J. Physiol. (1978), **282**, *pp.* 471–483
With 8 text-figures
Printed in Great Britain

DOPAMINE RECEPTORS IN THE CENTRAL THERMOREGULATORY PATHWAYS OF THE RAT

BY B. COX, R. KERWIN* AND T. F. LEE

From the Department of Pharmacology, Materia Medica and Therapeutics, Manchester University Medical School, Manchester M13 9PT

(*Received 6 March 1978*)

SUMMARY

1. Intrahypothalamic injection of either dopamine (10 μg) or apomorphine (10 μg) in a dose volume of 1 μl. caused an almost immediate rise in tail skin temperature and a concomitant fall in core temperature in the conscious rat maintained at an ambient temperature of 17 ± 1 °C.

2. The location of the dopamine-sensitive site was defined more accurately by reducing the dose volume to 0·5 μl. and injecting dopamine at different points throughout the preoptic and anterior hypothalamic region.

3. The largest mean fall in core temperature ($1{\cdot}13 \pm 0{\cdot}22$ °C) was obtained after injection into the preoptic region. Injections with their perimeters more than 0·4 mm rostral or caudal to this site were ineffective.

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

5. Bilateral, but not unilateral, injection of either pimozide (0·5 μg) or haloperidol (2·5 μg) into the preoptic region significantly reduced the increase in tail skin temperature so that the rats were less able to withstand the imposed heat load.

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

7. Tissue from the middle slice increased its rate of synthesis of 3,5-cyclic AMP in response to addition of dopamine 20 or 100 μM to the incubation medium. The posterior slice was inactive, but the anterior slice had similar activity to the middle slice.

8. The effect of dopamine on the middle slice was specifically blocked by haloperidol (0·1 μM), whereas the effects on the anterior slice were partially blocked by both haloperidol (0·1 μM) and propranolol (0·1 μM).

9. These results indicate that there is within a well defined area of the preoptic region a population of dopamine receptors, which play a part in the transmission of information from warm sensors to heat loss effectors.

* Present address: Department of Pharmacology, University of Bristol BS8 1TD.

INTRODUCTION

The first convincing evidence that drugs which stimulate dopamine receptors could lower core temperature in mice and rats was presented in 1972 (Barnett, Goldstein & Taber, 1972; Fuxe & Sjöqvist, 1972; Kruk, 1972). These experiments, primarily involving the dopamine-agonist apomorphine, were soon taken to indicate that dopamine itself played a physiological role in thermoregulation (Lagerspetz, Tirri, Tarkkonen & Julku, 1974) even though they measured pharmacological rather than physiological events. Other workers have also assumed both a hypothalamic location of the dopamine receptors and that they have a physiological role (Kennedy & Burks, 1974; Quock & Gale, 1974). However in these examples either the drugs were given by the intracerebroventricular route, so that the precise site of action was uncertain; or there was no attempt to test a physiological response, so that once again the claim concerning a physiological role was not adequately tested.

In some previous experiments we have shown that both dopamine and apomorphine lower core temperature in the rat when injected directly into the preoptic anterior hypothalamic area (Cox & Lee, 1977), thus confirming a hypothalamic location more directly. This study also showed that a systemic injection of a dopamine antagonist (pimozide) could reduce the response of the rat to an imposed heat load, thus providing circumstantial evidence that hypothalamic dopamine could play a part in thermoregulation.

However, these results still left a number of questions unanswered. In the present experiments an attempt has been made to define the dopamine sensitive site more precisely, to determine if dopamine antagonists are effective after local intrahypothalamic rather than systemic injection and to seek biochemical evidence for the existence of dopamine receptors at the presumed site of action.

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 or 1·0 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 both the centre of the injection and some idea of its spread could be determined by histological examination.

Temperature measurements

Core temperature was measured in lightly restrained rats with a rectal thermistor probe (L. Light Labs.) inserted to a depth of 40 mm. In experiments involving drug interactions tail skin temperature was measured by a strap-on thermometer attached to the base of the tail and

insulated from the environment. In the heat load experiments the tail skin temperature was measured by means of small surface thermistors of 4 mm diameter also 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 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 15 min earlier.

Measurement of 3,5-cyclic AMP

Three serial sections 0·8 mm thick were prepared from the preoptic anterior hypothalamus. The anterior slice corresponded to plates 16–20, the middle slice to plates 21–25 and the posterior slice to plates 26–30 in the stereotoxic atlas of Pellegrino & Cushman (1967). The ability of these slices to increase their rate of synthesis of 3,5-cyclic AMP was determined according to the method of Forn, Krueger & Greengard (1974). Slices from different rats were pooled and tissue weighing approximately 15 mg was cut into 0·26 × 0·26 × 0·8 mm slices on a McIlwain tissue chopper and immediately transferred to 1 ml. Krebs bicarbonate buffer (pH 7·4) which was equilibrated with a mixture of 95 % O_2 and 5 % CO_2 and preincubated for at least 60 min in a shaking water-bath at 37 °C. When antagonists were used they were added, at the desired concentration, to the preincubating medium and were present throughout the experiment. At the end of the preincubation the medium was changed to one also containing the desired concentration of the agonists in a final volume of 0·3 ml. The incubation was then continued for a further 10 min. The reaction was stopped by boiling for 1 min and 50 μl. portions of the medium were taken for assay of 3,5-cyclic AMP by the method of Tovey, Oldham & Whelan (1974). The tissue from each sample was then recovered and its protein content determined by the method of Lowry, Rosebrough, Farr & Randall (1951).

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 $P < 0·05$. For ease of comparison in all cases mean ± S.E. is presented as the index of the response.

Drugs used

Apomorphine hydrochloride (MacFarlan–Smith Ltd.), dopamine hydrochloride (Koch–Light Ltd.), haloperidol (Janssen Pharmaceuticals), noradrenaline bitartrate (Koch–Light Ltd.), pimozide (Janssen Pharmaceuticals), and propranolol hydrochloride (I.C.I.). For central injections the drug solutions were prepared in sterile, pyrogen-free 0·9 % (w/v) NaCl solution, except for apomorphine solution which also contained 0·1 % sodium metabisulphite as an antioxidant, haloperidol solution which contained 1 % lactic acid and pimozide solution which was prepared by dilution from a stock solution of 10 mg/ml. made by dissolving 100 mg of the drug in 3 drops glacial acetic acid and 3 drops absolute alcohol before making up to a final volume of 10 ml. with hot 5 % glucose solution. Appropriate vehicle injected controls were always run simultaneously. For the 3,5-cyclic AMP determinations drug solutions were prepared in Krebs bicarbonate buffer at a pH of 7·4, except for the catecholamine solutions which contained 0·1 μM-ascorbic acid as an antioxidant. All doses and concentrations refer to the free base.

RESULTS

Central injections

Apomorphine and dopamine (10 μg in 1 μl.) injected unilaterally into the preoptic anterior hypothalamus caused a fall in core temperature in rats (Table 1), which was significantly different from vehicle injected controls ($P < 0·01$). In all cases an

increase in tail skin temperature preceded the fall in core temperature as shown by the sample records in Fig. 1. The effects of intrahypothalamic injection of apomorphine and dopamine were blocked by systemic pretreatment with either pimozide or haloperidol (Table 1). Also the effect of systemic doses of apomorphine could be significantly reduced by bilateral injection of either pimozide or haloperidol into the preoptic anterior hypothalamus (Table 1). However, unilateral pretreatment with either pimozide or haloperidol failed to antagonize the hypothermic effect of apomorphine. Neither pimozide nor haloperidol caused any significant change in core and tail skin temperature when injected on their own by either the systemic or the central route.

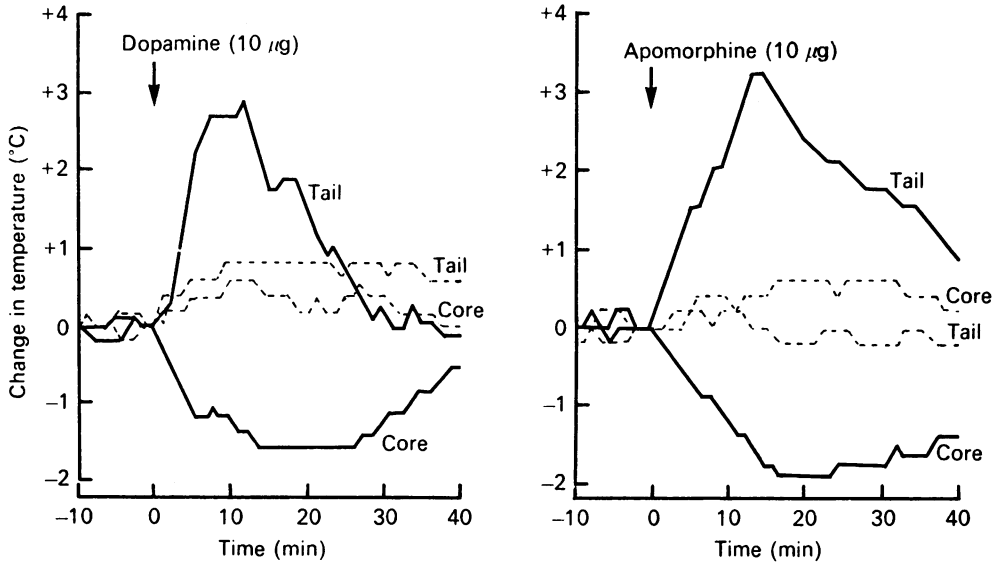

Fig. 1. Time course for the effect of intrahypothalamic injection of dopamine and apomorphine (10 μg in 1 μl.) on core and tail skin temperature in the rat. Continuous lines represent response to drug injection, interrupted line response to injection of same volume of appropriate vehicle.

Localization of the dopamine-sensitive site within the preoptic anterior hypothalamus

The location of the dopamine sensitive site was defined more accurately by injecting dopamine (10 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 seventy-two such injections are presented in Fig. 2. The most sensitive site was found to be in the location defined by the co-ordinates of anterior–posterior 1·8 mm, lateral 1·2 mm and depth 8·5 mm using bregma as the reference point (Pellegrino & Cushman, 1967). Direct injection of dopamine into this site caused a fall in core temperature of $1{\cdot}13 \pm 0{\cdot}22$ °C, and a significant fall in core temperature also occurred when dopamine was injected into the surrounding sites. However, injections with their perimeters more than 0·4 mm either rostral or caudal to the more responsive sites were ineffective. The spread of the injection volume was determined by injecting 0·5 μl. Indian ink into the preoptic region using exactly the same technique as that employed for the drug injections. The brain

was fixed and serial sections taken throughout the hypothalamus. The volume of 0·5 μl. ink solution was found to be the equivalent of a sphere of diameter 0·58 ± 0·02 mm.

TABLE 1. Effects of pimozide and haloperidol on the core temperature response of rats receiving intrahypothalamic (I.H.) or interperitoneal (I.P.) injections of apomorphine and dopamine

Drug	Dose	Route	Mean change in core temperature* (°C ± S.E. mean)	*n*
Saline	—	I.H.	+0·2 ± 0·1	7
Apomorphine	10 μg	I.H.	−1·0 ± 0·2†	8
Apomorphine + pimozide	10 μg 0·5 mg/kg	I.H. I.P.	+0·4 ± 0·1‡	3
Apomorphine + haloperidol	10 μg 1·0 mg/kg	I.H. I.P.	−0·03 ± 0·04‡	4
Dopamine	10 μg	I.H.	−0·7 ± 0·2†	11
Dopamine + pimozide	10 μg 0·5 mg/kg	I.H. I.P.	+0·1 ± 0·1§	4
Dopamine + haloperidol	10 μg 1·0 mg/kg	I.H. I.P.	+0·01 ± 0·1§	4
Vehicle + apomorphine	— 1·25 mg/kg	I.H. I.P.	−1·8 ± 0·3†	5
Pimozide + apomorphine	0·5 μg 1·25 mg/kg	I.H. I.P.	−0·9 ± 0·3§	8
Haloperidol + apomorphine	2·5 μg 1·25 mg/kg	I.H. I.P.	−0·9 ± 0·2§	5

* Mean for maximum change in core temperature occurring within 40 min of injection. Pre-treatment time, 2 hr for I.P. pimozide and 1 hr for I.P. haloperidol; 15 min for bilateral (I.H.) pimozide and haloperidol.

† Significantly different from corresponding saline control ($P < 0·01$).

‡ Significantly different from the concurrent agonist control ($P < 0·01$).

§ Significantly different from the concurrent agonist control ($P < 0·05$).

(Mann–Whitney U test).

Heat load experiments

The effect of radiant heat on core and tail skin temperature in the rat was investigated in rats receiving either vehicle or drug injection. Control rats responded to the heat load with an increased tail skin temperature and small increases in core temperature. Unilateral injection of either pimozide (0·5 μg) or haloperidol (2·5 μg) into the preoptic area had no significant effect on these responses (Fig. 3) although in both cases the increase in tail skin temperature was less in the drug pre-treated group. When a bilateral route of injection of either pimozide or haloperidol was used then significant differences did occur. In both cases the drug pre-treated rats

had a reduced rate of rise of tail skin temperature and a significantly elevated core temperature when compared with the corresponding controls (Fig. 4).

3,5-cyclic AMP determination

A comparison of the ability of serial slices of the rat hypothalamus to synthesize 3,5-cyclic AMP *in vitro* is shown in Fig. 5. Tissue prepared from the area where dopamine had its maximum effect *in vivo* significantly increased its production of

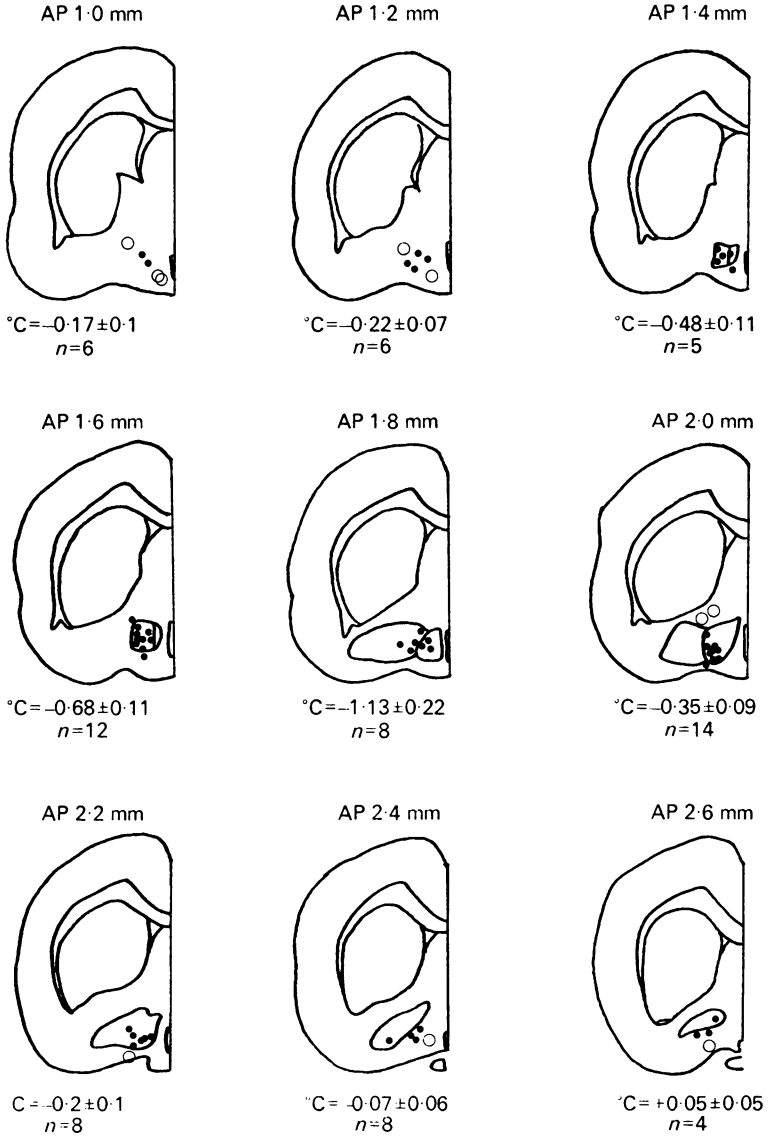

Fig. 2. Histological reconstruction in nine coronal planes of the sites at which dopamine (10 μg in 0·5 μl.) was injected in an attempt to elicit a hypothermia. AP is the anterior–posterior co-ordinates with bregma as zero (Pellegrino & Cushman, 1967). °C is mean change in temperature ± S.E. for n observations. ●, sites giving a fall in core temperature; ○, sites at which dopamine was ineffective.

3,5-cyclic AMP when either dopamine (20 or 100 μM) or noradrenaline (50 μM) were added to the incubation mixture. Tissue prepared from the posterior or caudal slice was unresponsive to dopamine 20 μM and there was only a small increase in 3,5-cyclic AMP when dopamine 100 μM was used. Noradrenaline (50 μM) was much

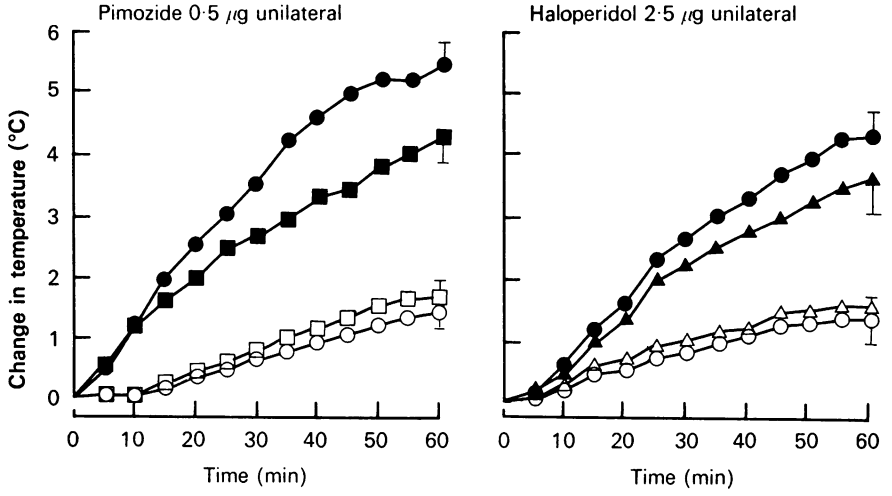

Fig. 3. Change in core (open symbols) and tail skin (filled symbols) temperature of rats in response to an imposed heat load (250 W infra-red lamp placed 0·65 m above the lightly restrained rat) for either vehicle (○, ●), pimozide (□, ■) 0·5 μg or haloperidol (△, ▲) 2·5 μg pre-treated rats. The injections were given by unilateral intrahypothalamic injection down previously implanted guide cannulae. Each point is the mean of six separate observations and vertical bars indicate standard error.

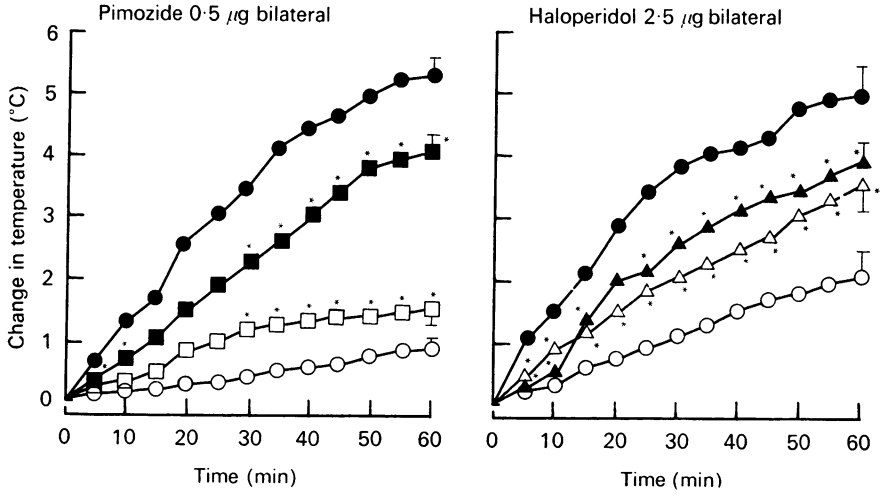

Fig. 4. Change in core (open symbols) and tail skin (filled symbols) temperature of rats in response to an imposed heat load (250 W infra-red lamp placed 0·65 m above the lightly restrained rat) for either vehicle (○, ●), pimozide (□, ■) 0·5 μg or haloperidol (△, ▲) 2·5 μg pre-treated rats. The injections were given by bilateral intrahypothalamic injection down previously implanted guide cannulae. Each point is the mean of six separate observations and vertical bars indicate standard error of the mean. * Significantly different from control, $P < 0.05$, Mann–Whitney U test.

more effective than dopamine on this slice. The anterior slice on the other hand showed a response pattern similar to that of the middle slice.

Preincubation of the tissues from the middle slice with haloperidol (0·1 μM) significantly reduced the response to dopamine (100 μM) but had no effect on the

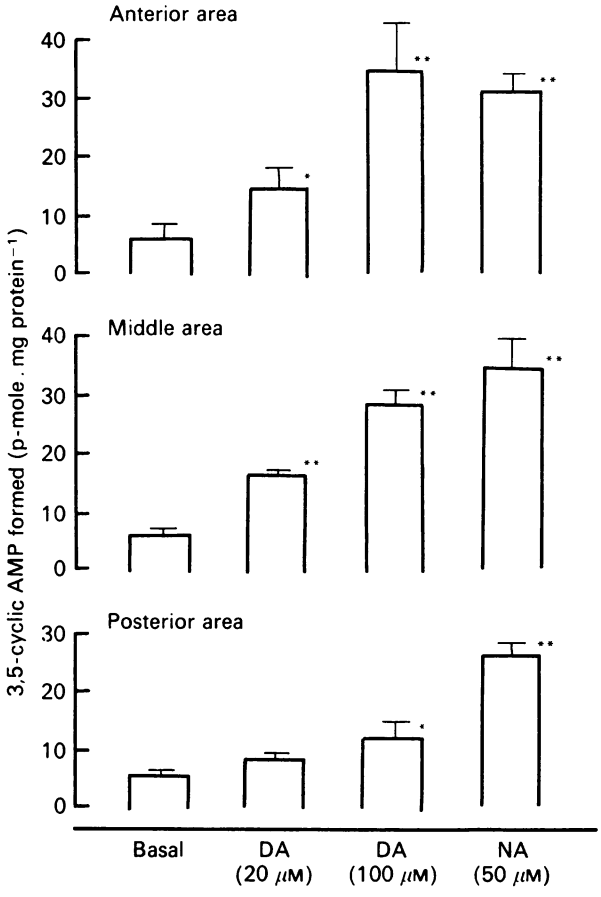

Fig. 5. Effect of dopamine (DA) and noradrenaline (NA) on the amount of 3,5-cyclic AMP formed in 10 min by rat brain slices taken from the anterior preoptic hypothalamic region. Each column represents the mean of at least five duplicate determinations and vertical bars indicate standard error. Significant difference from basal synthesis * $P < 0.05$, ** $P < 0.01$. Anterior area = plates 16–20, middle area plates 21–25 and posterior area plates 26–30 (Pellegrino & Cushman, 1967).

response to noradrenaline (50 μM). When propranolol (0·1 μM) was used the situation was reversed with the response to noradrenaline being reduced but that to dopamine being unaffected (Fig. 6). A similar experiment was performed on the anterior slice and then both haloperidol (0·1 μM) and propranolol (0·1 μM) reduced the response to dopamine (100 μM) (Fig. 7).

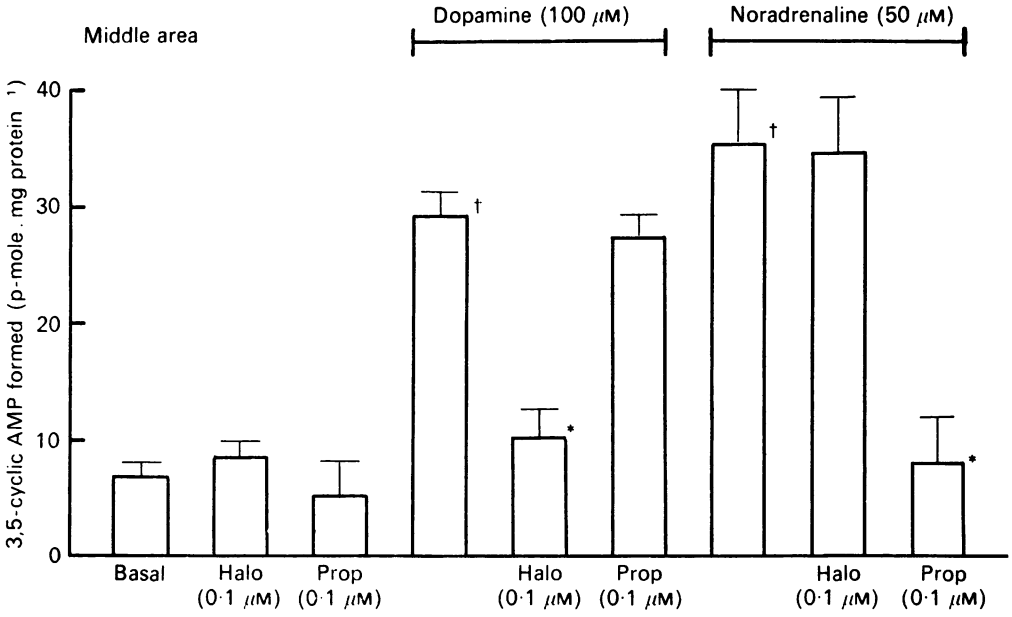

Fig. 6. Blockade by haloperidol (halo) and propranolol (prop) of the effects of dopamine and noradrenaline on the 3,5-cyclic AMP formed in 10 min by rat brain slices taken from the preoptic anterior hypothalamus plates 21–25 (Pellegrino & Cushman, 1967). Each column represents the mean of at least five duplicate determinations and vertical bars indicate standard error. † Significant difference from basal synthesis, $P < 0{\cdot}01$. * Significant difference from agonist alone, $P < 0{\cdot}01$, Mann–Whitney U test.

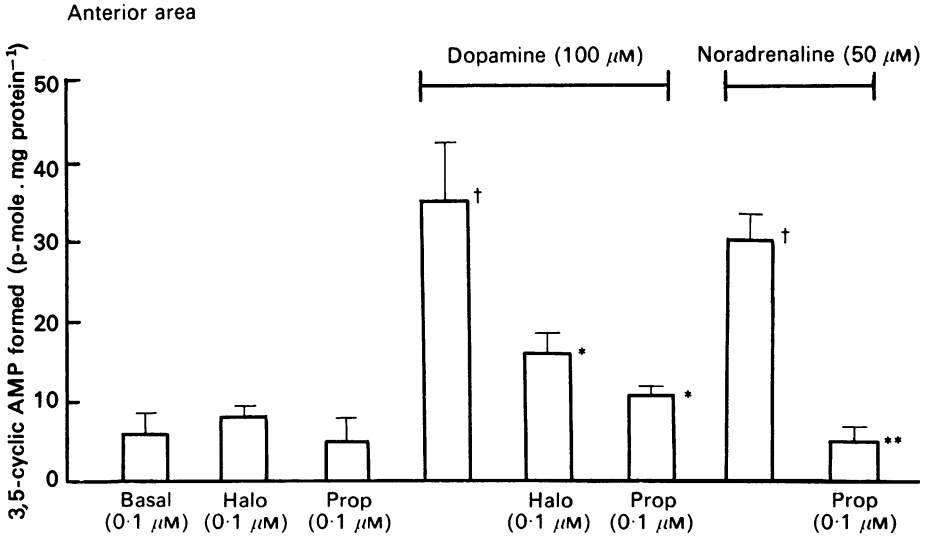

Fig. 7. Blockade by haloperidol (halo) and propranolol (prop) of the effects dopamine and noradrenaline on the 3,5-cyclic AMP formed in 10 min by rat brain slices taken from the preoptic anterior hypothalamus plates 16–20 (Pellegrino & Cushman, 1967). Each column represents the mean of at least five duplicate determinations and vertical bars indicate standard error. † Significant difference from basal synthesis, $P < 0{\cdot}01$. * Significant difference from agonist alone, $P < 0{\cdot}05$. ** Significant difference from agonist alone, $P < 0{\cdot}01$, Mann–Whitney U test.

DISCUSSION

One of the most widely quoted models for the role of hypothalamic neurotransmitters in thermoregulation is that of Bligh, Cottle & Maskrey (1971), which in its original form included acetylcholine, noradrenaline and 5-hydroxytryptamine. Dopamine was not included in this model, although there is now a large body of evidence that drugs acting on central dopamine receptors can modify core temperature in a wide variety of species (for a review see Cox, 1978). However, this evidence is essentially of a pharmacological rather than a physiological nature and therefore the aim of the present study was to investigate the possibility that endogenous dopamine might play a physiological role in thermoregulation.

The preoptic area of the anterior hypothalamus is regarded as the most important site for body temperature control (Hardy, 1961). It was of interest therefore to determine whether dopamine itself, or the dopaminergic agonist apomorphine, could modify core temperature when injected directly into this area of rat brain. This was found to be the case in that both dopamine and apomorphine lowered core temperature when injected into the preoptic area. Further, the dopamine-sensitive site appeared to have a precise location within the preoptic area, because injections with their centres more than 0·6 mm rostral or caudal to the site giving the maximum response were ineffective. The spread of the same volume of dye solution (0·5 μl.) was found to be equivalent to a sphere of approximate radius 0·3 mm and therefore there would not be any overlap between the dopamine solution injected at the most responsive site and injections made at the nearest unresponsive site. Thus these findings not only suggest a precise dopamine-sensitive area, they also indicate that there is little or no diffusion of active drug away from the sphere of injection. That the injected dopamine was acting via dopamine receptors was supported by the finding that the specific dopamine antagonist pimozide (Anden, Butcher, Corrodi, Fuxe & Ungerstedt, 1970) and another dopamine antagonist haloperidol could prevent the response to centrally administered dopamine. Further, the finding that bilateral intrahypothalamic injection of these antagonists reduced the hypothermic effect of a systemic injection of apomorphine also supports the contention that the dopamine-sensitive sites are located within this preoptic region.

One problem in accepting a physiological role for dopamine was that, under the conditions of the experiment, the dopamine antagonists themselves did not modify core temperature. If dopamine were indeed playing a physiological role in heat loss processes then pimozide and haloperidol might have been expected to cause a hyperthermia. However, the ambient temperature of this study was 17 °C and it would be surprising if the postulated dopaminergic heat loss system was being utilized under these conditions. It was decided therefore to test the effect of the dopamine antagonists on the response of the rats to an imposed heat lead, when an endogenous heat loss system would be active. The hypothermic response to central dopamine injection was accompanied by vasodilation of the tail skin blood vessels and change in vasomotor tone in the tail is an important mechanism for thermoregulation in the rat (Rand, Burton & Ing, 1965). Thus it would be predicted that blockade of a hypothalamic dopaminergic system would reduce the vasodilator response which is usually seen when rats are exposed to a heat load. This in fact proved to be the case

when bilateral intrahypothalamic injections of the antagonists were used. Unilateral injections were ineffective, suggesting that dopamine receptors on both sides of the brain had to be blocked before the rat was rendered incapable of coping with the heat load.

In all the above studies it has been presumed that dopamine and its antagonists were acting via specific dopamine receptors. However, evidence for the existence of these receptors is not easily gained in *in-vivo* studies. Therefore in the final series of experiments *in-vitro* evidence was sought for the existence of dopamine-specific receptors within that area of hypothalamus in which dopamine was active *in vivo*.

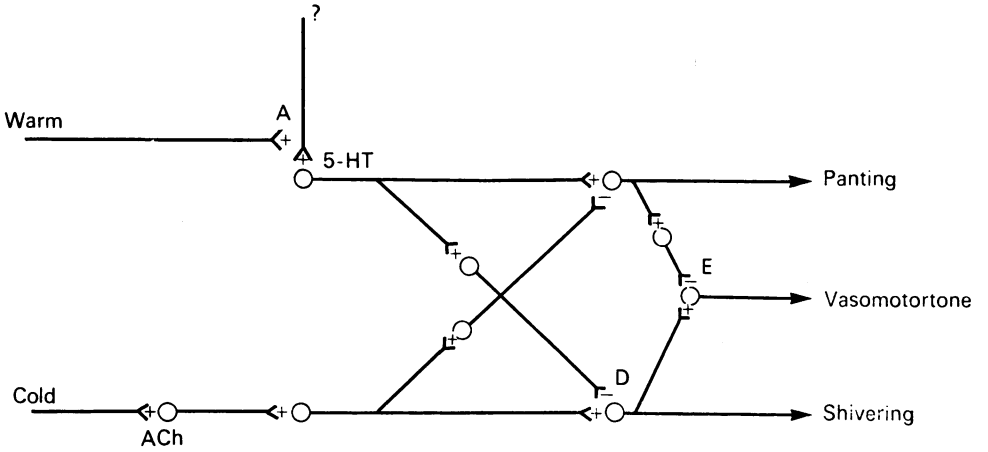

Fig. 8. Modification of the neuronal model of temperature regulation described by Bligh, Cottle & Maskrey (1971) to indicate the possible synapses at which dopamine could act as a neurotransmitter.

These experiments involved the measurement of the ability of tissue slices to synthesize 3,5-cyclic AMP since there is in brain a specific dopamine-receptor linked adenylate cyclase (Brown & Makman, 1972; Horn, Cuello & Muller, 1974; Kebabian, Petzold & Greengard, 1972; Trabucchi, Govoni, Tonon & Spano, 1976). Tissue slices prepared from the *in-vivo* active site increased their production of 3,5-cyclic AMP in response to dopamine and this effect was blocked by haloperidol, but not the β-adrenoceptor blocking drug propranolol. The propranolol was an effective antagonist of the noradrenaline induced increase of 3,5-cyclic AMP in these slices. Thus there does appear to be a population of dopamine specific receptors at the active site. Dopamine was relatively ineffective in tissue slices prepared from a more caudal area. Tissue prepared from an area anterior to the active site did respond to dopamine but the antagonist studies suggest that this was not simply due to activation of dopamine receptors.

Thus taken together these experiments suggest that there is within a well-defined region of the preoptic area a dopaminergic system involved in the mediation of heat loss responses. Examination of the model of Bligh *et al.* (1971) reveals a number of synapses at which dopamine could conceivably be the neurotransmitter (Fig. 8). Thus it could act at site E, the final step in the pathway for inhibition of vasomotor tone. Alternatively it could act at site D, in which case it would replace noradrenaline

in the original model. This is a reasonable suggestion since dopamine nerve terminals within the hypothalamus mainly originate from intrahypothalamic cell bodies whereas no noradrenaline nerve cell bodies have been identified in the hypothalamus (Fuxe, Hökfelt, Andersson, Ferland, Johansson, Ganten, Eneroth, Gustafsson, Skett, Said & Mutt, 1978). Also, no obvious impairment of the crossing inhibitory effects of intraventricular injections of 5-HT and carbachol were observed after noradrenaline depletion by central pre-treatment with 6-OHDA in sheep (Bligh, Davis, Sharman & Smith, 1977), which would also argue against the involvement of noradrenaline. Finally dopamine could act at an earlier point in the model, for example at A. The original model of Bligh *et al.* (1971) showed at this point a 5-HT containing cell body. However, as is the case with noradrenaline, nerve cell bodies for 5-HT neurones appear to be extrahypothalamic (Dahlström & Fuxe, 1965). Therefore the model has been further modified to suggest an interaction between a dopaminergic nerve and the terminal of a 5-HT containing neurone whose cell body lies outside the hypothalamus, probably within the mid-brain raphé. This suggestion seems a viable proposition because a 5-HT link in dopamine-receptor mediated hypothermia has already been postulated (Maj, 1975, 1976). Thus it has been reported that lesions of the mid-brain raphé can reduce dopamine-receptor mediated hypothermia. Whether any or all of these postulated sites are actually involved remains to be determined.

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