejected as cations (i.e. the electrode positive). The current applied was less than 100 nA, usually between 10 and 40. Retaining currents of 10–15 nA were applied to each drug barrel to minimize the spontaneous diffusion of substances out of the pipettes (Bradley & Candy, 1970).

Recording. The recording barrel was connected to a solid-state preamplifier leading to an oscilloscope and an audiomonitor. Action potentials were fed into the level discriminator and converted into pulses of standard size and duration. The pulses were then fed into a linear counting device built into a data processing computer (Nihonkohden, ATAC-401) and set to recycle every second. The counter output, together with the local brain temperature and the amount of the current applied to the neurones, were displayed continuously on an ink-writing oscillograph. In some of the experiments, action potentials were recorded in the FM tape recorder (TEAC R-351F) for further analysis of the data after the experiments. The micro-electrodes explored the preoptic area between the optic chiasma and the base of the anterior commissure within 1 mm of the mid line. The mid-brain was explored in the reticular formation at the level of P7, 1·0–2·0 mm lateral from the mid line and just dorsal of the red nucleus. The locations of the cells were estimated from the scale on the micromanipulator and not verified histologically. After the successful isolation of a spontaneously active cell, its thermal responsiveness was examined by changing the local brain temperature slowly over a range usually between 34 and 41° C. In some cases, the brain temperature could not be raised above 39° C because of some technical difficulties involved in the thermode system. Then, the pharmacological studies were performed while the hypothalamic temperature was clamped at a fixed point between 37 and 39° C. To ensure the results, thermal and chemical responsiveness of the cells were examined at least twice. Long intervals were allowed between each application of drugs, since the repeated application of 5-HT and NA at short interval sometimes resulted in a desensitization of the cells to the compounds. Neurones giving ambiguous responses to a drug application were classified as unresponsive to that substance.

Terminology. The terms 'thermo-sensitive neurones' or 'temperature-sensitive neurones' have been generally used to describe the neurones which respond to small changes in local brain temperature (Nakayama *et al.* 1963; Hardy, Hellon & Sutherland, 1964; Cunningham, Stolwijk, Murakami & Hardy, 1967; Wit & Wang, 1968; Eisenman, 1969). These terms do not necessarily mean that the neurones are directly sensitive to temperature. These neurones could be interneurones which receive temperature signals synaptically from thermo-sensors. Eisenman & Jackson (1967) suggested one way of making the distinction between these two types of cells. The criteria they used were the slope and the shape of thermal response curve of the unit, reaction to barbiturates and localization of the neurone. These criteria are reasonable enough to identify the interneurones, provided the temperature of a neurone under study is accurately estimated. However, the criteria may provide no direct evidences for the inherent thermo-sensitivity of the neurones. In the present study, not all the units were examined by applying the above criteria. Therefore, it would be appropriate to use the term 'thermo-responsive neurones' rather than 'thermo-sensitive neurones'.

RESULTS

Preoptic neurones

Investigations were made on a total of eighty-one preoptic neurones which showed the spontaneous and stable activities for periods long enough to allow the thermal and pharmacological studies. Of these, nineteen units were found to be warm-responsive, showing an increase in firing rate with elevation of local brain temperature. Seven units were cold-responsive and showed the opposite type of response to temperature changes. The remaining fifty-five neurones were thermally unresponsive within the range of 34–41° C. Pharmacological examinations were sometimes omitted for temperature-unresponsive neurones to facilitate the work, since the procedures for testing chemical and thermal responsiveness were time consuming. Such cells were not included in the data presented here. If they were included, about 20% of the preoptic neurones responded to temperature changes, as reported previously (Nakayama *et al.* 1963).

Temperature-unresponsive neurones. The data on the pharmacological responsiveness of the temperature-unresponsive neurones in the preoptic region are summarized in Table 1. There is no uniformity in responses to different substances among the individual neurones studied. Out of fifty-four neurones, forty units responded to iontophoretic application of 5-HT. NA accelerated or reduced the firing rate of twenty-nine of fifty-one units tested. On the other hand, ACh-sensitive neurones were only eleven (25%) of forty-four neurones examined. If the results obtained from the thermo-responsive neurones are added to these data, the proportion of ACh-sensitive neurones becomes much lower (16·7%). A report from another laboratory showed that ACh- and NA-sensitive cells were more frequently observed than 5-HT-sensitive cells in the hypothalamus (Bloom *et al.* 1963). This difference is probably due to the location of the neurones

recorded. In the present study, the micro-electrode explorations were strictly confined within the region of preoptic area, while the results of Bloom *et al.* (1963) were obtained from a random sample of neurones in the entire hypothalamus. The pharmacological responses of temperature-unresponsive neurones were not affected by the changes in local brain temperature within the range of 34 and 40° C.

TABLE 1. Responses of preoptic neurones to 5-HT, NA and ACh. Not all cells were tested on all three compounds. ↑, increase in firing rate. ↓, decrease in firing rate. No, no change in firing rate. n.t., not tested. n.l., the number of 'non-linear' units. Number in parentheses is the total number of cells studied

Thermally unresponsive neurones (55)

	↑	↓	no
5-HT (54)	8	32	14
NA (51)	14	15	22
ACh (44)	10	1	33

Warm-responsive neurones (19)

No. of units	5-HT	NA	ACh	Remarks
8	↑	↓	No	Fig. 1; 1 (n.l.)
1	↑	↓	n.t.	—
2	↑	n.t.	No	1 (n.l.)
2	↑	No	No	—
2	↑	No	n.t.	1 (n.l.)
2	No	↓	No	—
2	n.t.	↓	No	—

Cold-responsive neurones (7)

4	↓	↑	No	Fig. 2
1	↓	n.t.	No	—
1	↓	No	n.t.	—
1	No	↑	No	—

Warm-responsive neurones. A total of nineteen warm-responsive neurones were investigated. They increased the firing rate in response to an increase in local brain temperature. Of these, sixteen units responded to temperatures linearly at least within the range of 35 and 39° C. The temperature responsiveness of sixteen units varied from 10·0 to 1·9 impulses/sec °C, with a mean value of 4·4. The average firing rate of the warm-units at 37° C was 12·4 impulses/sec. These features of the cells are in fair agreement with the results on warm-responsive neurones previously reported (Nakayama *et al.* 1963; Hardy *et al.* 1964; Cunningham *et al.* 1967; Hellon, 1967). The remaining three units showed linear thermal responses between the temperatures of 35 and 38° C. But the firing rates of the units did not change when the temperatures exceeded 38° C. The temperature

responsiveness of three units over the 'linear' portion were 1·3, 1·8 and 2·3 impulses/sec ° C, respectively.

Shown in Fig. 1 are the thermal and drug responses of a preoptic warm-responsive neurone. This unit showed a linear thermal response over the range of 35–39° C. While the hypothalamic temperature was clamped at 36·0° C, 5-HT was ejected with a current of 18 nA (Fig. 1*B*). After a latency of about 10 sec, the unit gradually increased its rate of firing, which reached a peak 24 sec after the beginning of the application. After the drug application was terminated, the increased rate of firing persisted for about 15 sec and then slowly subsided to the control level. In contrast,

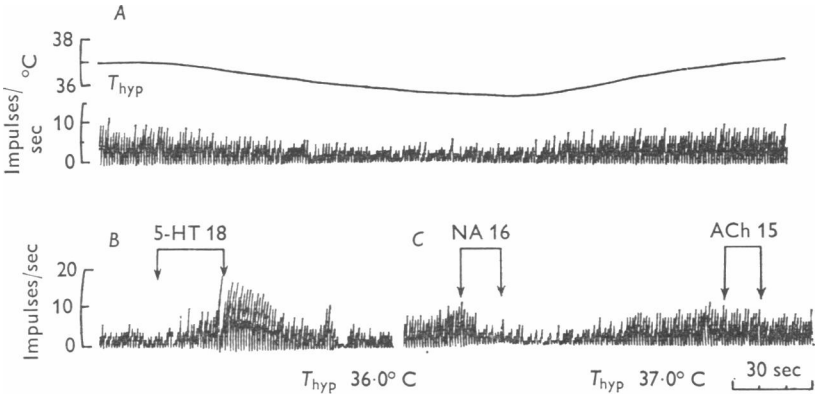

Fig. 1. The electrical activity of a preoptic warm-responsive neurone. The continuous records of firing rate (impulses/sec) are shown in this and all subsequent Figures. The drugs were applied iontophoretically between the arrows. The numbers accompanying the names of drugs are the ejecting current in nA. The drug was applied at the brain temperature indicated in each record. *A*, the response to local hypothalamic temperature (T_{hyp}). *B*, excitation by 5-HT application while keeping the hypothalamic temperature at 36·0° C. *C*, depression by NA and no response to ACh at T_{hyp} of 37·0° C.

NA slowed the firing rate of this neurone and ACh had no effect at hypothalamic temperature of 37·0° C (Fig. 1*C*). The effects of the amines and ACh were essentially unaffected by the level of hypothalamic temperatures within the range of 35–39° C. At lower temperatures some of the neurones took longer to return to the previous rate of firing after the withdrawal of the compounds. All the results for warm-responsive neurones are summarized in Table 1. Out of seventeen warm-units tested, 5-HT excited fifteen units and had no effect on two units which were depressed by NA. NA reduced the firing rate of thirteen units and four units were not affected. None of the warm-units were insensitive to both 5-HT and NA. They responded to at least one of the two amines. Nine units responded

to both of 5-HT and NA, as shown in Fig. 1. No differences in thermal responses were found between the nine cells which responded to both of the amines and six cells which were unresponsive to one of the amines. Three 'non-linear' units responded to 5-HT with increased rate of firing. NA were applied to two of them and depressed one unit and had no effect on another. ACh were without effect on any of sixteen warm-responsive neurones tested.

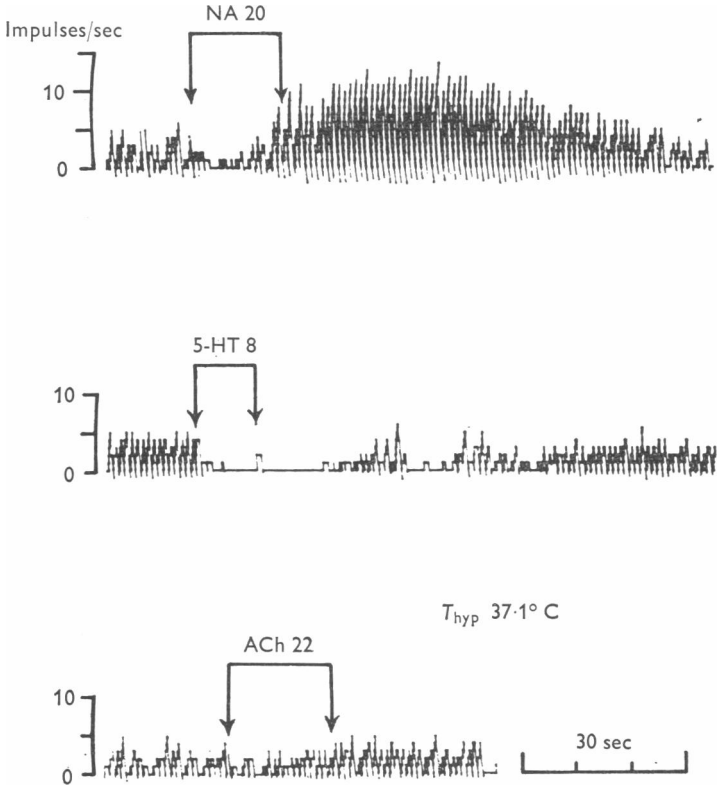

Fig. 2. The electrical activity of a preoptic cold-responsive neurone. Excitation by NA (top), depression by 5-HT (middle) and no response to ACh (bottom). Slight inhibitory effects of anodal current during the application of drugs are observed in the records. Note the prolonged effects of NA and 5-HT.

Cold-responsive neurones. Since cold-responsive neurones are found less frequently in the preoptic region, only seven such neurones were subjected to pharmacological study. Thermal responses of these units were similar to those of cold-units reported previously (Hardy *et al.* 1964; Cunningham *et al.* 1967). They showed an increase in firing rate with the decrease in local brain temperature. The temperature responsiveness of seven cold-

responsive units varied from −0·6 to −4·4 impulses/sec ° C with a mean value of −2·0. Generally, the responses of the cold-units to the amines were quite opposite to those of the warm-units (Table 1). Six of seven units were depressed by 5-HT and four of six 5-HT-sensitive units were excited by NA, as shown in Fig. 2 (middle and top). One unit was not influenced by 5-HT, but was excited by NA. Out of six cold-units examined, NA excited five units and had no effect on one unit which was depressed by 5-HT. ACh had no effect on six cold-units examined (Fig. 2, bottom).

TABLE 2. Responses of mid-brain neurones to 5-HT, NA and ACh. Mech. stim., the number of neurones which responded to mechanical stimulation of the body surface. Symbols the same as Table 1

Thermally unresponsive neurones (32)

	↑	↓	No
5-HT (32)	2	8	22
NA (32)	5	6	21
ACh (31)	6	4	21

Cold-responsive neurones (14)

No. of units	5-HT	NA	ACh	Mech. stim.	Remarks
4	↑	↓	↑	3, Yes	Fig. 3
4	↑	↓	No	1, Yes	—
4	↑	No	No	3, Yes	—
2	↑	No	↑	1, Yes	Fig. 4

Warm-responsive neurones (5)

4	↓	No	No	None	Fig. 5
1	↓	No	↓	None	—

Mid-brain neurones

Fifty-one units in the mid-brain reticular formation were studied for their thermal and pharmacological responsiveness. Of these, fourteen units were cold-responsive and five were warm-responsive. Results of all the reticular neurones are presented in Table 2.

Cold-responsive neurones. Fourteen reticular neurones responded to mid-brain cooling with an increase in firing rate. A linear relationship was found between the firing rate of the neurones and the decrease in temperature over a range of 33–39° C. They showed little adaptation of firing to the local temperature at the steady state. The temperature responsiveness of these units varied from −8·9 to −1·2 impulses/sec ° C with a mean of −3·9. This figure is comparable to the positive value obtained for preoptic warm-units. These results on mid-brain cold-units are quite similar to the observation reported previously (Nakayama & Hardy, 1969). In the present

experiments, eight of these mid-brain neurones were influenced by mechanical stimulation given to a large area of the body surface, as shown by arrows in Figs. 3*B* and 4*D*. A summary of the results is presented in Table 2. All the fourteen units were excited by iontophoretic application of 5-HT, as shown in Figs. 3*B* and 4*C*. On the other hand, NA depressed eight cold-units (Fig. 3*C*) and had no effect on the remaining six units (Fig. 4*D*).

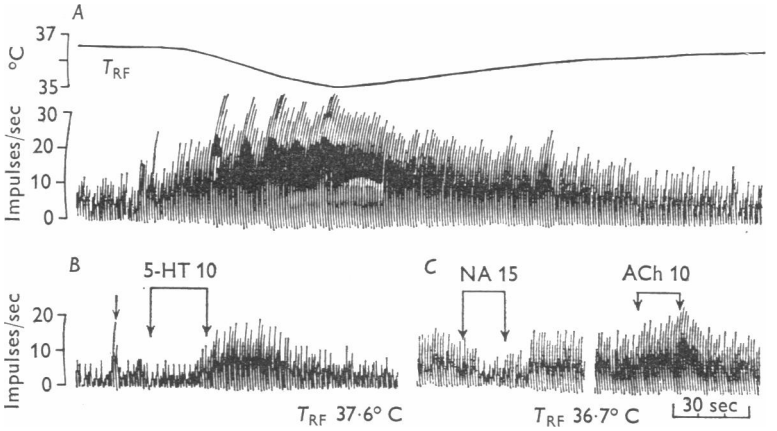

Fig. 3. The electrical activity of a cold-responsive neurone in the mid-brain reticular formation. *A*, the response to changes in mid-brain temperature (T_{RF}). *B*, excitation by 5-HT at T_{RF} of 37·6° C. *C*, depression by NA and excitation by ACh at T_{RF} of 36·7° C. This neurone responded to an air blow on the fur of the back, as indicated by an arrow in *B*. Note the rapid onset of effect of ACh and delayed and prolonged effects of 5-HT and NA in this figure and Fig. 4.

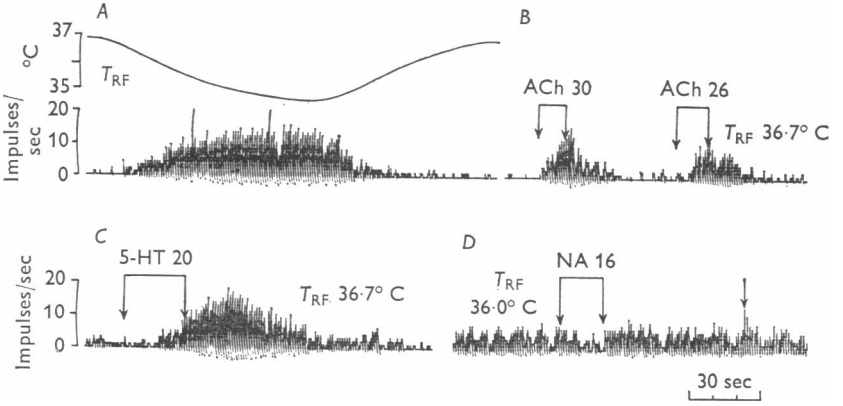

Fig. 4. The electrical activity of a cold-responsive neurone in the mid-brain reticular formation. *A*, the response to changes in mid-brain temperature. *B*, excitation by ACh. *C*, excitation by 5-HT. *D*, no response to NA. This unit was driven by mechanical stimulation given to the body surface, as shown by an arrow in *D*.

ACh excited six units (Fig. 4*B*) and was ineffective on eight units. During the period of depression by NA, the mechanical stimulation usually could activate the units. No consistent difference was found in pharmacological responses between the mechanically responsive and unresponsive neurones.

Warm-responsive neurones. In contrast to the preoptic region, the warm-responsive neurones are less frequently encountered in the mid-brain reticular formation. Five units were recorded in this study. The average thermal responsiveness of the units was 3·2 impulses/sec. ° C. All five warm-responsive units were depressed by 5-HT but were not affected by NA (Fig. 5*B* and *C*). ACh depressed one warm-unit, but had no effect on four units. These five neurones were not influenced by mechanical stimulation, but the presence of mechano-responsive warm-units had been reported (Nakayama & Hardy, 1969).

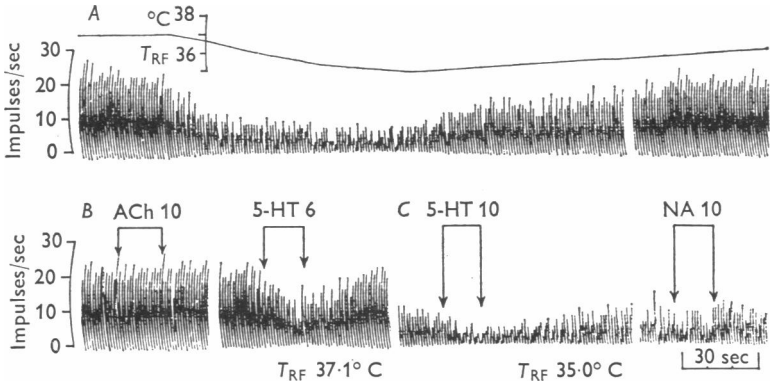

Fig. 5. The electrical activity of a warm-responsive neurone in the mid-brain reticular formation. *A*, the response to mid-brain temperature. The record of firing rate is interrupted during the time required for clearing the memory buffer of on-line data processing computer. *B*, no response to ACh and depression by 5-HT at T_{RF} of 37·1° C. *C*, 5-HT also depressed the firing rate when tested at 35·0° C. NA had no effect.

DISCUSSION

The present study showed that 5-HT accelerated the firing rate of warm-responsive neurones and depressed the activities of cold-responsive neurones in the preoptic area of rabbit. Micro-injection of 5-HT into this region would thus be expected to activate heat loss mechanism and depress heat production, resulting in hypothermia as shown by Cooper *et al.* (1965). Noradrenaline, on the contrary, depressed the preoptic warm-responsive neurones and excited the cold-responsive neurones. These actions of NA would be expected to cause hyperthermia, which was also demonstrated by the micro-injection experiments (Cooper *et al.* 1965). Thus, the thermo-

regulatory responses produced by microinjected amines are explained, at least in part, by their direct actions on the thermo-responsive neurones in the preoptic region. ACh, when injected together with eserine into the anterior hypothalamus in the rabbit, had no effect on body temperature (Cooper *et al.* 1965). This finding is also in agreement with the unresponsiveness of preoptic thermo-responsive neurones to ACh observed in the present study.

Cunningham *et al.* (1967) showed that preoptic warm-responsive neurones in the dog were depressed by 5-HT and epinephrine administered intraventricularly. The results are consistent with the rise in body temperature produced by the micro-injection of 5-HT, but not the effect of catecholamines (Feldberg *et al.* 1967). Using the technique of micro-iontophoresis, Beckman & Eisenman (1970) demonstrated that the warm-responsive neurones in the hypothalamus in rat and cat which were considered to be thermodetectors were relatively insensitive to 5-HT, NA and ACh, but thermo-responsive neurones of both animals which were considered to be interneurones responded to ACh and NA. The responses of presumed interneurones in the rat may explain the results of micro-injection experiments of ACh and NA, but not of 5-HT (Feldberg & Lotti, 1967; Beckman & Carlisle, 1969; Beckman, 1970). Furthermore, the responses of interneurones in the cat conflict with the results of injection experiments (Feldberg & Myers, 1965). The discrepancy between the results of Beckman & Eisenman and our own is not readily explained. We could not find any hypothalamic thermo-responsive neurones which were unresponsive to both 5-HT and NA. All the thermo-responsive neurones in the preoptic area responded to at least one of the two amines, usually to both in the definite directions.

The thermo-responsive neurones in the mid-brain reticular formation of the rabbit were extensively studied by Nakayama & Hardy (1969). By changing the local preoptic and mid-brain temperatures independently, they showed that none of the mid-brain thermo-responsive neurones was influenced by changes in preoptic temperature. The mid-brain cold-cells were highly responsive to a fall in local temperature, comparable in responsiveness to preoptic warm-cells. An increase in oxygen consumption was observed in unanaesthetized rabbits during the cooling of mid-brain while the preoptic temperature was kept constant (Hardy, 1969). In the mid-brain, 5-HT depressed the warm-units and excited the cold-units, while NA depressed half of the cold units and had no effect on warm units. The responses of mid-brain thermo-responsive neurones to the amines are thus almost opposite to those of preoptic neurones (Table 3). These results indicate that to be responsive to temperature and to be influenced by monoamines are two independent functions of the neurones.

In contrast to the effects of monoamines, the action of pyrogens has

been shown to be same on the preoptic and the mid-brain thermo-responsive neurones, i.e. depression of warm-responsive neurones and facilitation of cold-responsive neurones (Cabanac, Stolwijk & Hardy, 1968; Wit & Wang, 1968; Eisenman, 1969; Nakayama & Hori, 1973) (Table 3). Micro-injections of leucocyte pyrogen into the anterior hypothalamus and the mid-brain induced fever in the rabbit (Rosendorff & Mooney, 1971). If the pyrogen-induced fevers are produced by the changes in the activities of central thermo-responsive neurones, the discrepancy between the actions of monoamines and pyrogens on thermo-responsive neurones provides evidence against the idea that pyrogens act through the release of the monoamines.

TABLE 3. Effects of amines and pyrogen on the central thermo-responsive neurones in the rabbit

	Preoptic neurones		Mid-brain neurones	
	Warm	Cold	Warm	Cold
5-HT	↑	↓	↓	↑
NA	↓	↑	No	↓, No
Pyrogen	↓	↑	↓	↑

Both 5-HT and NA and their enzymes for synthesis and break-down are present in large amounts in the hypothalamus (Vogt, 1954; Bogdanski, Weissbach & Udenfriend, 1957; Udenfriend & Creveling, 1959). Histochemical studies have shown that 5-HT and NA are present in the nerve terminals in the preoptic area and hypothalamus (Fuxe, 1965). The state of activity of monoamine nerve terminals in rat was histochemically demonstrated to change when the animal was exposed to hot and cold environments (Corrodi, Fuxe & Hökfelt, 1967). Thermoregulatory responses were induced in rabbits by changing the level of endogenous catecholamines (Cranston, Hellon, Luff & Rawlins, 1972) as well as by micro-injections of exogenous monoamines. In the monkey, 5-HT release at the preoptic area increased when the animal was placed in the cold environment (Myers & Beleslin, 1971). If the findings in the rat and the monkey may be extended to the rabbit, these observations, together with 5-HT- and NA-sensitivities of preoptic thermo-responsive neurones, support the idea that the hypothalamic monoamines may have some role in the central mechanism of thermoregulation, presumably by modulating the activity of preoptic thermo-responsive neurones. Since the monoamine-containing nerve fibres emanate mainly from the brain stem (Dahlström & Fuxe, 1964), some neural influences from the brain stem may be exerted on hypothalamic neurones relating to thermoregulation. In this connexion, it is interesting to

consider the role of thermo-responsive neurones in the mid-brain reticular formation, but at present no experimental data is available for speculation on this question.

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