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IS ACETYLCHOLINE INVOLVED IN A DOPAMINE RECEPTOR MEDIATED HYPOTHERMIA IN MICE AND RATS?

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1 Apomorphine and oxotremorine caused a dose-related fall in core temperature in the mouse and a fall in core temperature preceded by an increase in tail-skin temperature in the rat.

2 In both species the slope of the dose-response curve was greater for oxotremorine (8.2 ± 0.6 mice, 0.9 ± 0.1 rats) than it was for apomorphine (1.7 ± 0.3 mice, 0.5 ± 0.07 rats).

3 The mouse was more sensitive than the rat to the effects of both agonists.

4 Atropine (0.625 to 5 mg/kg) and hyoscine (0.5 and 1 mg/kg) caused a dose-related rightward shift of the dose-response curve to oxotremorine in mice, but pimozide (0.25 to 1 mg/kg) was ineffective. Similar results were obtained in the rat.

5 Pimozide (0.125 to 1 mg/kg) caused a dose-related rightward shift of the dose-response curve to apomorphine in mice, but atropine (1.25 to 1 mg/kg) and hyoscine (0.5 and 1 mg/kg) were ineffective. Similar results were obtained in the rat.

6 Intrahypothalamic injection of apomorphine (10 μg) and oxotremorine (1.25 μg) caused a fall in core temperature in rats. Pimozide (0.5 mg/kg i.p.) caused reversal of the effect of apomorphine but did not significantly change the response to oxotremorine. Atropine (2.5 mg/kg i.p.) blocked the effect of oxotremorine, but not that of apomorphine.

7 These results suggest that there are both central dopamine and central muscarinic acetylcholine receptors which mediate a fall in core temperature in rodents, but do not support the hypothesis that any connection exists between these two receptor populations.

Introduction

Since Feldberg & Myers (1963) introduced their new concept of temperature regulation, based on a balance between noradrenaline and 5-hydroxytryptamine in the hypothalamus, much work has been concentrated on the role of these two amines in thermoregulation. Consequently, models for the hypothalamic control of body temperature have usually included noradrenaline and 5-hydroxytryptamine as putative neurotransmitters at synapses within the anterior and posterior hypothalamus (Maskrey & Bligh, 1971; Myers, 1975). Acetylcholine has also routinely been incorporated into these models, but dopamine has rarely been considered. However, since 1971 evidence has been accumulating which suggests that stimulation of central dopamine receptors can bring about thermoregulatory events in a variety of species (for a review see Cox, 1977) and it now seems pertinent to consider the inclusion of dopamine in any future model.

Apomorphine, a drug believed to act directly on central dopamine receptors (Ernst, 1967), lowered core temperature after intraperitoneal injection in the mouse (Fuxe & Sjöqvist, 1972) and after intracerebroventricular injection in the rat (Kruk, 1972). Pimozide was found to be an effective antagonist in both species, suggesting that the effect was indeed mediated via dopamine receptors. The possibility that acetylcholine was involved in the dopamine receptor mediated hypothermia has been advanced (Glick & Marsanico, 1974), since the temperature effects of apomorphine in mice were reported to be blocked by hyoscine. These findings were contrary to those of Fuxe & Sjöqvist (1972) who showed that atropine in the relatively high dose of 20 mg/kg was ineffective against apomorphine-induced hypothermia in the mouse. Also Glick & Marsanico (1974) postulated a site of action in the caudate nucleus whereas other

workers have suggested a hypothalamic site for the hypothermia-mediating dopamine receptors (Kennedy & Burks, 1974; Quock & Gale, 1974).

If dopamine receptors are ultimately to be considered for a physiological role in the control of body temperature then it is important to determine firstly the location of the receptors and secondly if a 'cholinergic link' exists. This will help to determine where dopamine is to be placed in the existing models. Therefore, the work to be reported provides more information on the interactions between dopamine-agonists and acetylcholine-antagonists in mice and rats. Wherever possible dose-response curves rather than individual dose studies have been carried out.

Methods

Albino mice of ASH strain and of either sex weighing 25 to 40 g were used in the experiments. In any one series, mice of the same sex were used and the weight range was within 10 grams. Sprague-Dawley male rats weighing 300 to 400 g were used with a within series weight range not exceeding 50 grams. The ambient temperature was maintained at 17 ± 1°C throughout and animals were acclimatized at this temperature for at least 2 h before an experiment was started.

Measurement of core temperature in mice and rats

Core temperature in mice was measured by means of a thermistor probe (L. Light Labs Ltd) inserted into the oesophagus to a depth of 2 cm and retained *in situ* until a constant temperature reading was obtained. Mice were allowed freedom of movement between temperature measurements. Oesophageal temperatures were recorded immediately before injection and at known intervals after the injection for a 70 min period. The experiments were arranged so that each test group included all the doses of the test drug and the 'saline control'. In some experiments mice were pre-treated with atropine (30 min), hyoscine (30 min) or pimozide (2 hours). Dose-response curves were obtained by calculating the maximum change in temperature which occurred within 70 min of injection for each individual mouse.

Core temperature was measured in lightly restrained rats by a rectal thermistor probe (L. Light Labs) inserted to a depth of 4 cm. Tail-skin temperature was measured by a strap-on thermometer attached to the base of the tail and insulated from the environment. Rats were tested immediately before and at 10 min intervals after drug or saline injection for a period of 70 min so that drug-induced changes in temperature could be determined for each rat. In some experiments rats were pretreated with either atropine (30 min) or pimozide (2 hours). Dose-response curves were obtained by the same methods as those used in mice.

Central injection of drugs

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 co-ordinates used, with bregma as the reference point, were anterior-posterior 1.8 mm, lateral 1.2 mm and depth 5.0 mm. With these co-ordinates the tip of the guide cannula lay 3 mm above the desired point of injection in the preoptic anterior hypothalamus. Drug injections were made seven days later via an injection cannula that was inserted into the guide cannula and that extended 3 mm past its tip. The volume of the central injections was 1 μl injected over a 45 s period. After completion of the experiment the injection sites were verified histologically.

Statistics

Comparisons between groups were made with 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 means ± s.e. mean are presented as the index of response. The slope of the log dose-response curves and the ED_{50} were calculated from a linear regression analysis.

Drugs

The drugs used were apomorphine hydrochloride (MacFarlan-Smith Ltd.), atropine sulphate (BDH), hyoscine hydrobromide (BDH), oxotremorine (R. Emanuel) and pimozide (Janssen). Drug solutions were prepared in a sterile, pyrogen-free 0.9% w/v Na Cl solution (saline), except for apomorphine: in this case the solution contained in addition 0.1% sodium metabisulphite to act as an antioxidant. A stock solution of pimozide was prepared by dissolving 100 mg of the drug in 3 drops glacial acetic acid and 3 drops absolute ethanol before the solution was made up to a final volume of 10 ml with a hot 5% w/v glucose solution. Solutions for injection were prepared by dilution of the stock solution with pyrogen-free saline. Controls injected with the appropriate vehicle were studied simultaneously. All drug doses refer to the free base.

Results

Intraperitoneal injections

The time course of the change in oesophageal temperature after injection of either oxotremorine or apo-

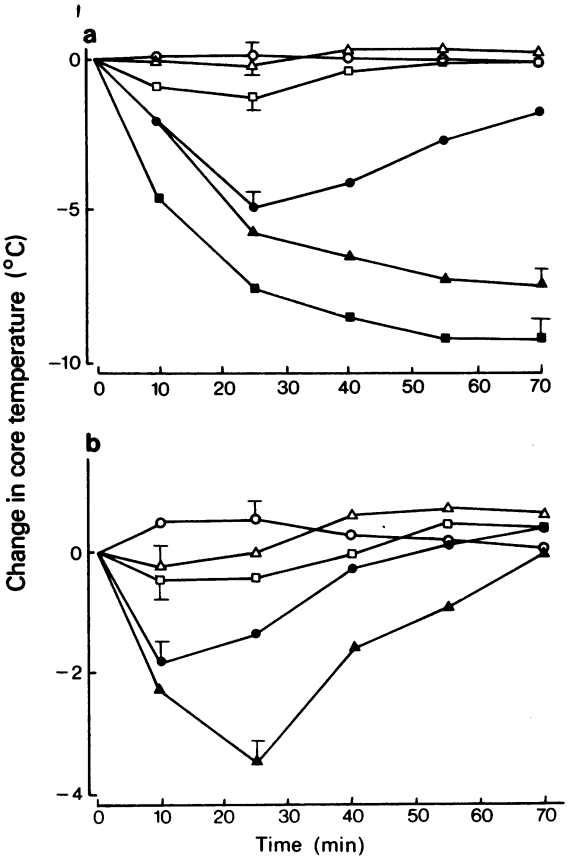

Figure 1 Time course of the core temperature response to intraperitoneal injections of oxotremorine (a) and apomorphine (b) in mice. Each point represents the mean change in oesphageal temperature for 5 mice after the injection of saline (○); oxotremorine 0.0125 (△), 0.025 (□), 0.05 (●), 0.1 (▲) and 0.2 (■) mg/kg or apomorphine 0.08 (△), 0.32 (□), 1.25 (●) and 5.0 (▲) mg/kg. Vertical bars indicate s.e. mean.

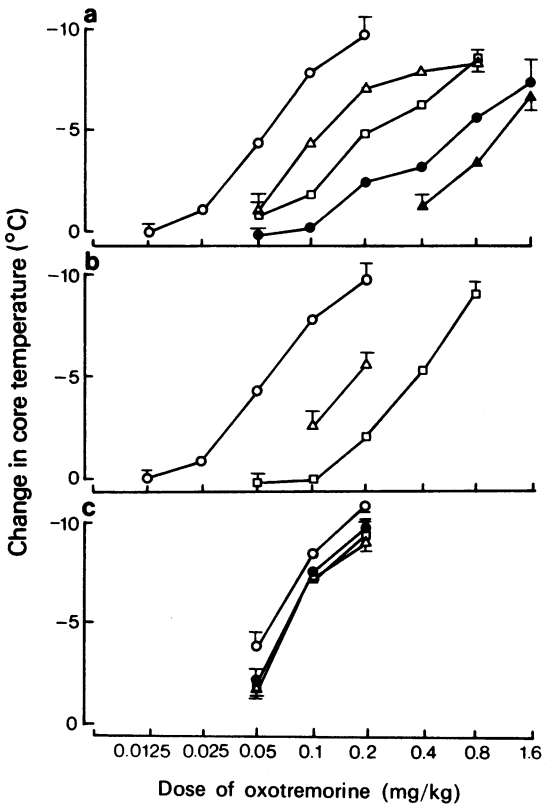

Figure 2 Dose-response curves to intraperitoneal injections of oxotremorine in mice pretreated with atropine (a), hyoscine (b) or pimozide (c). Each point is the mean maximum change in oesophageal temperature of 5 mice, for control mice (○), mice pretreated with atropine (a): 0.625 (△), 1.25 (□), 2.5 (●) and 5.0 (▲) mg/kg; hyoscine (b): 0.5 (△) and 1.0 (□) mg/kg and pimozide (c): 0.25 (△), 0.5 (□) and 1.0 (●) mg/kg. Vertical bars indicate s.e. mean.

morphine in mice is shown in Figure 1. Control mice had a mean oesophageal temperature of 36.9 ± 0.4°C at the beginning of the experiment. Injection of oxotremorine produced a dose-related fall in core temperature which was significant ($P < 0.01$) when 0.05 mg/kg or more was used. Similar results were obtained with apomorphine over the dose-range 0.32 to 5 mg/kg. The fall in core temperature after oxotremorine was more persistent than that observed after apomorphine injection.

Dose-response curves for oxotremorine and apomorphine were obtained by recording the maximum fall in core temperature for each individual mouse and calculating the mean maximum fall in temperature for each dose. Dose-response curves for oxotremorine are shown in Figure 2. Pretreatment of the mice with either atropine (Figure 2a) or hyoscine (Figure 2b) produced a dose-related rightward shift of the dose-response curves whereas pretreatment with pimozide (Figure 2c) had little or no effect. When apomorphine was used (Figure 3) pimozide produced a dose-related rightward shift of the dose-response curve (Figure 3a) but atropine (Figure 3b) and hyoscine (Figure 3c) were ineffective. The slope of the log dose-response curves for oxotremorine in mice was 8.2 ± 0.6, with a t of correlation of 12.9 for 25 trials. The ED_{50} calculated from the log dose-response regression line was 0.055 mg/kg with 95% confidence limits of 0.047 to 0.064. Corresponding values for apomorphine were slope 1.7 ± 0.3, with a t of 6.6 for

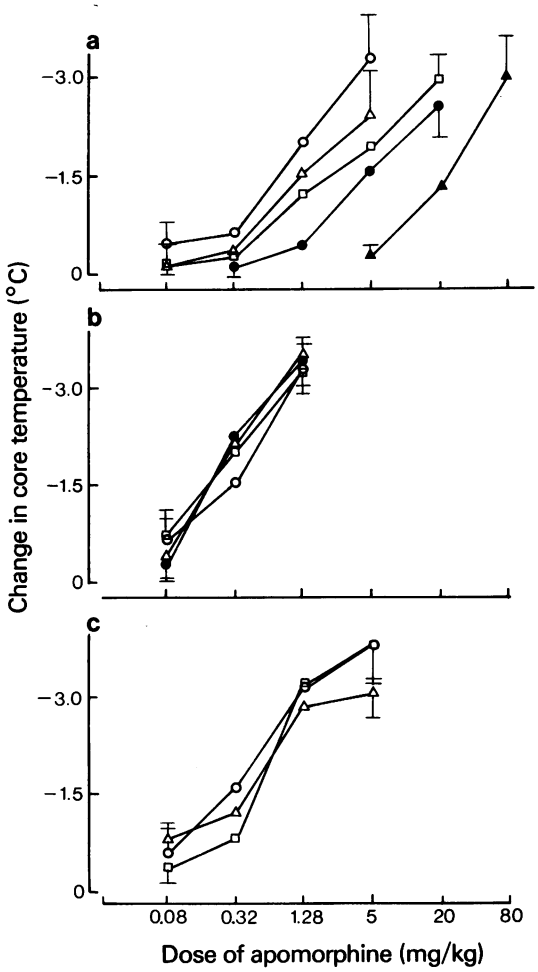

Figure 3 Dose-response curves to intraperitoneal injections of apomorphine in mice pretreated with pimozide (a), atropine (b) or hyoscine (c). Each point is the mean maximum change in oesophageal temperature of 5 mice for control mice (○), mice pretreated with pimozide (a): 0.125 (△), 0.25 (□) 0.5 (●) and 1.0 (▲) mg/kg; atropine (b): 1.25 (△), 5.0 (□) and 10.0 (●) mg/kg and hyoscine (c): 0.5 (△) and 1.0 (□) mg/kg. Vertical bars indicate s.e. mean.

20 trials. The ED_{50} was 0.5 mg/kg with 95% confidence limits of 0.32 to 0.80. By determining the ED_{50} for the agonists after antagonist pretreatment, it was possible to calculate the ratio:

$$\frac{ED_{50} \text{ after drug pretreatment, mg/kg}}{ED_{50} \text{ for concurrent saline control, mg/kg}}$$

The values for these ratios in mice are shown in Table 1.

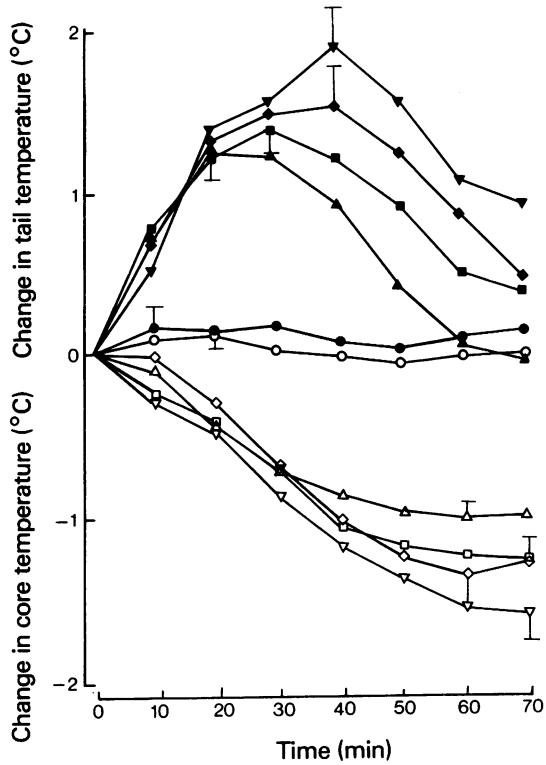

Figure 4 Time course of the core (open symbols) and tail (closed symbols) temperature response to intraperitoneal injection of oxotremorine in rats. Each point represents the mean change in temperature for between 6 and 8 rats after injection of saline (○, ●) or oxotremorine 0.625 (△, ▲) 0.125 (□, ■), 0.25 (◇, ◆) and 0.5 (▽, ▼) mg/kg. Vertical bars indicate s.e. mean.

The time course of the change in core and tail temperature after injection of either oxotremorine or apomorphine in rats is shown in Figures 4 and 5 respectively. Control rats had a mean core temperature of 38.4 ± 0.4°C and a mean tail temperature of 19.4 ± 0.4°C. Both drugs caused a dose-related increase in tail-skin temperature which preceded the fall in core temperature. Dose-response curves were obtained by recording the maximum change in core temperature for each individual rat and calculating the maximum fall at each dose level (Figure 6). The slope of the oxotremorine log dose-response curve was 0.9 ± 0.1 with a t of correlation of 7.7 for 35 trials and a calculated ED_{50} of 0.08 mg/kg (95% confidence limits 0.04 to 0.11). The slope of the apomorphine log dose-response line was 0.5 ± 0.07 with a t of 7.2 for 46 trials and a calculated ED_{50} of 0.4 mg/kg (95% confidence limits 0.28 to 0.55).

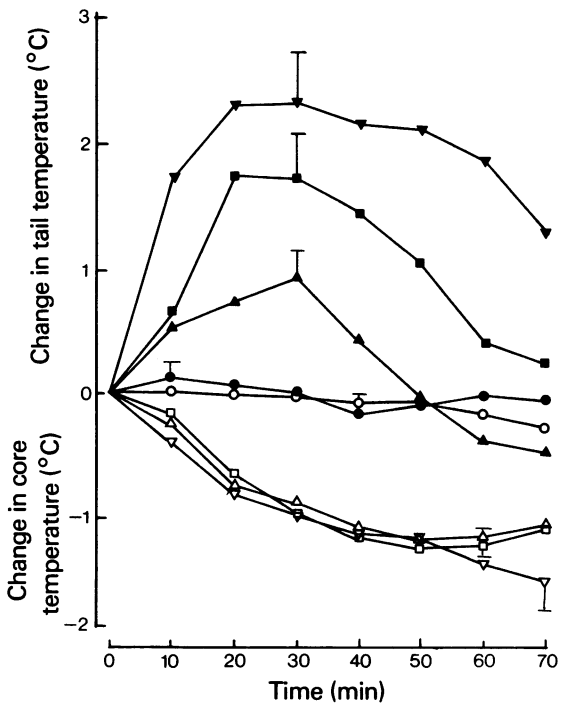

Figure 5 Time course of the core (open symbols) and tail (closed symbols) temperature response to intraperitoneal injection of apomorphine in rats. Each point represents the mean change in temperature for between 8 to 12 rats after injection of saline (○, ●), or apomorphine 0.32 (△, ▲), 0.625 (□, ■), and 1.25 (▽, ▼) mg/kg. Vertical bars indicate the s.e. mean.

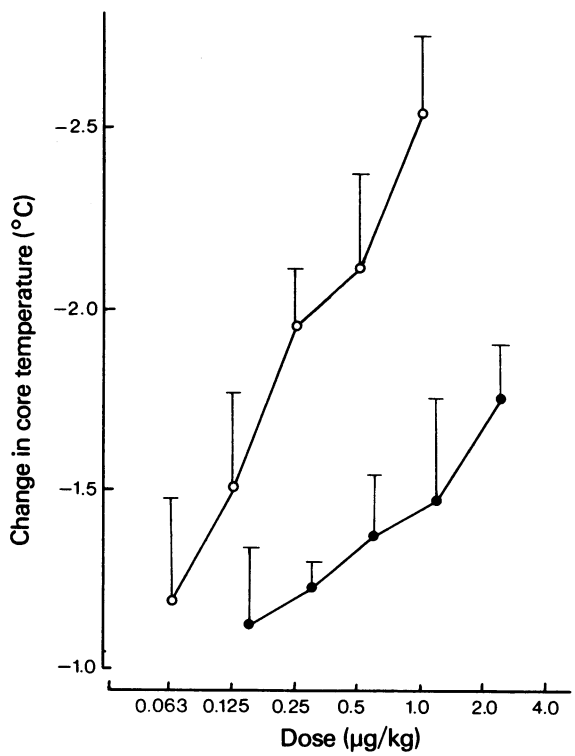

Figure 6 Dose-response curves to intraperitoneal injection of oxotremorine (○) and apomorphine (●) in rats. Each point is the mean maximum change in core temperature for between 6 to 12 rats. Vertical bars indicate s.e. mean.

The effects of atropine, hyoscine and pimozide on a sub-maximal response to oxotremorine are shown in Figure 7. Both atropine (2.5 mg/kg) and hyoscine (1 mg/kg) caused significant antagonism of oxotremorine but pimozide (0.125 to 0.5 mg/kg) had no significant effect. In contrast, when apomorphine was the agonist (Figure 8) pimozide caused a dose-related

Table 1 Ability of atropine, hyoscine and pimozide to block core temperature changes induced by apomorphine or oxotremorine in mice expressed as antilog of log [ED_{50} after drug pretreatment (mg/kg) − log ED_{50} in concurrent control (mg/kg)]

Pretreatment (mg/kg)	*Antilog [log ED_{50}(drug) − log ED_{50}(control)]*	
	Oxotremorine	*Apomorphine*
Saline	1	1
Atropine 1.25	3.8*	0.6
Atropine 2.5	11.3*	/
Atropine 5.0	18.0*	0.6
Hyoscine 0.5	2.9*	1.5
Hyoscine 1.0	5.8*	1.2
Pimozide 0.25	1.4	4.3*
Pimozide 0.5	1.4	7.6*
Pimozide 1.0	1.3	28.7*

* indicates a significant antagonism in that ED_{50}(drug) fell outside the 95% confidence limits of the ED_{50}(control).
/ indicates no experiment.

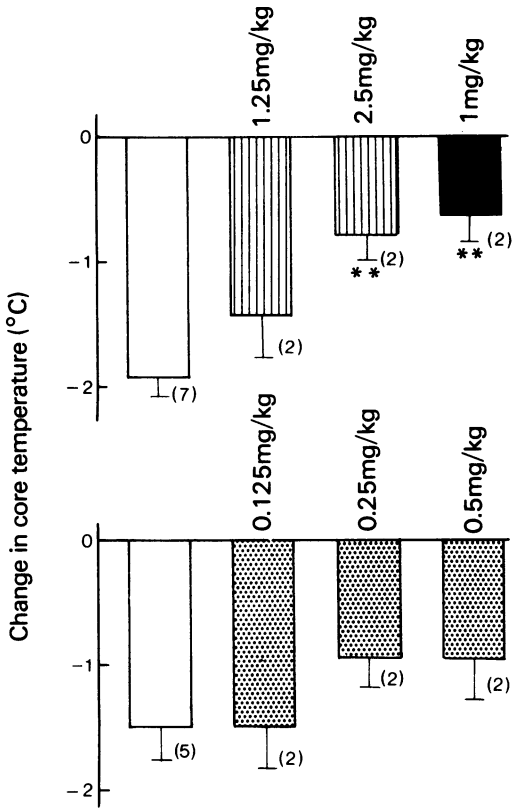

Figure 7 Change in core temperature of rats after intraperitoneal injection of oxotremorine 0.25 mg/kg alone (open columns) or after intraperitoneal pretreatment with atropine (striped columns), hyoscine (closed column) or pimozide (dotted columns). Doses of antagonists are shown above each column, which represents mean maximum fall in core temperature with vertical bars indicating s.e. mean. Figures in parentheses indicate the group size. $^{**}P < 0.01$.

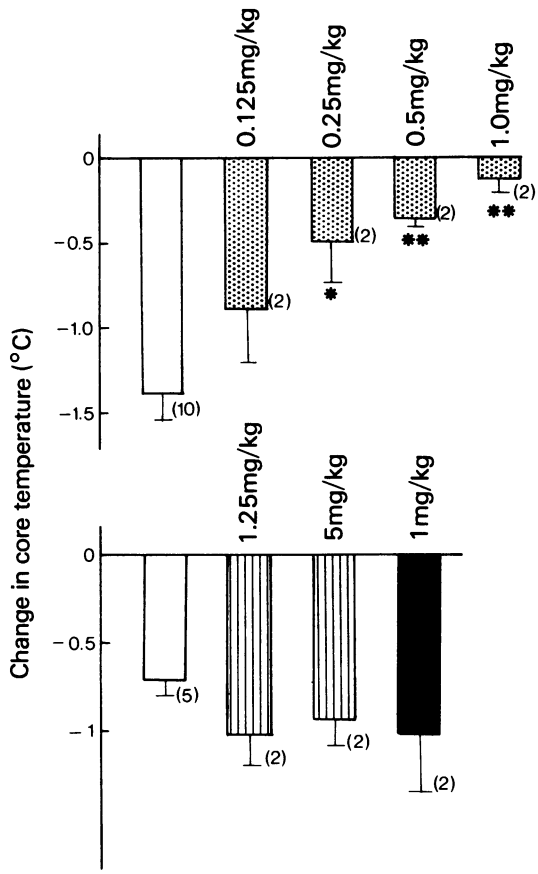

Figure 8 Change in core temperature of rats after intraperitoneal injection of apomorphine 0.625 mg/kg alone (open columns) or after intraperitoneal pretreatment with pimozide (dotted columns), atropine (striped columns) or hyoscine (closed column). Doses of antagonists used are shown above each column, which represents mean maximum fall in core temperature with vertical bars indicating s.e. mean. Figures in parentheses indicate the group size. $^{*}P < 0.05$; $^{**}P < 0.01$.

antagonism but atropine and hyoscine were ineffective as antagonists. Using log dose-response data the ratio:

$$\frac{ED_{50} \text{ after drug pretreatment, mg/kg}}{ED_{50} \text{ for concurrent saline control, mg/kg}}$$

was calculated for the various combinations of agonists and antagonists in the rat and are shown in Table 2.

Central injections

Direct injection of apomorphine (10 μg in 1 μl) or oxotremorine (1.25 μg in 1 μl) into the preoptic anterior hypothalamus of the rat caused a significant fall in core temperature (Figure 9). Pimozide (0.5 mg/kg i.p.) reversed the response to apomorphine but had no significant effect on the response to oxotremorine. Atropine (2.5 mg/kg i.p.) significantly reduced the response to oxotremorine but was ineffective as an antagonist of apomorphine.

Discussion

As described in the Introduction, there are alternative hypotheses for dopamine receptor mediated hypothermia. One hypothesis suggests that the receptors are located within the caudate and that there is a

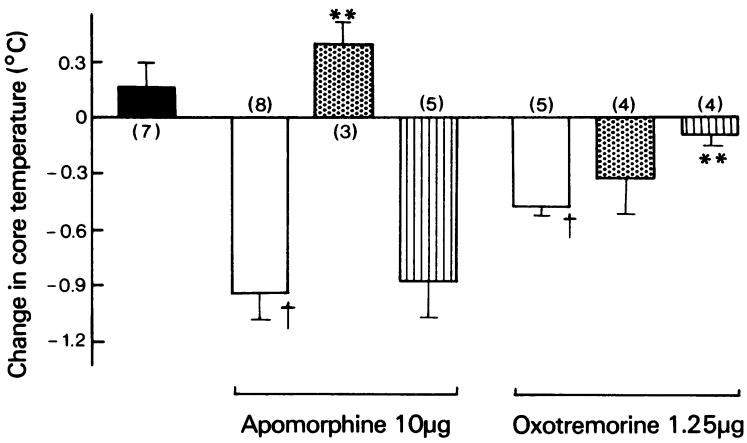

Figure 9 Change in core temperature after intrahypothalamic injection of either apomorphine 10μg or oxotremorine 1.25 μg alone (open columns) or after pretreatment with pimozide 0.5 mg/kg i.p. (dotted columns) or atropine 2.5 mg/kg (striped columns). The closed column represents the response to 1 μl intrahypothalamic saline. Each column represents the mean maximum fall in core temperature with vertical bars indicating s.e. mean. Figures in parentheses indicate the group size.
† significantly different from saline control, $P < 0.01$; ** significantly different from appropriate agonist control, $P < 0.01$.

'cholinergic link' in the hypothalamus. The other suggests a direct action within the hypothalamus with no evidence for a 'cholinergic link'. The experiments in our study were an attempt to investigate this problem further.

In the first series of experiments involving drug interactions the drugs were administered intraperitoneally. This ensured a wide distribution of the drugs, providing the best possibility for drug interaction. As a consequence of the intraperitoneal route it was not possible to use the putative transmitters themselves, instead oxotremorine a muscarinic agonist (Cho, Haslett & Jenden, 1962; Cox & Hecker, 1971) and apomorphine an agonist at dopamine receptors (Andén, Rubenson, Fuxe & Hökfelt, 1967) were used. They were chosen because they pass the blood brain barrier and are relatively resistant to inactivation (Bebbington & Brimblecombe, 1965; Butterworth, Poignant & Andén, 1975).

From the time course studies there was a clear dose-dependency for the effects of both agonists in mice. There was a difference in the time course of

Table 2 Ability of atropine, hyoscine and pimozide to block core temperature changes induced by apomorphine or oxotremorine in rats, expressed as antilog of [log ED_{50} after drug pretreatment (mg/kg) − log ED_{50} in concurrent control (mg/kg)]

Pretreatment (mg/kg)	*Antilog [log ED_{50}(drug) − log ED_{50}(control)]*	
	Oxotremorine	*Apomorphine*
Saline	1	1
Pimozide 0.125	1.8	4.9*
Pimozide 0.25	3.0	9.3*
Pimozide 0.5	3.6	13.6*
Pimozide 1.0	3.6	49.7*
Atropine 1.25	4.3+	0.3+
Atropine 2.5	11.1*	/
Atropine 5.0	/	0.2+
Hyoscine 1.0	20.3*	0.3+

* indicates a significant antagonism in that ED_{50}(drug) fell outside the 95% confidence limits of the ED_{50}(control).
/ indicates no experiment and + indicates a significant change in slope.

the response to apomorphine and oxotremorine, but by 70 min the peak effect had been reached. In the rat the dose-dependency was less clear. However, this apparent lack of dose-dependency was mainly due to individual variations in the time course. By plotting the mean of the maximum change in core temperature for each individual rat a clear dose-dependency emerged. Therefore, this system of expressing the dose-response data was used. The mouse was more sensitive to the agonists than the rat and showed a steeper log dose-response curve. Presumably this greater response was due to the increased susceptibility to heat loss in the mouse which has a larger surface area-body weight ratio. Measurement of tail temperature in the rat indicated that a peripheral vasodilatation occurred which would increase heat loss and therefore contribute to the fall in core temperature. Oxotremorine, the muscarinic agonist, could produce a vasodilatation by a peripheral action, thereby throwing doubt on its usefulness when studying central mechanisms. However, as a fall in core temperature occurs in the presence of a maximally effective blocking dose of the quaternary atropine derivative, atropine methonitrate (Hecker, 1971), then it would seem that the core temperature response to oxotremorine has a large central component independent of peripherally located muscarinic receptors.

In the mouse, both atropine and hyoscine produced a parallel shift to the right in the oxotremorine log dose-response curve with no change in the maximum response, a picture strongly resembling that seen with competitive antagonists *in vitro* (Arunlakshana & Schild, 1959). From the dose-ratios shown in Table 1 it can be seen that atropine and hyoscine were very effective antagonists of oxotremorine, but in contrast they were ineffective against apomorphine. Indeed in the case of atropine against apomorphine, the ratios obtained were less than one, indicating a small shift to the left in the log dose-response curve. Therefore in our experiments we could find no evidence for a 'cholinergic link' in apomorphine-induced hypothermia in the mouse. This agrees with the findings of Fuxe & Sjöqvist (1972), but is in conflict with those of Glick & Marsanico (1974). A possible explanation for the discrepancy was the different ambient temperature of the studies; Glick & Marsanico (1974) worked at 25 $\pm$ 1°C whereas the present study was carried out at 17 $\pm$ 1°C. Therefore the postulated 'cholinergic link' may only be active at the higher ambient temperatures. However, against this suggestion is a recent report (Poole & Stephenson, 1977) which shows that the ambient temperature of both studies fell within the thermoneutral range of 18 $\pm$ 1.9°C to 28.1 $\pm$ 1.0°C (mean $\pm$ s.d.).

The findings in the rat were consistent with those in the mouse except that the results were complicated by changes in slope of the log dose-response curve. This was particularly evident for apomorphine after atropine or hyoscine. However, there was no evidence for a significant antagonism by the muscarinic antagonists which if anything increased the response to apomorphine. In contrast these same doses of atropine and hyoscine were extremely effective against oxotremorine. Pimozide produced a dose-related block of apomorphine confirming that the apomorphine was acting on dopamine receptors.

A recent report (Jacob & Suaudeau, 1977) has suggested that atropine can block the response to intraventricular injection of dopamine. In our studies both apomorphine and oxotemorine injected directly into the preoptic anterior hypothalamus caused a lowering of core temperature in rats and suggest a hypothalamic location for the receptors mediating the hypothermia. Further, apomorphine was blocked by intraperitoneal pimozide but not by intraperitoneal atropine, whereas the reverse was true for oxotremorine. In all cases the doses used had been demonstrated to be selective against the peripherally administered agonists. Therefore, from these central studies, as in the peripheral studies, there is no support for a 'cholinergic link'.

In none of the studies involving either rats or mice did the antagonists themselves significantly modify either core or tail-skin temperature. Therefore it seems unlikely that any non-specific effects of the antagonists are contributing to the observed results. The question therefore arises, if there are dopamine receptors located within the preoptic anterior hypothalamus, do they have a physiological role? Some evidence is accruing that this may be the case in the rat (Cox & Lee, 1977) and in the goat (De Roij, Frens, Bakker & Németh, 1977). However, the position of dopamine within existing models is still uncertain. From our studies it seems unlikely that it exists in series with cholinergic synapses but from other studies it seems a 5-hydroxytryptamine link is a possibility (Maj, 1976).

A preliminary account of some of the work described in this paper was presented to the Third Symposium on the Pharmacology of Thermoregulation, Banff, Alberta, Canada in 1976.

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