REFERENCES

Baty, J. D., Robinson, P. R. (1977) Clin. Pharmacol. Ther. 21: 177–186

Cummings, A. J., King, M. L., Martin, B. K. (1967) Br. J. Pharmacol. Chemother. 29: 150–157

Mahgoub, A., Idle, J. R., Dring, L. G., Lancaster, R., Smith, R. L. (1977) Lancet 2: 584–586

Martin, B. K. (1967) Nature (London) 214: 247–249

Sato, M. (1978) in: Estabrook, R. W., Lindenlaub, E. (eds) 'The Induction of Drug Metabolism', Symposia Medica Hoechst, Vol. 14, F. K. Schattauer, Stuttgart-New York. p. 638

Sloan, T. P., Idle, J. R., Lancaster, R., Smith, R. L. (1978a) 7th Internat. Congress Pharmacol. 2866

Sloan, T. P., Mahgoub, A., Lancaster, R., Idle, J. R., Smith, R. L. (1978b) Br. Med. J. 2: 655–657

Vogel, A. I. (1951) A Text Book of Practical Organic Chemistry, 2nd edition, Longmans, London. p 554

Possible involvement of 5-hydroxytryptamine in dopamine-receptor-mediated hypothermia in the rat

B. Cox*, T. F. Lee, *Department of Pharmacology, Materia Medica and Therapeutics, Manchester University Medical School, Manchester M13 9PT, U.K.*

In most species dopamine agonists cause a fall in core temperature which is specifically antagonized by dopamine antagonists (for review see Cox 1979). In a previous study, the preoptic anterior hypothalamus was shown to be the most responsive site to central injection of dopamine agonists (Cox & Lee 1977). However, since other putative neurotransmitters, such as acetylcholine and 5-hydroxytryptamine (5-HT), are also reported to be present in the hypothalamus and to have an important role in thermoregulation, the relationship between dopamine and other transmitters in thermoregulation has been investigated. In 1974, a cholinergic link in dopamine-receptor-mediated hypothermia in mice was suggested by Glick & Marsanico. They reported that the hypothermia induced by intraperitoneal apomorphine injection was not only blocked by haloperidol, but also by hyoscine. More recently, this proposal received further support from the experiments of Jacob & Suaudeau (1977), who reported that the hypothermic response to intracisternal dopamine injection was significantly reduced by subcutaneous pretreatment with atropine. However, other workers have reported that atropine was ineffective in blocking the hypothermic effect of apomorphine (Fuxe & Sjöqvist 1972). Recently, an involvement of 5-HT in dopamine-receptor-mediated hypothermia has also been suggested. Dopamine agonist-induced hypothermia has been reported to be prevented by either 5,6-hydroxytryptamine or electrolytic lesions of the dorsal raphe nuclei (Maj & Przewlocka 1975; Przewlocki 1977). Further, Grabowska et al (1973) have shown that the hypothermia induced by apomorphine in rodents could be antagonized by lysergic acid diethylamide and butyrophenones. As with acetylcholine, some results contrary to those mentioned above have also been reported in that methysergide was found to be ineffective against the hypothermic response to the dopamine agonists (Grabowska et al 1973; Burks & Rosenfeld 1977). Therefore in this study, further investigations have been made to determine the relationship, if any, between central cholinergic and 5-hydroxytryptaminergic tracts in dopamine-receptor-mediated hypothermia in the rat.

Male Sprague-Dawley rats, 250 to 300 g, were used at an ambient temperature of 17 ± 1 °C. For the systemic injections, drugs were administered intraperitoneally in 1 ml kg^{-1}; and for central injections, drugs were given in 1 μl down guide cannulae which had been implanted 7 days previously into the preoptic anterior hypothalamus under pentobarbitone (45 mg kg^{-1}, i.p.) anaesthesia. The concurrent control group received the appropriate vehicle injected by the same route. Core temperature was measured by a rectal probe inserted to a depth of 4 cm. At the end of the experiment all the central injection sites were verified histologically.

In this study two types of experiment were performed. In the first series the effect of intrahypothalamic injection of various agonists were compared in controls and in rats pretreated systemically with various antagonists. Unilateral intrahypothalamic injection of the dopamine agonists, apomorphine and dopamine, caused a dose-related fall in core temperature of the rat (Fig. 1a, b). The significant fall in core temperature induced by dopamine (10 μg) or apomorphine (10 μg) was prevented by systemic pretreatment with the dopamine receptor antagonists, pimozide (2 h) and haloperidol (1 h). However, systemic pretreatment with atropine, methysergide and cyproheptadine (all for 1 h) failed to antagonize the hypothermic response to central dopamine agonist injection (Table 1). Oxotremorine (OT) and 5-HT also produced a dose-related fall in core temperature when administered

* Correspondence.

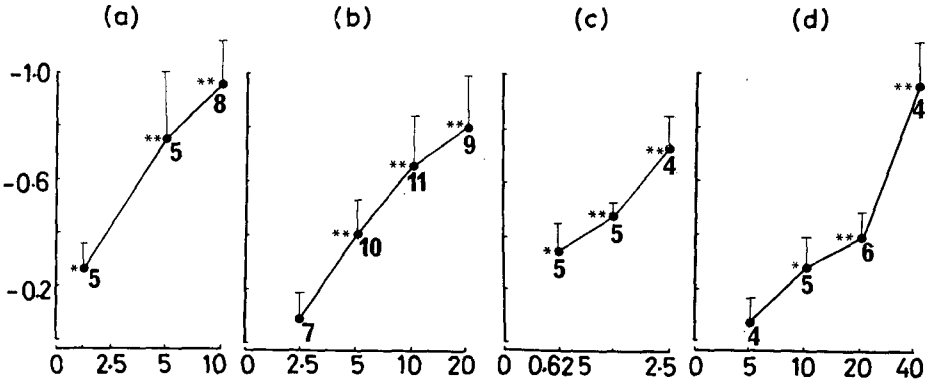

FIG. 1. Dose response curves to intrahypothalamic injection of (a) apomorphine, (b) dopamine, (c) oxotremorine and (d) 5-hydroxytryptamine in the rat. Each point is the mean maximum change in core temperature (°C: ordinate) from the number of rats indicated on curves. Vertical bars indicate standard error of the mean. Significance of difference from vehicle control, * $P<0.05$; ** $P<0.01$ (Mann-Whitney U test). Abscissa: dose (μg).

unilaterally into the preoptic anterior hypothalamus (Fig. 1c, d). The significant hypothermia induced by OT (1·25 μg) or 5-HT (20 μg) was antagonized only by their specific receptor antagonists, atropine, and methysergide or cyproheptadine respectively (Table 1). In all cases, the antagonists by themselves did not cause any significant change in core temperature from that seen after injection of 1 μl of saline into the hypothalamus of the controls (+0·2 ± 0·1 °C).

In the second series of experiments both antagonists and agonists were injected unilaterally into the same site within the preoptic anterior hypothalamus. Central pretreatment with the dopamine antagonists, pimozide and haloperidol, specifically antagonized the hypothermic effect of the dopamine agonists (Table 2). Conversely, atropine had a pronounced effect on the response to OT but was ineffective in blocking the responses to either the dopamine agonists or 5-HT (Table 2). Unilateral intrahypothalamic pretreatment with either cyproheptadine or methysergide was found to block not only the response to 5-HT, but also to be effective against the dopamine agonists. However, these two antagonists failed to prevent the hypothermic effect of OT. As in the systemic experiments, none of the antagonists caused any significant change in body temperature on their own.

According to the results of this study, the doses of atropine used were sufficient to antagonize OT-induced hypothermia. However, these same doses were ineffective against the fall in core temperature induced by the dopamine agonists whatever the route of injection. The ineffectiveness of atropine in blocking the hypothermic effective of apomorphine argues against a cholinergic link and supports the findings of Fuxe & Sjoqvist (1972).

As noted earlier, the involvement of 5-HT in dopamine-receptor-mediated hypothermia has been suggested. Methysergide and cyproheptadine, specific 5-HT receptor blocking agents (Douglas 1975), were used in the present study; and in confirmation of some earlier reports (Grabowska et al 1973), it was found that systemic pretreatment with either methysergide or cyproheptadine failed to prevent the hypothermic response to central injection of the dopamine agonists. However, methysergide and cyproheptadine significantly antagonized the response to these drugs when they were injected into the same preoptic site. This blocking effect appeared not simply to be a non-

Table 1. Effects of systemic pretreatment with various receptor antagonists against the hypothermic response to intrahypothalamic injection of various agonists in rats†.

Drugs	Apomorphine 10 μg	Dopamine 10 μg	OT 1·25 μg	5-HT 20 μg
Vehicle 1 ml kg^{-1}	−0·95 ± 0·17 (8)	−0·67 ± 0·18 (11)	−0·48 ± 0·05 (5)	−0·40 ± 0·09 (6)
Pimozide 0·5 mg kg^{-1}	+0·40 ± 0·10 (3)**	+0·05 ± 0·13 (4)*	−0·33 ± 0·22 (4)	−0·24 ± 0·11 (4)
Haloperidol 1 mg kg^{-1}	−0·07 ± 0·04 (4)**	+0·01 ± 0·11 (4)*	—	—
Atropine 2·5 mg kg^{-1}	−0·96 ± 0·23 (5)	−0·45 ± 0·20 (4)	−0·08 ± 0·06 (4)**	−0·34 ± 0·11 (4)
Methysergide 5 mg kg^{-1}	−0·76 ± 0·18 (7)	−0·40 ± 0·09 (5)	−0·38 ± 0·17 (4)	−0·03 ± 0·03 (4)**
Cyproheptadine 5 mg kg^{-1}	−0·67 ± 0·21 (7)	−0·41 ± 0·12 (5)	—	+0·08 ± 0·12 (5)**

† Results represent the mean maximum change in core temperature (°C ±s.e.) for the number of rats indicated in parentheses. Significance of difference from the concurrent control, *$P<0.05$; **$P<0.01$ (Mann-Whitney U test).

— Experiment not carried out.

Table 2. Effects of intrahypothalamic pretreatment with antagonists on the hypothermic response to intrahypothalamic injection of various agonists in the rat†.

Drugs	Apomorphine 10 μg	Dopamine 10 μg	OT 1·25 μg	5-HT 20 μg
Vehicle 1 μl	−0·94 ± 0·21 (5)	−0·67 ± 0·18 (11)	−0·52 ± 0·17 (4)	−0·43 ± 0·12 (5)
Pimozide 0·5 μg	−0·23 ± 0·16 (4)*	−0·05 ± 0·13 (4)*	−0·31 ± 0·10 (4)	−0·38 ± 0·05 (4)
Haloperidol 2·5 μg	−0·18 ± 0·09 (4)*	−0·01 ± 0·06 (4)*	—	—
Atropine 2·5 μg	−0·83 ± 0·03 (5)	−0·48 ± 0·13 (4)	+0·00 ± 0·22 (3)*	−0·35 ± 0·13 (4)
Methysergide 5 μg	−0·49 ± 0·05 (7)*	−0·18 ± 0·10 (4)*	−0·41 ± 0·10 (4)	−0·05 ± 0·03 (6)**
Cyproheptadine 5 μg	−0·30 ± 0·11 (5)*	−0·08 ± 0·09 (4)*	—	+0·19 ± 0·14 (9)*

† The results represent the mean maximum change in core temperature (°C ± s.e.) for the number of rats indicated in parentheses. Significance of the difference from the concurrent control, *$P<0·05$; **$P<0·01$ (Mann-Whitney U test).
— Experiment not carried out.
For all antagonists pretreatment time was 15 min.

specific effect, since there was no effect on the hypothermia induced by central OT injection. Similar findings have been reported by De Roij et al (1977, 1978). They found that central pretreatment with methysergide could antagonize the response to central dopamine injection in goats, but that this pretreatment did not affect central noradrenaline injection. These findings lead the authors to suggest that there may be a 5-HT link in dopamine-receptor-mediated hypothermia. However, from our studies, methysergide and cyproheptodine can only effectively block the response to dopamine when present in the large amounts achieved by central injection into the same preoptic site. Therefore there are two possibilities. One is that the drugs are acting on dopamine-receptors as well as 5-HT receptors, but there is no good evidence to support this suggestion. The other possibility is that the concentrations of methysergide and cyproheptadine achieved in brain after systemic injection is insufficient to compete with the local release of 5-HT caused by the dopamine-agonists. From the available evidence this seems the more likely.

Thus the results of this study may lead to the following conclusions. First, as atropine was ineffective against the response of central dopamine-agonist injection, it is unlikely that there is a cholinergic link in dopamine-receptor-mediated hypothermia in rats. Second, since methysergide and cyproheptadine were effective against the central dopamine agonist injection, when administered centrally into the same preoptic site, a 5-HT link in dopamine-receptor-mediated hypothermia in rats may be present.

The generous gift of methysergide maleate from Sandoz Ltd. is gratefully acknowledged.

November 7, 1978

REFERENCES

Burks, T. F., Rosenfeld, G. C. (1977) Drugs, Biogenic Amines and Body Temperature, Karger, Basel, pp. 204–206

Cox, B. (1979) in: Lomax, P., Schönbaum, E. (eds) Body Temperature, Drug Effects and Therapeutic Implications. Marcel Dekker, New York in press

Cox, B., Lee, T. F. (1977) Br. J. Pharmacol. 61: 83–86

De Roij, T. A. J. M., Frens, J. M., Bakker, J., Németh, F. (1977) Eur. J. Pharmacol. 43: 1–7

De Roij, T. A. J. M., Frens, J. M., Woutersen-Van Nijnenten, F. & Vianen-Meijerink, M. (1978) Ibid. 49: 395–405

Douglas, W. W. (1975) in: Goodman, L. S., Gillman, A. (eds) The Pharmacological Basis of Therapeutics, 5th edn, Collier-MacMillan. London. pp. 622–623

Fuxe, K., Sjöqvist, F. (1972) J. Pharm. Pharmacol. 24: 702–705

Glick, S. D., Marsanico, R. G. (1974) Br. J. Pharmacol. 51: 353–357

Grabowska, M., Michaluk, J., Antkiewicz, L. (1973) Eur. J. Pharmacol. 23: 82–89

Jacob, J. J. C., Suaudeau, C. R. (1977) Drugs, Biogenic Amines and Body Temperature, Karger, Basel. pp. 196–203

Maj, J. Przewlocka, B. (1975) Pol. J. Pharmacol. Pharm. 27: Suppl. 151–154

Przewlocki, R. (1977) Ibid. 29: 263–270