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SPECIFIC RESPONSES OF RAT RAPHÉ NEURONES TO SKIN TEMPERATURE

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SUMMARY

1. The responses of single neurones in the nuclei raphés magnus, medianus, dorsalis and pontis to changes in skin temperature were recorded in rats anaesthetized with urethane. Skin temperature was altered by means of a water-perfused jacket.

2. Of 210 neurones studied, thirty-five were specifically excited by warming the skin whilst twenty were cold responsive. The greatest proportion of cells responding to skin temperature were in the nucleus raphé magnus, whilst few neurones in the raphé dorsalis and pontis were influenced.

3. The warm units had peak activity at a mean skin temperature of 37·7 °C whilst the cold cells had a corresponding maximal rate at 29·0 °C. Mechanical and noxious peripheral stimulation, blood pressure changes and temperatures other than that of skin did not affect the neurones.

4. The neurones influenced by skin temperature were histologically verified as being within the raphé system.

5. LSD inhibited all neurones tested, indicating that the cells were serotonergic.

6. The responses to skin temperature were unchanged in rats with mid-collicular sections suggesting an ascending thermal system.

7. The results suggest that any involvement of 5-HT in central thermoregulation is in terms of an afferent thermal pathway mediated by serotonergic raphé neurones.

INTRODUCTION

In a series of papers beginning in 1963, Feldberg & Myers proposed that the integrity of hypothalamic thermoregulation is dependent on the balanced release of two monoamines, noradrenaline (NA) and 5-hydroxytryptamine (5-HT) (Feldberg & Myers, 1963, 1964). NA acts to lower

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body temperature, whilst 5-HT has an opposite effect, although conflicting results have been obtained in other studies (Hellon, 1974). This monoamine hypothesis provided no suggestions as to the mechanisms governing release of the monoamines. The rationale behind this paper was to investigate the possibility that 5-HT containing brain stem neurones in the raphé nuclei may form a link between the skin thermoreceptors and the hypothalamus. Hence the effects of 5-HT on thermoregulation may be mediated by terminal release of the monoamine following activation of the raphé cell bodies by skin temperature changes.

The widespread system of serotonergic fibres and terminals in the C.N.S. has been shown to originate from the cell bodies in the raphé nuclei of the brain stem (Dahlström & Fuxe, 1964). Detailed mapping of the raphé projections followed development of the fluorescence technique (Fuxe, 1965), and autoradiographic and histological techniques have verified these pathways (Conrad, Leonard & Pfaff, 1974). Amongst the extensive raphé projections is an input to terminals in the preoptic area of the anterior hypothalamus (PO/AH) (Fuxe, 1965), an area vital to the central control of body temperature.

In the present experiments the nucleus predominantly studied was the nucleus raphé (n.r.) magnus as this is the only raphé nucleus described to receive an input from the spinal cord (Brodal, Walberg & Taber, 1960). The spinal afferents run in the ventrolateral quadrant of the cord, the funiculus in which skin thermal afferents are known to ascend. This suggests a possible input to the raphé from peripheral thermoreceptors, hence the responses of single units in the n.r. magnus and also the n.r. medianus, dorsalis and pontis to changes in skin temperature were investigated.

D-lysergic acid diethylamide (LSD) was used to identify the neurones as serotonergic. The responses of units to other sensory modalities and to temperatures other than that of the skin were monitored to investigate the specificity of the response. Mid-collicular decerebrate rats were used in some experiments to abolish possible forebrain inputs to the raphé cells.

A preliminary account of this work has been communicated to the Physiological Society (Dickenson, 1976).

METHODS

Preparation of the animal

Male Sprague–Dawley rats weighing between 250 and 300 g were used in all the experiments. The rats were anaesthetized with urethane (I.P.) at a dose of 1·5 $g.kg^{-1}$ body weight, sufficient to induce areflexia. A tracheal cannula was inserted. The rat was placed in a headholder with a 15° angle between the incisor bar and the ear bar so as to bring the brain stem into a horizontal plane (Palkovits & Jacobowitz, 1974).

In preliminary experiments the stereotaxic co-ordinates for the raphé nuclei were determined. After exposure of the skull, a burr hole was made just posterior to the lambda for recording from the n.r. dorsalis and n.r. medianus, on the junction of the interparietal and occipital bones for the n.r. magnus and intermediate between the two for recording for the n.r. pontis. The dura mater was retracted and in some cases the atlanto-occipital membrane was cut to allow drainage of c.s.f. The decerebrate animals were prepared with an additional craniotomy extending the width of the skull just posterior to the superior sagittal sinus. A stiff wire loop was inserted between the colliculi to section the brain stem. The decerebrate animals were still under urethane anaesthesia, as the purpose of the decerebration was to section the brain, not to prepare an unanaesthetized animal. In some experiments blood pressure was measured by a transducer after cannulation of the right carotid artery.

Skin temperature control

The rat was shaved and enclosed in a specially constructed close-fitting water-perfused jacket. Only the head and tail were external to the jacket. The jacket was perfused with water mixed from two baths, maintained at 9 and 55 °C. Skin temperature could be changed at rates of up to 5 °C min^{-1}. The jacket was provided with a single inlet manifold with twelve outlets connected by thin-walled tubing to a corresponding outlet manifold. The twelve lengths of connecting tubing were sewn in a zig-zag fashion over the inner surface of the jacket. Mean skin temperature was monitored by means of eight copper–constantan thermocouples arranged in parallel and affixed to the body of the rat by means of a bead of cyano-acrylic glue. Deep body temperature (rectal) was maintained between 36 and 38 °C by manipulation of the jacket temperature. A thermistor was implanted into the raphé in some experiments to monitor brain stem temperatures.

Recording and specificity of response

Metal-filled electrodes (Dowben & Rose, 1953) were used on occasions but predominantly pontamine blue dye filled electrodes were used enabling recording sites to be marked. Tip sizes were typically 1–3 μm in diameter.

The electrode was zeroed in the vertical and horizontal planes with reference to the ear bar and the rat moved in relation to the electrode to obtain the correct co-ordinate using a stereotaxic carriage (Lister & Woodget, 1972). The co-ordinates were accurate to 10 μm. The mid line on which the raphé nuclei lie was gauged from the course of the sagittal suture. Action potentials were amplified, displayed on an oscilloscope and counted over 5 or 10 sec intervals by a spike discriminator. Each discriminated action potential was also heard as an audio pulse. The counter output was displayed on a pen recorder as was deep body temperature, brain stem temperature or blood pressure. Skin temperature was displayed on a potentiometric recorder. All measurements were also recorded in parallel on magnetic tape for later analysis. Electrode penetrations were made at mean skin temperatures of 30 or 37 °C to facilitate finding cold or warm responsive units. Once a neurone had been tentatively characterized as being within the raphé from the stereotaxic co-ordinates and its slow regular firing rate (Aghajanian, Foote & Sheard, 1970) the cell was tested by changing skin temperature in a cyclic manner. When a raphé unit did respond to skin temperature the cell was tested over several temperature cycles to confirm the reproducibility of the response.

Stability of the recording site allowed cells to be held for 45–60 min. After the series of skin temperature changes the neurones were tested for responses to other modalities. The skin of the rat was mechanically stimulated by light stroking with a

brush and noxious stimulation was applied by a strong pinch with a pair of forceps. A 4 cm^2 brass plate, either hot or cold, was used to thermally stimulate small defined areas of the trunk. Some units were tested for the effect of I.V. or I.P. LSD on firing rate. LSD reversibly inhibits serotonergic raphé cells at low concentrations (Aghajanian *et al.* 1970). Incremental doses were used to utilise the minimum concentration of LSD. Skin temperature tests were continued following the injection. To avoid residual drug effects no further cells were tested after administration of LSD.

Analysis of data

The output of the spike counter was summed over 5 or 10 sec epochs and displayed on a chart recorder. Temperatures were displayed on the other channel of the recorder. Temperatures at appropriate intervals were plotted against the firing rate of the neurone over the epoch corresponding to the particular temperature. The means of the firing rates were calculated for the increments in temperature.

Inter-spike interval histograms were constructed for some neurones both in spontaneous and thermally stimulated states. These histograms were made on a histogram analyser (Lewin, 1972). A thousand action potentials were fed in from the tape recorder for each histogram. The intervals were sorted into bins (10 msec wide) and were displayed on an oscilloscope screen against the number of intervals in each bin.

Anatomical correlates

The site of neurones were marked as already described. The brain stem was removed and fixed in 3% formalin and then formalin-sucrose. Transverse sections, 30 μm thick, were cut on the freezing microtome and relevant sections were stained with Pyronin Y or haematoxylin–eosin. The position of the dye marks were plotted on representative sections of the rat brain.

RESULTS

Recordings were made from 210 neurones in the nuclei raphés magnus, medianus, dorsalis and pontis. The recordings were from single units and were adjudged to be from perikarya rather than from nerve fibres or terminals. The cells exhibited a biphasic wide action potential with a low amplitude, typically 100 μV.

In all four nuclei two populations of neurones responding to skin temperature could be characterized. One population of thirty-five warm responsive cells was excited by increased skin temperature whilst a second population of twenty cold responsive cells was activated by decreasing skin temperature. Table 1 lists the numbers of cells responding in each of the nuclei. There were marked differences in the proportions of cells influenced by skin temperature. Out of ninety-two cells in the n.r. magnus forty responded to skin temperature changes, whereas nine out of fifty-two of n.r. medianus units and only four out of fifty-eight cells in the n.r. dorsalis were influenced. The thermal response characteristics of cells in all nuclei, however, were essentially identical and so will be discussed in terms of a general raphé response.

Specificity of modality

Blood pressure and heart rate remained constant over a skin temperature range greater than the operating range of the cells. Hence the raphé responses are not due to cardiovascular effects. Mechanical stimulation of the skin applied by light stroking with a brush and noxious pinching were without effect on the activity of the units. Heating and cooling the tail or scrotum were insufficient to drive the cells as was thermal stimulation of 4 cm^2 areas of skin on the trunk.

TABLE 1. Showing the numbers of warm and cold units responding to skin temperature in each of the four raphé nuclei studied

Nucleus	Total cells	Warm	Cold
N.r. magnus	92	25	15
N.r. medianus	52	6	3
N.r. dorsalis	58	3	1
N.r. pontis	8	1	1

Neuronal characteristics

Spontaneous rates

Cells in the n.r. dorsalis and medianus are known to have typical slow regular spontaneous rates (Aghajanian *et al.* 1970). From this study, it is clear that all raphé units have similar rates as neurones in the n.r. magnus and pontis have firing rates between 0·5 and 4 impulses sec^{-1} when not thermally stimulated. Units in the n.r. magnus tended to be in the upper end of this range. Interval histograms show a regularity of rate and a shift in the mode when a cell was thermally stimulated (Fig. 1). Cells subsequently found to be lateral to the mid line or between the raphé (Fig. 9) had fast irregular rates and showed no response to skin temperature changes.

Responses to changes in skin temperature

No cell responded to both heating and cooling the skin. Fig. 2 illustrates the response of a unit in the n.r. magnus to heating the skin. As the skin was warmed the unit activity gradually increased from 0·5 spike sec^{-1} to a maximal rate of 2–2·5 spikes sec^{-1}. The increase in activity of the unit followed the changes in skin temperature. In the lower half of the Fig. (2*B*) the non-linearity of the relationship between firing rate and mean skin temperature is shown. This unit had a low thermally evoked firing rate.

Once the optimum temperature for the peak firing rate of these cells had been reached further heating of the skin caused a diminition of activity (Fig. 3). The regular firing rate at a constant skin temperature of 37·5 °C

is decreased markedly following a step increase of skin temperature to 39 °C. Cooling of the skin followed by a warming cycle lead to a re-establishment of the original response. This re-establishment and the regular rate at a fixed skin temperature indicate that the falling-off in activity is due only to the increased temperature and not fatigue or loss of the cell.

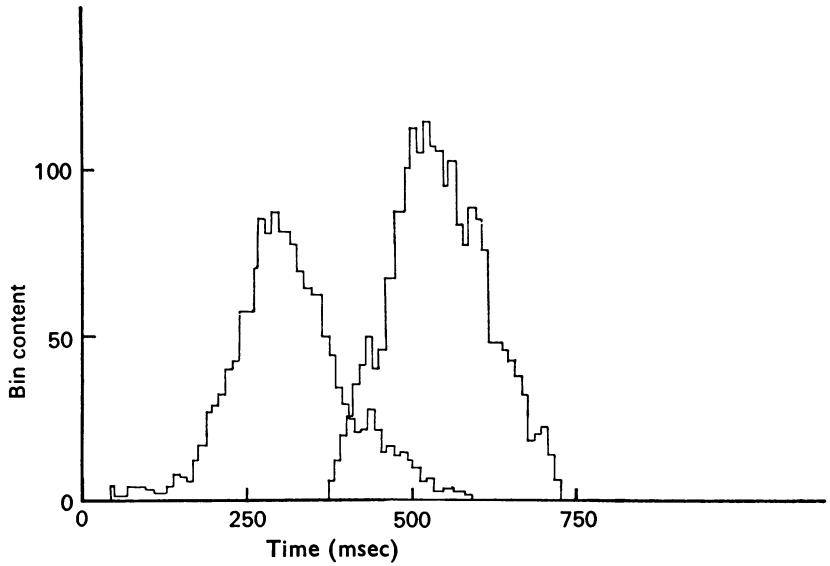

Fig. 1. Histograms of the intervals between successive spikes for a warm responsive neurone in the n.r. magnus. 10 msec bins were used. The vertical scale expresses the number of intervals in each bin. The right histogram is derived from intervals obtained whilst skin temperature was at 32 °C. The modal interval was 550 msec. The left histogram shows the mode of 300 msec with a skin temperature of 36 °C.

The response of a raphé unit excited by cooling the skin is illustrated in Fig. 4. The unit had a slow rate of 1 spike sec^{-1} with mean skin temperatures above 33 °C. Decreasing skin temperature below this level lead to a gradual increase in the activity of the neurone. Further cooling below the optimum temperature for these cells resulted in decreased activity similar to the decline shown by the warm responsive population.

Fig. 5 shows the relationship between mean skin temperature and neuronal activity for both populations of raphé units responsive to skin temperature. The figure contains all cells that were tested over three or more temperature cycles. Both populations of raphé cells had minimal firing rates of about 1 spike sec^{-1}. Maximal activity was also similar for both groups and at their respective peak skin temperatures the neuronal activity was 5–6 spikes sec^{-1}. The peak mean skin temperature for the

warm responsive population of cells was $37{\cdot}7 \pm 0{\cdot}3$ °C whereas the cold population had maximal rates at a mean skin temperature of $29{\cdot}0 \pm 0{\cdot}5$ °C. The falling-off of the firing rate following thermal stimulation past the peak temperatures is evident from the Figure.

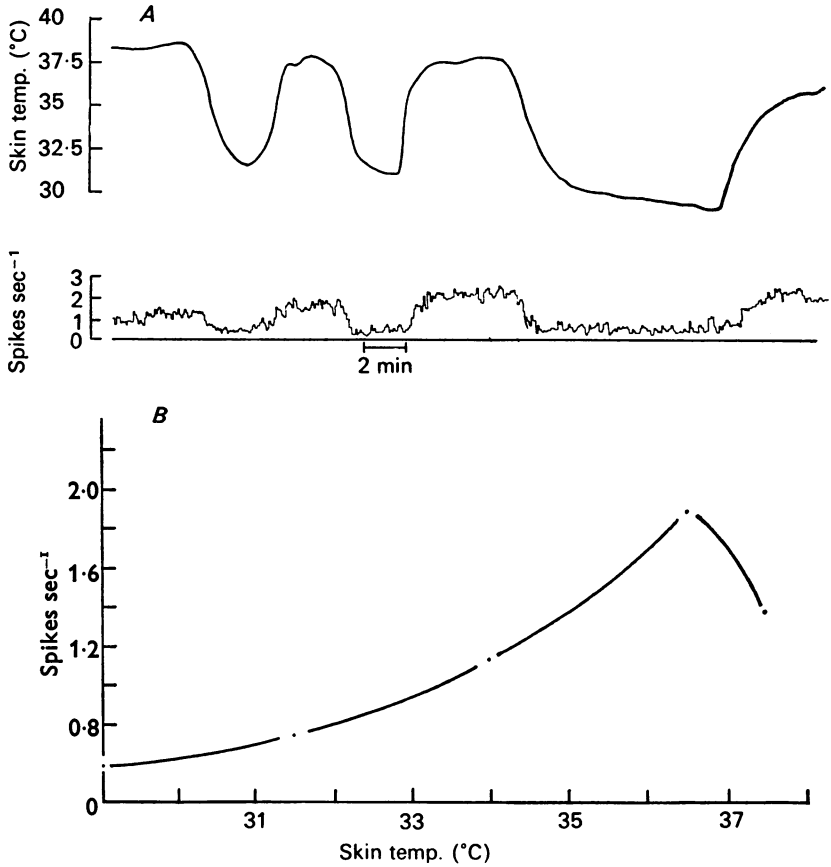

Fig. 2. *A*, warm responsive neurone in the n.r. magnus. The upper curve indicates mean skin temperature; the lower trace is the neuronal activity counted over 5 sec periods and expressed as spikes sec^{-1}. *B*, relation between mean skin temperature and activity (5 sec counting period) for the above neurone.

Specificity of response

Temperature

The neurones responsive to temperature were solely influenced by skin temperature. The unit activity was not affected or modulated by differing levels of deep body temperature as indicated by rectal temperature (Fig. 6). The neurone illustrated has an activity curve following the changes in

skin temperature. The activity-skin temperature relationship is the same when the body temperature is at 36·5 or 38·3 °C, both in terms of rate of firing and shape of the curve. Under the experimental conditions the brain stem temperature was independent of the level of skin temperature and so the neuronal responses are unlikely to have been evoked by local brain-temperature changes.

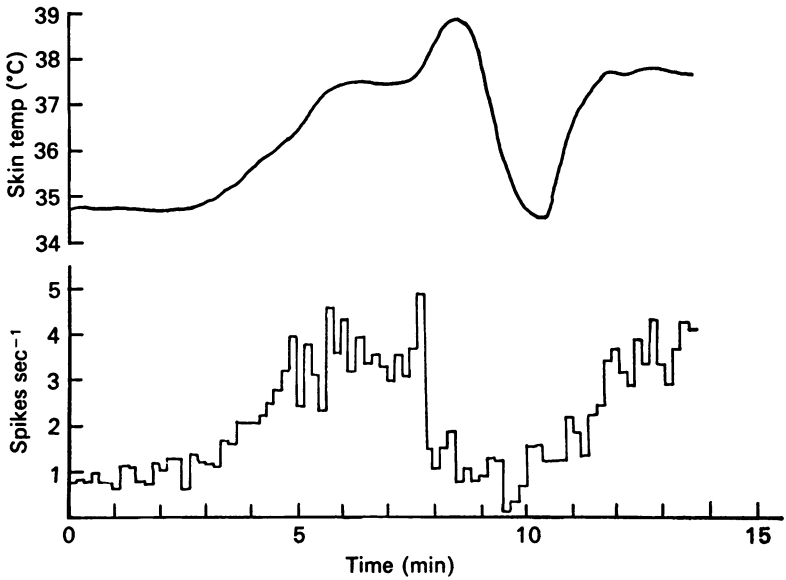

Fig. 3. The activity of a warm responsive neurone in the n.r. medianus to continued heating of the skin above the peak temperature for the unit. Curves as in Fig. 2 except for a 10 sec counting period. Heating the skin above 37·5 °C causes a fall-off in firing rate of the neurone. Cooling followed by re-heating the skin led to a re-establishment of the original response.

Pharmacology

I.V. and I.P. injections of D-lysergic acid diethylamide (LSD) in the dose range 10–70 $\mu g.kg^{-1}$ body weight inhibited the fourteen temperature responsive neurones tested. An example of the effect of LSD on a warm responsive unit is illustrated in Fig. 7. LSD (12 $\mu g.kg^{-1}$) injected I.V. at the start of a warming phase blocked the thermally evoked activity almost completely with a 30 sec latency. The spontaneous rate of the cell was also inhibited. The inhibition of firing lasted 15–17 min and after recovery the responses of the unit to skin temperature were unchanged. Thus LSD reversibly inhibited the spontaneous and temperature activated firing of the neurone. For all cells the latency of inhibition was 0·5–5 min, the longer periods following intraperitoneal injection. Eight warm

responsive units and six cold responsive units in the n.r. magnus, medianus and dorsalis were tested with LSD and gave similar results. Three thermally insensitive cells in the raphé were tested and also inhibited.

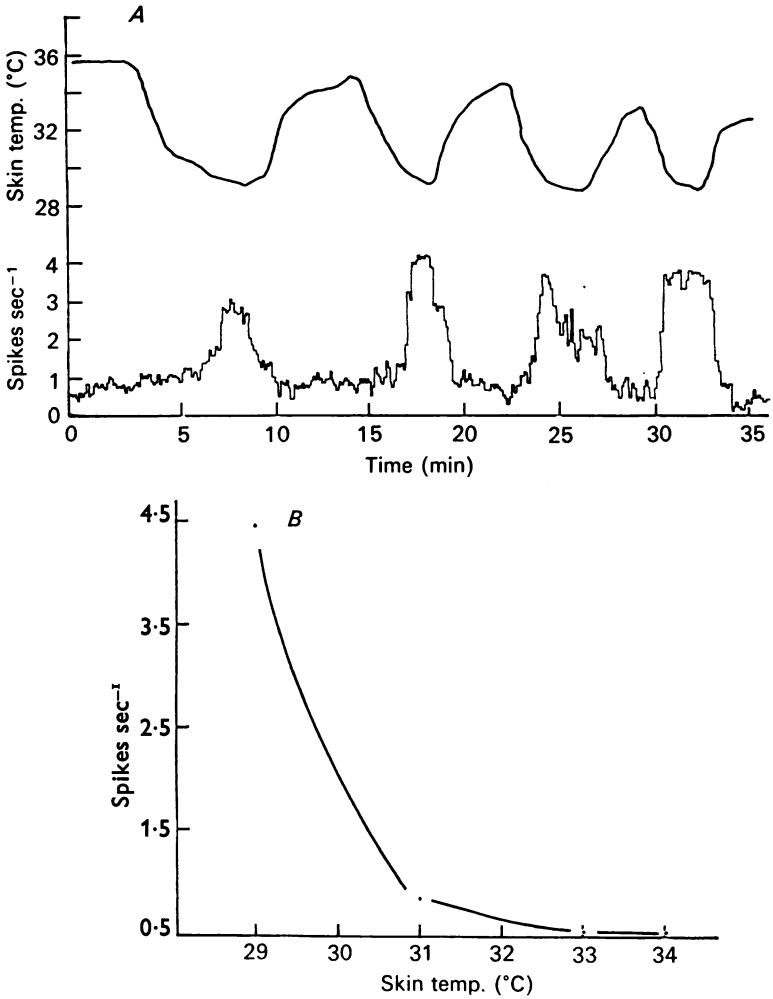

Fig. 4. *A*, cold responsive neurone in the n.r. magnus. Curves as in Fig. 2 but with a 10 sec counting period. *B*, relation between mean skin temperature and activity for this neurone. Curves as in Fig. 2*B*.

Anatomy

Of the 210 cells in this study, ninety-seven recording sites were marked and seventy-eight were subsequently recovered in histological sections. The blue dye mark and the four raphé nuclei could be visualized in the stained sections and hence the position of the cells in relation to the raphé

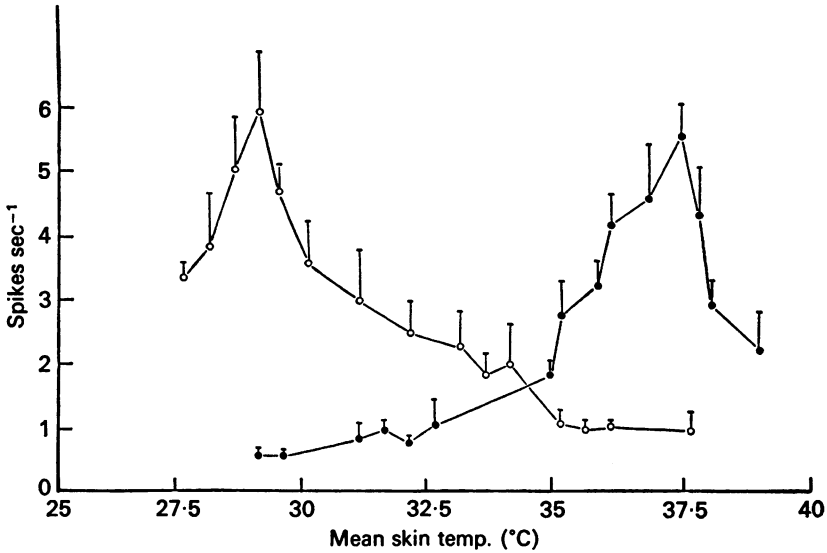

Fig. 5. Relation between activity and temperature for forty-two neurones tested over three or more temperature cycles. Activity over 10 sec period corresponding to 0·5 °C temperature increments for each cell. The open circles represent cold responsive cells, the filled circles warm responsive neurones. $n = 25$ for the warm population and $n = 17$ for the cold units. The vertical bars represent S.E. of the means.

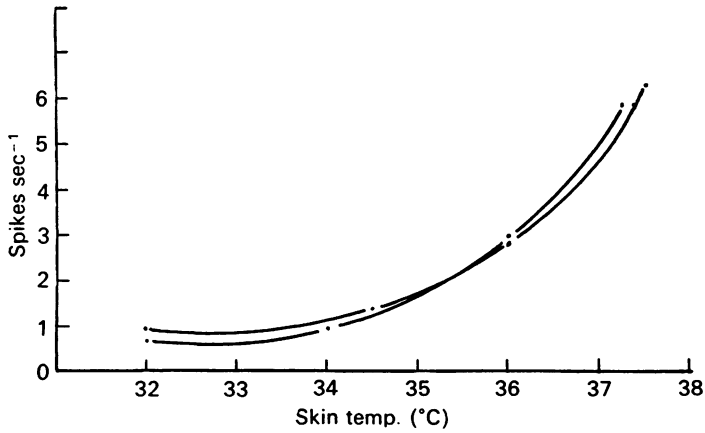

Fig. 6. The lack of modulation of the neuronal response to skin temperature by differing levels of body temperature. The temperature–activity curve for a warm responsive cell in the n.r. dorsalis. The neurone was tested over three skin temperature cycles with the body temperature at 36·5 ± 0·2 °C and then tested over two further cycles with a body temperature of 38·3 ± 0·3 °C.

could be plotted. The positions of the temperature responsive neurones in the vicinity of the raphé nuclei are shown in Fig. 8. All the neurones responsive to skin temperature were clustered within a particular raphé nucleus. There was no obvious separation of the warm, cold and non-temperature sensitive neurones in the nuclei. The insensitive sites were both within and surrounding the raphé nuclei.

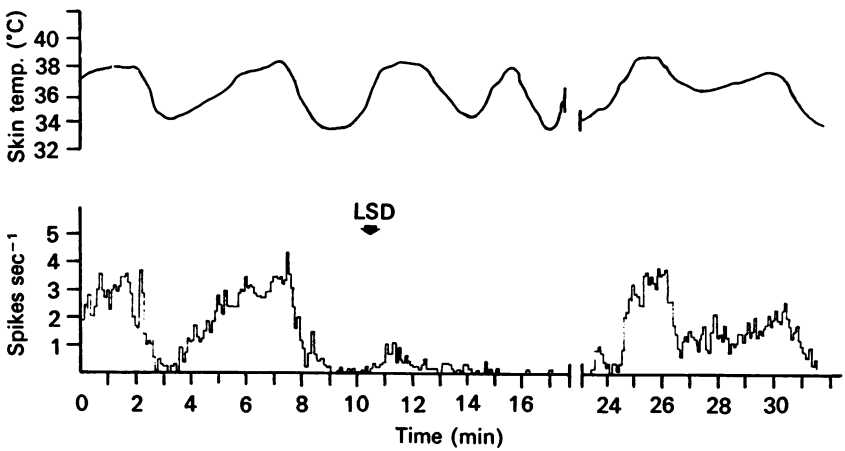

Fig. 7. The reversible inhibition of n.r. magnus neurone by D-LSD. Curves as in Fig. 2. Note the break in the curve and change in time scale. LSD (12 $\mu g.kg^{-1}$ I.V.) reversibly inhibited the spontaneous and thermally evoked activity of the neurone.

Decerebrate animals

The responses of neurones in the n.r. magnus to changes in skin temperature were also studied in decerebrate animals with mid-collicular sections. Because of the proximity of the section to the rostral raphé nuclei only neurones in the magnus were tested in these preparations. Six warm responsive neurones and three cold responsive cells were recorded. The responses to skin temperature changes were identical to those in intact animals in terms of thresholds, spontaneous and evoked rates and temperature responses (Fig. 9). The extent of the decerebration was checked histologically and results from animals with incomplete sections were discarded.

DISCUSSION

The ideas on which these experiments were based have been largely verified. I have found that the activity of a significant proportion of neurones in the raphé nuclei, particularly the n.r. magnus, can be specifically related to the skin temperature of the rat. The specificity of the

relation can be considered to be physiological, pharmacological and anatomical.

The peripheral thermal stimulation could be applied at various brain and deep body temperatures and on no occasion did the reported cells

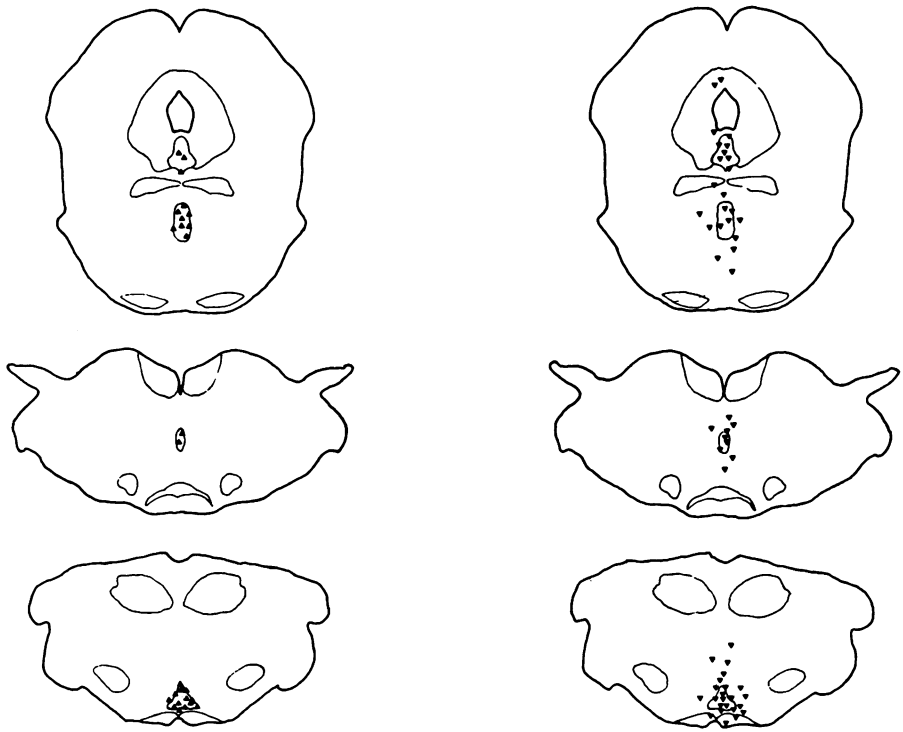

Fig. 8. Positions of marked neurones in transverse sections of the mid brain and brain stem in the same plane as the electrode penetration. The triangles in the three sections on the left show the positions of neurones that responded to skin temperature. These are clustered in the four raphé nuclei. The inverted triangles in the sections on the right mark the neurones that did not respond to skin temperature.

respond to or were affected by temperature other than that of the skin. The lack of mechanical or noxious input to the cells further substantiates the specificity of the response. Peripheral temperature changes may affect blood pressure or heart rate. In this study these cardiovascular parameters were uninfluenced by skin temperature changes which caused maximal firing of the raphé cells. Hence the neuronal response is not due to perturbations in blood pressure and heart rate.

The neurones reported here were all located within the raphé nuclei implying a specific raphé system responsive to skin temperature. The

greater number of temperature units in the caudal n.r. magnus presumably reflects the spinal afferent input to this nucleus (Brodal *et al.* 1960). The n.r. dorsalis and n.r. pontis have very few units responding to skin temperature and their role in the ascending pathway would seem to be

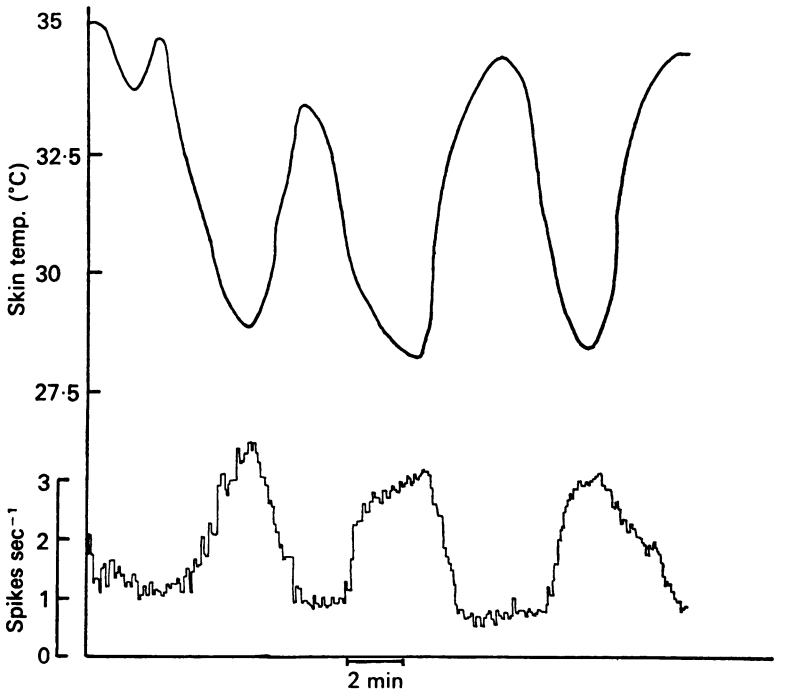

Fig. 9. A cold responsive neurone in the n.r. magnus of a rat with a mid-collicular section. Curves as in Fig. 2. The response to skin temperature is identical to that of neurones in intact rats.

minor. The number of cells responding in the n.r. medianus suggests either a relay to this nucleus from the n.r. magnus or perhaps a parallel input from the cord.

It was possible that the raphé responses were not activated by an ascending afferent pathway from the peripheral thermoreceptors but by descending forebrain impulses, perhaps an output from the PO/AH thermoregulatory centre. The lack of influence of decerebration on temperature responsive units in the n.r. magnus rules out this possibility and confirms the idea of an ascending thermal pathway.

Although the cells of origin of 5-HT in the C.N.S. are contained within the raphé not all raphé neurones are serotonergic. Aghajanian & Haigler (1974) have shown that LSD in low doses inhibits only 5-HT containing raphé cells or raphé cells with a 5-HT mediated input. There is no effect

on post-synaptic projection areas. The inhibition by LSD of all raphé temperature responsive cells tested strongly suggests a raphé serotonergic neuronal pool influenced only by skin thermal stimuli.

The activity–temperature relationship for the cold responsive raphé cells is similar to that of the cold skin thermoreceptors. Cutaneous cold receptors have maximum static activity between 26 and 30 °C (Hensel, 1973), which agrees with the optimal temperature for the raphé cold units of 29 °C. However, the warm receptors in the skin are most active at 40–45 °C whereas the warm responsive raphé neurones are maximally excited at 37·7 °C and show a fall off in rate above this temperature. This discrepancy is not readily explicable. The raphé neurones exhibited only static responses but the slow rates of change of skin temperature would preclude dynamic effects (Molinari & Kenshalo, 1976). The lack of a small defined receptive field for the raphé thermal neurones suggests a large degree of convergence as the actual skin receptors have point-like receptive fields. The convergence of thermal inputs from scrotal receptors has been demonstrated in the dorsal horn, thalamus and sensory cortex of the rat (Hellon & Mitchell, 1975).

There are several previous studies regarding raphé neuronal responses to temperature but none of these have included the n.r. magnus, the only raphé nucleus with a direct spinal input (Brodal *et al.* 1960). Neurones in the n.r. dorsalis and n.r. medianus have been reported which respond to local brain stem temperature changes in the cat (Cronin & Baker, 1976) and rat (Hori & Harada, 1976). The neurones I have reported did not respond to local temperature but this was not used as a direct stimulus. Eleven units, again in the n.r. dorsalis and medianus, were found to increase firing when body temperature was raised (Weiss & Aghajanian, 1971). External heating was used to change body temperature and so the responses might have been due to skin temperature changes. I have found no raphé units which responded to, or were influenced by body temperature. This negative finding has been reported by others (Bramwell, 1974; Trulson & Jacobs, 1976) and also in the only other investigation of raphé cells and skin temperature (Jahns, 1976). Jahns recorded from neurones in the n.r. dorsalis and n.r. medianus of the rat whilst changing scrotal skin temperature. He found a much greater number of warm than cold responsive units, and a paucity of temperature units in the n.r. dorsalis. These findings are in general agreement with the results reported here. Although the units were within the raphé, Jahns did not identify them as serotonergic and some had fast rates, uncharacteristic of raphé neurones. The neurones responded to increasing scrotal temperature up to 38 °C in a similar fashion to those I have reported, but above this temperature Jahns reported periodicities in the cell's firing whereas the units I have

recorded showed a fall-off in firing at 38 °C. These periodicities may be due to noxious inputs from the scrotal skin or the response may not be elicited from less specialized skin areas such as on the trunk.

The existence of serotonergic raphé cells responding to skin temperature does not imply a causal relationship between this neuronal system and thermoregulation. However, the specificity of the response and the known involvement of 5-HT in thermoregulation argues for an afferent thermal pathway mediated by 5-HT. A crucial piece of supporting evidence is the existence of a functional raphé-PO/AH link. The n.r. dorsalis and n.r. medianus have been shown to project via serotonergic fibres to the PO/AH (Fuxe, 1965) but the n.r. magnus, which predominates in number of cells responsive to skin temperature was said to project only to the cord. More recently, however an autoradiographic study in the cat has revealed a significant projection from the n.r. magnus to the PO/AH area (Bobillier, Seguin, Petitjean, Salvert, Touret & Jouvet, 1976). Although the technique does not provide identification of the projection as serotonergic it is strong evidence for a raphé-PO/AH link. Physiological evidence for a raphé projection to the PO/AH exists. Eisenman (1974) has demonstrated activity, evoked by raphé stimulation, in PO/AH cells responding to local temperature. Cells in the PO/AH respond to skin temperature changes with similar neuronal characteristics to the raphé units reported here (Knox, Campbell & Lomax, 1973).

If it is assumed that the two populations of raphé neurones I have described form inputs to the thermoregulatory system, the release of serotonin from their terminals might be expected to have opposite effects on that system. The early experiments where 5-HT was microinjected into the PO/AH produced conflicting results (see review Hellon, 1974). Very recently, a more careful re-evaluation of the effects of 5-HT microinjections into the PO/AH has been made by Komiskey & Rudy (1977). They found that injections into the rostral hypothalamus produced hyperthermia whilst sites in the preoptic area led to hypothermia. The temperature changes produced by 5-HT were of rapid onset and short duration and were shown to be specific and physiological by methysergide blocking the response. These dual responses agree well with the concept of two groups of raphé neurones projecting to the PO/AH. Komiskey & Rudy's findings also suggest that the two raphé projections may have anatomically distinct destinations.

There has long been uncertainty as to the pathway through which thermal information ascending in the somatosensory system reached the hypothalamic thermoregulatory neurones. The raphé neurones I have described could well form at least part of this pathway and would seem to be the neuronal basis for the effects of 5-HT on temperature. However

such a proposition clearly requires testing with more direct evidence than has so far been provided.

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