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FURTHER EVIDENCE FOR A PHYSIOLOGICAL ROLE FOR HYPOTHALAMIC DOPAMINE IN THERMOREGULATION IN THE RAT

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SUMMARY

1. Intrahypothalamic injection of either dopamine or noradrenaline in a dose volume of 1 μl. caused a fall in core temperature in lightly restrained rats maintained at an ambient temperature of 17 ± 1 °C.

2. The hypothermic effects of dopamine (10 μg) and noradrenaline (2 μg) were selectively antagonized by systemic pre-treatment with pimozide (0·5 mg/kg) and phentolamine (1 mg/kg) respectively.

3. The location of the dopamine- and noradrenaline-sensitive sites were defined more accurately by reducing the dose volume to 0·5 μl. and making injections at different points throughout the preoptic region.

4. Both the dopamine- and the noradrenaline-sensitive sites were located within the preoptic region, but they did not have identical locations being separated by a distance of 0·4 mm.

5. Unilateral intrahypothalamic injection of 6-hydroxydopamine (10 μg in 2 μl.) caused a significant fall in core temperature, which was antagonized by systemic injection of either pimozide or phentolamine.

6. Rats placed 0·65 m below a 250 W infra-red lamp responded to the imposed heat load by vasodilation of tail skin blood vessels, indicated by an increased tail skin temperature.

7. Rats were tested two weeks after bilateral intrahypothalamic injection of 6-hydroxydopamine (10 μg in 2 μl.). This pre-treatment significantly reduced the increase in tail skin temperature so that the rats were less able to withstand the imposed heat load. Rats receiving similar 6-hydroxydopamine pre-treatment following injection of desipramine (25 mg/kg, I.P.) were also less able to cope with a heat load.

8. Three serial sections (0·8 mm thick) were prepared from the preoptic area of the rat brain, one anterior, one posterior and one corresponding to the dopamine-sensitive site.

9. Pre-treatment with 6-hydroxydopamine reduced both the dopamine and the noradrenaline concentration in the dopamine-sensitive site. Pre-treatment with desipramine and 6-hydroxydopamine selectively reduced dopamine.

10. These results indicate that there are receptors for both dopamine and noradrenaline in the preoptic anterior hypothalamus, which mediate a fall in core temperature in rats, but the evidence suggests that it is endogenous dopamine which is more likely to play an important physiological role.

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INTRODUCTION

The model of Bligh, Cottle & Maskrey (1971) has contributed much to the understanding of the involvement of hypothalamic neurotransmitters in thermoregulation and in its original form it contains acetylcholine, 5-hydroxytryptamine and noradrenaline. Recently Bligh and his group have presented evidence that casts doubt on a role for noradrenaline in the sheep (Bligh, Davis, Sharman & Smith, 1977) and similar doubts have been expressed concerning its role in the rat (Van Zoeren & Stricker, 1976).

In an extensive and well designed series of experiments De Roij and co-workers have provided evidence to suggest that dopamine should be considered for a physiological role in thermoregulation in the sheep and goat (De Roij, Frens, Bakker & Nemeth, 1977; De Roij, Bligh, Smith & Frens, 1978) and it has been suggested that perhaps dopamine should replace noradrenaline in at least some of the synapses occupied by noradrenaline in the original model (Cox, Kerwin & Lee, 1978).

The claim that dopamine has a physiological role in the rat was based on studies using central injections of dopamine and dopamine antagonists. Thus the evidence relies heavily on the assumption that the injected dopamine is not simply acting on receptors for noradrenaline, and that the dopamine antagonists are not, in the doses used, capable of blocking receptors for noradrenaline. Therefore, in an attempt to avoid these problems the present study has used a number of different approaches. First the relative sensitivity of the hypothalamus to injections of dopamine and noradrenaline has been measured and the distribution of the sensitive sites compared. Secondly, the specificity of the antagonists has been tested directly and thirdly the effects of specific depletion of hypothalamic dopamine on the ability of rats to respond to an imposed heat load have been determined.

METHODS

Male Sprague–Dawley rats weighing 250–350 g were used in all the experiments. Within any one experimental group the weight range was never greater than 50 g. The ambient temperature was maintained at 17 ± 1 °C throughout the study and rats were acclimatized at this temperature for at least 2 hr before commencing the experiment.

Central injections

Stainless steel guide cannulae (0·5 mm external diameter) were implanted into the brains of rats anaesthetized with pentobarbitone (45 mg/kg I.P.) using a David Kopf stereotaxic frame, according to the technique of Pellegrino & Cushman (1967). The guide cannula was implanted so that its tip lay 3 mm above the desired point of injection. Drug injections were made at least 7 days later via an injection cannula which was inserted into the guide cannula and which extended 3 mm beyond its tip. The dose volume of the injection was either 0·5, 1·0 or 2·0 μl. injected over a 45 sec period (see Results). After completion of an experiment an equivalent volume of Indian ink dye was injected so that the site of injection could be determined by histological examination.

Temperature measurements

Core temperature was measured in lightly restrained rats with a rectal thermistor probe (Yellow Springs Instruments) inserted to a depth of 40 mm. The tail skin temperature was measured by means of small surface thermistors of 4 mm diameter lightly strapped to the base of the tail and insulated from the environment.

Heat load experiments

Rats were placed in restraining boxes 0·65 m below a 250 W infra-red lamp for 60 min and change in core and tail skin temperature was measured. An insulating panel protected the tail and core thermistors from the radiant heat source. Responses of control rats injected with appropriate vehicle were compared with those of rats which had received drug injections directly into the preoptic anterior hypothalamus.

Estimation of drug diffusion within the brain

[^{3}H]dopamine hydrochloride (specific activity 5 Ci/m-mole; Radiochemical Centre, Amersham) was added into a standard dopamine solution to produce a final concentration of 5 μg/μl. Using an identical technique to that used in the experimental studies, 2 μl. of this solution was injected into the preoptic anterior hypothalamus of the rat. After 30 min, the rat was killed by decapitation and the brain was rapidly excised. Serial sections 50 μm thick were prepared from the preoptic anterior hypothalamus using a cryostat. Each brain slice was transferred into a counting vial containing 0·3 ml. soluene-350 (Packard Instrument Co.) and left to stand for 45 min at room temperature to allow the brain tissue to dissolve. The sample solution was then adjusted to pH 7 using 0·05 N-HCl and distilled water was added to make up the final volume to 1 ml. The radioactivity of the sample was then measured after the addition of 10 ml. emulsifier scintillator (Special M1-96) (Packard Instrument Co.) using a Packard Tri-Carb Liquid Scintillation Spectrometer 2425.

Measurement of brain amines

Three serial sections 0·8 mm thick were prepared from the preoptic anterior hypothalamus using the optic chiasma as a reference point. The anterior slice corresponded to co-ordinates 3·2 to 2·4 mm, the middle slice to co-ordinates 2·2 to 1·4 mm and the posterior slice to co-ordinates 1·2 to 0·4 mm anterior to bregma in the stereotaxic atlas of Pellegrino & Cushman (1967). Slices from ten different rats, giving a total weight of 100 mg, were used for each determination. The concentration of dopamine and noradrenaline within these slices was determined according to the method of Welch & Welch (1969). The recovery of internal standards of dopamine and noradrenaline was found to be $88{\cdot}6 \pm 3{\cdot}7$ % and $58{\cdot}9 \pm 6{\cdot}1$ % respectively.

Statistics

Comparisons between groups were made using the non-parametric Mann–Whitney U test and unless otherwise stated a significant difference between groups was taken as $P < 0{\cdot}05$. For ease of comparison in all cases mean ± S.E. is presented as the index of the response.

Drugs used

Dopamine hydrochloride (Koch–Light Ltd.), desipramine hydrochloride (Geigy Pharmaceuticals), 6-hydroxydopamine hydrobromide (Sigma Ltd), noradrenaline bitartrate (Koch–Light Ltd), phentolamine mesylate (CIBA Ltd) and pimozide (Janssen Pharmaceuticals). For central injections the drug solutions were prepared in sterile, pyrogen-free 0·9% (w/v) NaCl solution, except for 6-hydroxydopamine which was prepared in 0·2% ascorbic acid solution and pimozide which was prepared by dilution from a stock solution of 10 mg/ml. made by dissolving 100 mg of the drug in three drops glacial acetic acid and three drops absolute alcohol before making up to a final volume of 10 ml. with hot 5% (w/v) glucose solution. Appropriate vehicle injected controls were always run simultaneously. All doses refer to the free base.

RESULTS

Central injections

Control rats had an initial mean core temperature of $38{\cdot}9 \pm 0{\cdot}15$ °C at the beginning of the experiment, which was not significantly changed by unilateral intrahypothalamic injection of 1 μl. saline solution ($+0{\cdot}17 \pm 0{\cdot}12$ °C). Dopamine (dose volume of 1 μl.), also injected unilaterally, caused a fall in core temperature, which

was dose-related and which became significant when the 5 μg dose was used ($P < 0{\cdot}05$) (Fig. 1*A*). The response to 10 μg dopamine was significantly inhibited by systemic pre-treatment with pimozide (0·5 mg/kg, 2 hr) ($P < 0{\cdot}05$), but not by phentolamine (1 mg/kg, 1 hr) (Fig. 1*B*). Unilateral intrahypothalamic injection of noradrenaline also caused a fall in core temperature, but there was no clear dose relationship (Fig. 1*A*). The maximal effective dose was 2 μg and a further increase in the dose

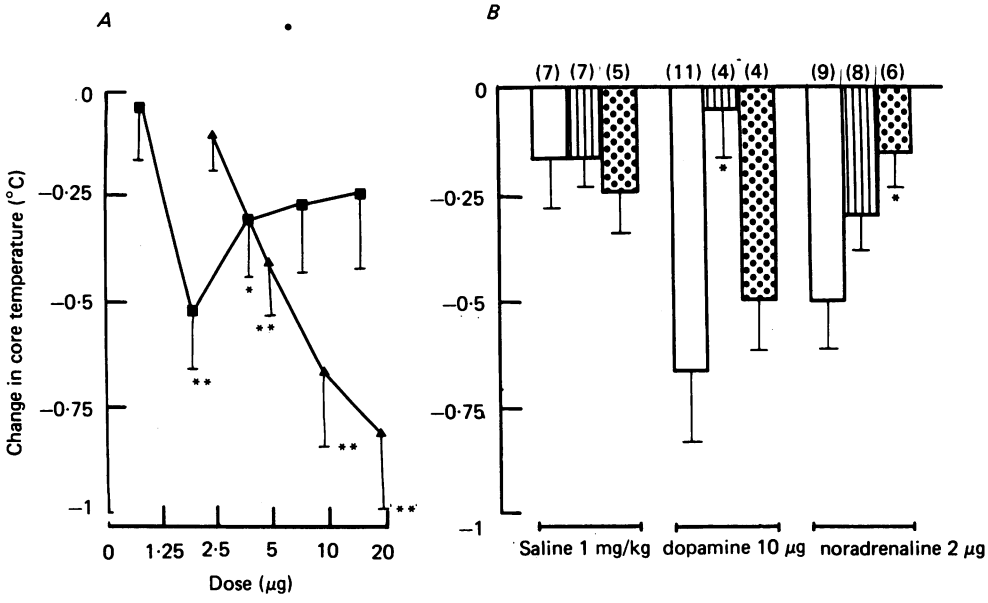

Fig. 1. *A*, dose–response curves to intrahypothalamic injection of dopamine (▲) and noradrenaline (■). Each point is the mean maximum change in core temperature for five to eleven rats. Vertical bars indicate standard error. Significant difference from saline control, *, $P<0{\cdot}05$, **, $P<0{\cdot}01$. *B*, change in core temperature of rats after intrahypothalamic injection of either dopamine 10 μg or noradrenaline 2 μg (open columns) or after I.P. pre-treatment with pimozide 0·5 mg/kg (striped columns) or phentolamine 1 mg/kg (dotted columns). Each column represents the mean maximum change in core temperature. Vertical bars indicate S.E. of mean. Figures in parentheses indicate the group size. * Significantly different from appropriate agonist control, $P<0{\cdot}05$.

caused no greater fall in core temperature. The response to noradrenaline was antagonized by systemic pre-treatment with phentolamine (1 mg/kg) ($P < 0{\cdot}05$), but not by pimozide (0·5 mg/kg) (Fig. 1*B*). Neither pimozide nor phentolamine caused any significant change in core temperature when injected on their own by the systemic route (Fig. 1*B*).

Localization of the dopamine- and noradrenaline-sensitive sites within the preoptic anterior hypothalamus

The location of the dopamine- and noradrenaline-sensitive sites were defined more accurately by injection of either dopamine (10 μg in 0·5 μl.) or noradrenaline (2 μg in 0·5 μl.) stereotactically into different sites within the preoptic area of the

anterior hypothalamus and measuring the ensuing fall in core temperature. The results from such injections are presented in Fig. 2. The site most sensitive to dopamine was found to be in a location defined by the co-ordinates of anterior–posterior (AP) 1·8 mm, lateral (L) 1·2 mm and depth (D) 8·5 mm using bregma as a reference point (Pellegrino & Cushman, 1967). For noradrenaline the most sensitive

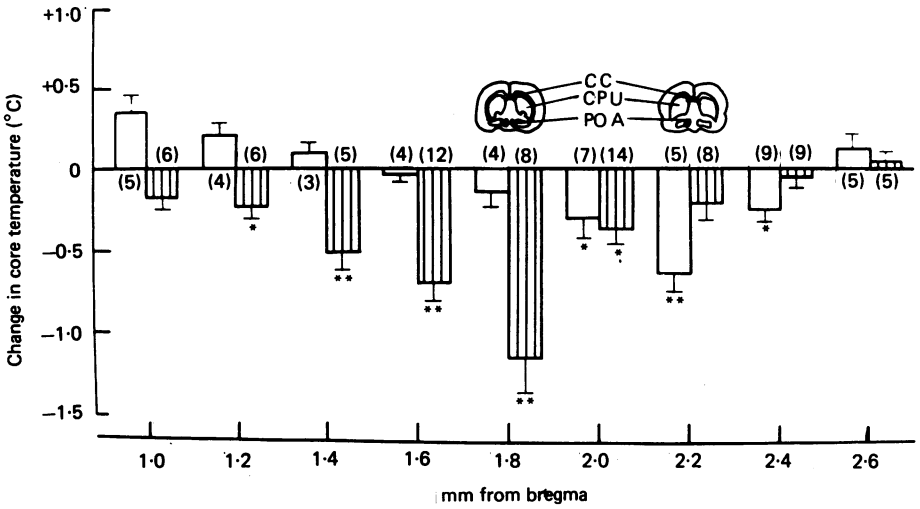

Fig. 2. Change in core temperature after injection of either dopamine 10 μg in 0·5 μl. (striped columns) or noradrenaline 2 μg in 0·5 μl. (open columns) into various sites within the preoptic anterior hypothalamic region. Each column represents the mean change in core temperature from the number of rats indicated in parentheses. Vertical bars indicate S.E. of mean. Significantly different from saline control: *, $P<0·05$; **, $P<0·01$. Histological insets show location of most responsive site (●) in each case. CC = corpus callosum; CPU = caudate nucleus; POA = lateral preoptic area.

site was located at AP 2·2 mm, L 1·4 mm and D 9·3 mm. Direct injection of dopamine and noradrenaline into their respective sensitive sites caused falls in core temperature of 1·13 ± 0·22 and 0·62 ± 0·12 °C respectively, and significant falls in core temperature also occurred when the drugs were injected into surrounding sites. However, injections with their perimeters more than 0·4 mm either rostral or caudal to the more responsive sites were ineffective.

Effects of central injection of 6-hydroxydopamine

Unilateral injection of 6-hydroxydopamine (10 μg in 2 μl.) into the preoptic anterior hypothalamus (AP 1·8, L 1·2 and D 8·5 mm) caused a fall in core temperature in rats which was significantly different from vehicle-injected controls (Fig. 3). Systemic pre-treatment with either pimozide (0·5 mg/kg) or phentolamine (1 mg/kg) significantly reduced the hypothermic response to intrahypothalamic 6-hydroxydopamine injection (Fig. 3).

Two weeks after intrahypothalamic pre-treatment with either 6-hydroxydopamine (10 μg in 2 μl., bilaterally) or 6-hydroxydopamine (10 μg) 30 min after I.P. desipramine (25 mg/kg) the hypothermic response to unilateral intrahypothalamic

injection (AP 1·8, L 1·2 and D 8·5 mm) of dopamine (10 μg in 1 μl.) was still present and was slightly enhanced when compared with the concurrent controls. However, the differences did not achieve the accepted level of statistical significance (Table 1).

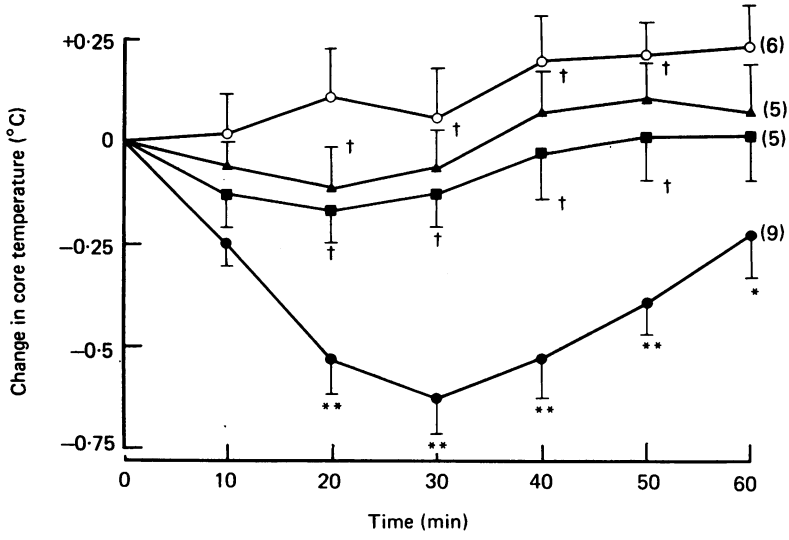

Fig. 3. Time course of the core temperature response after intrahypothalamic injection of either 0·2% ascorbic acid 2 ml. (○) or 6-hydroxydopamine 10 μg in 2 μl. (●) or after systemic pre-treatment with pimozide 0·5 mg/kg (▲) or phentolamine 1 mg/kg (■). Each point represents the mean change in core temperature from number of rats indicated in parentheses. Vertical bars indicate S.E. of mean. Significantly different from ascorbic acid control; *, $P<0·05$; **, $P<0·01$. † Significantly different from concurrent agonist control, $P<0·01$.

TABLE 1. Effect of intrahypothalamic dopamine (10 μg) injection on the core temperature response of rats after 6-hydroxydopamine pre-treatment†

Pre-treatment	Dose	Route	Mean change in core temperature (°C ± S.E. of mean)	n
0·2% ascorbic acid	2 μl.	I.H.	−0·54 ± 0·12	8
6-hydroxydopamine	10 μg	I.H.	−0·83 ± 0·24	5
6-hydroxydopamine + desipramine	10 μg / 25 mg/kg	I.H. / I.P.	−0·95 ± 0·12	4

† I.H. indicates bilateral intrahypothalamic injection, I.P. indicates intraperitoneal injection.

Heat load

The effect of radiant heat on core and tail skin temperature in rats was investigated 2 weeks after injection of either vehicle (2 μl.) or 6-hydroxydopamine (10 μg in 2 μl.) into the preoptic anterior hypothalamus. Control rats responded to the heat load with an increased tail skin temperature and small increases in core temperature.

In contrast, rats pre-treated with either 6-hydroxydopamine alone or 6-hydroxydopamine after desipramine (25 mg/kg, I.P.) had a reduced rate of rise in tall skin temperature and a significantly elevated core temperature when compared with the corresponding controls (Fig. 4).

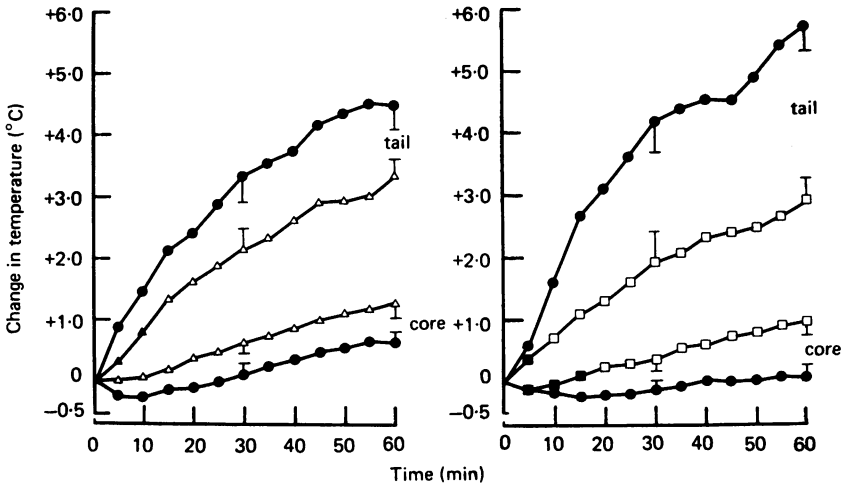

Fig. 4. Change in core and tail skin temperature of rats in response to an imposed heat load (250 W infra-red lamp placed 0·65 m above the lightly restrained rat) after bilateral intrahypothalamic injection of vehicle 2 μl./site (circles), 6-hydroxydopamine 10 μg/site (triangles) or 6-hydroxydopamine 10 μg/site with systemic desipramine 25 mg/kg (squares). Each point is the mean of five separate observations and vertical bars indicate standard error. Open symbols indicate a significant difference when compared with the concurrent control, $P < 0{\cdot}05$.

Brain amine assays

The concentration of dopamine in the anterior, middle and posterior slices were $0{\cdot}32 \pm 0{\cdot}05$, $0{\cdot}34 \pm 0{\cdot}06$ and $0{\cdot}24 \pm 0{\cdot}02$ ng/mg respectively. Corresponding values for noradrenaline were $0{\cdot}2 \pm 0{\cdot}04$, $0{\cdot}27 \pm 0{\cdot}04$ and $0{\cdot}24 \pm 0{\cdot}03$ ng/mg ($n = 33$).

The effects of 6-hydroxydopamine, injected bilaterally (AP 1·8, L 1·2 and D 8·5 mm), on the concentrations of noradrenaline and dopamine in the three slices are shown in Table 2. There was a significant reduction in noradrenaline in the anterior and middle slices, but a significant fall in dopamine concentration only occurred in the middle slice. When combined 6-hydroxydopamine and desipramine pretreatment was used there was no significant change in noradrenaline concentration in any of the slices, but the effect on dopamine in the middle slice was still evident (Table 2).

Estimation of drug diffusion after central injection

Rats were killed 30 min after injection of labelled [^{3}H]dopamine into the preoptic area using the co-ordinates of AP 1·8 mm, L 1·2 mm and D 8·5 mm with bregma as the reference point (Pellegrino & Cushman, 1967). The radioactivity in serial sections

TABLE 2. Change in hypothalamic dopamine (DA) and noradrenaline (NA) concentrations in rats after 6-hydroxydopamine pre-treatment†

Treatment	Anterior slices		Middle slices		Posterior slices	
	DA	NA	DA	NA	DA	NA
0·2 % ascorbic acid	100	100	100	100	100	100
6-hydroxydopamine (10 μg, I.H.)	140 ± 20	40 ± 15*	43 ± 7*	37 ± 6**	97 ± 18	79 ± 21
6-hydroxydopamine (10 μg, I.H.) + Desipramine (25 mg/kg, I.P.)	145 ± 18	80 ± 10	36 ± 5**	87 ± 21	100 ± 24	118 ± 5

† Percentage change in dopamine and noradrenaline concentration in rat brain hypothalamic slices 2 weeks after drug pre-treatment. Each value is the mean from seven to nine duplicate determinations. Significant difference from concurrent control. *, $P < 0.05$; **, $P < 0.01$ Anterior slices = 3·2 to 2·4, middle slices = 2·2 to 1·4 and posterior slices = 1·2 to 0·4 mm anterior to bregma (Pellegrino & Cushman, 1967).

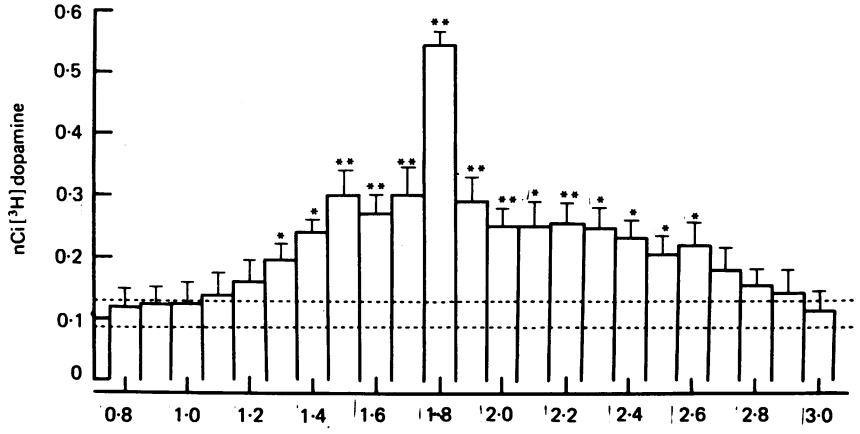

Fig. 5. Radioactivity distribution after intrahypothalamic injection of 2 μl. [³H]-dopamine in rats. Each column represents the mean of five duplicate determinations and vertical bars indicate S.E. of mean. The dotted lines represent the background control ± S.E. of mean. Significant difference from background control: *, $P < 0.05$; **, $P < 0.01$.

prepared from the preoptic region was measured and the results are shown in Fig. 5. The highest concentration of radioactive material was found in the slice corresponding to the centre of the injection and there was a rapid decline in the amount of radioactivity in sections taken either side of this region. A significant increase over background was found in the range 0·8 mm anterior to 0·5 mm posterior to the centre of injection ($P < 0.05$).

DISCUSSION

In previous experiments we have shown that unilateral intrahypothalamic injection of dopamine agonists caused a fall in core temperature (Cox & Lee, 1977) and presented evidence that hypothalamic dopamine could have a physiological role in thermoregulation (Cox, Kerwin & Lee, 1978). However, some reports have claimed that the thermoregulatory events after the injection of dopamine agonists might be mediated via an adrenergic pathway (Burks & Rosenfeld, 1977; Schelkunov & Stabrovsky, 1971). Therefore the aim of the present study was first to investigate whether noradrenaline played a part in the response to dopamine and secondly to seek further evidence for a physiological role for dopamine in thermoregulation.

The first approach was to determine if dopamine and noradrenaline modified core temperature in the same manner. Unilateral intrahypothalamic injection of either dopamine or noradrenaline were shown to produce a dose-related fall in core temperature. However, these hypothermic effects were found to be different in a number of ways. Thus the response to central dopamine injection was of greater magnitude than the response to noradrenaline. Also the sensitive sites for dopamine and noradrenaline were found to have separate locations within the preoptic anterior hypothalamus, as the dopamine-sensitive site was about 0·4 mm caudal to the noradrenaline-sensitive site. Finally, the hypothermic response induced by either dopamine or noradrenaline could be blocked selectively by their respective antagonists, pimozide and phentolamine. Thus these results suggest that there are both central dopaminergic and adrenergic receptors within the hypothalamus that mediate a fall in core temperature in rats, but it seems unlikely that any connexion exists between these two receptor populations.

In order to provide more information concerning the possibility of a physiological role for dopamine, 6-hydroxydopamine, a selective catecholamine depleting agent (for review see Kostrzewa & Jacobowitz, 1974), was used. Acute unilateral intrahypothalamic injection of 6-hydroxydopamine into the previously defined dopamine-sensitive site caused a significant fall in core temperature, which was antagonized by systemic pre-treatment with either pimozide or phentolamine. This presumably occurred as a result of noradrenaline and dopamine being released from degenerating nerve terminals and it seems likely therefore that noradrenaline is involved even though the 6-hydroxydopamine was administered into the dopamine-sensitive area. However, the distribution volume of 2 μl. of [^{3}H]dopamine injected into the hypothalamus (the same volume as was used for the 6-hydroxydopamine) was found to be equivalent to a sphere of radius 0·7 mm. Therefore, injection of the same volume of 6-hydroxydopamine would encompass both the dopamine and the noradrenaline sites as these were only 0·4 mm apart. The simplest explanation of the results with the antagonists is that the 6-hydroxydopamine-induced hypothermia is due to the summation effect of both dopamine and noradrenaline rather than any linkage between two receptor populations. The involvement of both dopamine and noradrenaline in 6-hydroxydopamine-induced hypothermia has also been suggested by other workers (Breese & Howard, 1971; Reid, 1975).

Pre-treatment with 6-hydroxydopamine significantly reduced the vasodilator response in the tail blood vessels of rats exposed to imposed heat load, with a sub-

sequent increase in core temperature. These results are similar to those obtained previously for dopamine-receptor antagonists (Cox *et al.* 1978). However, in the present study 6-hydroxydopamine caused depletion of both hypothalamic dopamine and noradrenaline. Thus it was not possible to decide whether either endogenous noradrenaline or dopamine present in the thermoregulatory centres was essential for a normal heat load response. Therefore a second series of experiments was carried out in an attempt to resolve this problem by combining bilateral intrahypothalamic 6-hydroxydopamine with systemic desipramine pre-treatment. Rats pre-treated in this way also failed to maintain their core temperature within the physiological range under an imposed heat load. Since it has been reported that only dopaminergic neurones are affected by the combined treatment with 6-hydroxydopamine and desipramine (Breese & Taylor, 1970), then, this suggests that loss of hypothalamic dopamine was responsible for the thermoregulatory deficit. In a separate series of experiments it was found that this combined pre-treatment did indeed produce selective dopamine depletion within the dopamine-sensitive site. Thus the weight of evidence from these studies supports the suggestion that it is the dopamine that is important. In contrast noradrenaline appears to be less important and similar conclusions have been made by Van Zoeren & Stricker (1976). They found that depletion of preoptic noradrenaline by 6-hydroxydopamine did not disrupt thermoregulation in rats either in heat or cold, even when the depletion was by more than 90%. Before finally accepting the importance of dopamine one further control was required. The lack of a response to a heat load after 6-hydroxydopamine could be due to non-specific tissue damage and the change in catecholamine concentration simply a reflexion of that damage. However, if there was damage to the area then a reduced response to dopamine itself would be expected. In fact central injections of dopamine after 6-hydroxydopamine not only caused a significant fall in core temperature but there was also a suggestion of an increased response, which suggested that post-synaptic dopaminergic receptors and the post-synaptic effector cells were unaffected by 6-hydroxydopamine. This strongly indicates that endogenous dopamine does indeed play an important physiological role in the thermoregulatory centres.

Thus taken together these experiments suggest that there are both dopaminergic and noradrenergic receptors within the preoptic area, which mediate a fall in core temperature after drug injection. However, from the heat load experiments, endogenous dopamine appears to play an important physiological role in the thermoregulatory centre, whereas endogenous noradrenaline seems less likely to subserve a physiological function.

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