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Hypothermic effect of apomorphine in the mouse

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A new effect of apomorphine in lowering body temperature in mice is presented. The hypothermic effect is antagonized by haloperidol and pimozide, which block dopamine receptors in brain, and by desipramine and protriptyline which preferentially inhibit amine uptake in noradrenaline neurons. The finding may indicate that dopaminergic mechanisms are involved in temperature control in mice.

In 1963, Feldberg & Myers proposed that 5-hydroxytryptamine (5-HT) and noradrenaline neurons participated in temperature regulation in the hypothalamus. Measurements of turnover of noradrenaline and 5-HT after exposure of animals to various environmental temperatures have added support to this view (Corrodi, Fuxe & Hökfelt, 1967a, b; Simmonds & Iversen, 1969). In animals exposed to a high environmental temperature the turnover of noradrenaline and 5-HT was increased, while a low environmental temperature elicited a decrease in 5-HT turnover but no change in noradrenaline turnover. These and previous observations obtained after intraventricular and intracerebral injections of amines (Feldberg & Myers, 1963, 1965; Myers & Yaksh, 1969) suggest that 5-HT and noradrenaline neurons have a modulating influence on the thermo-regulatory mechanisms in the hypothalamus.

Whilst examining the hypothermic effect of oxotremorine in mice and rats we became interested in the possible role of dopamine neurons in thermo-regulation (Corrodi, Fuxe & others, 1967). Further work showed that apomorphine, considered to be a selective stimulant of dopamine receptors in brain (Ernst, 1967; Andén, Fuxe & others, 1967), lowered body temperature in mice. We now deal with this finding*.

MATERIAL AND METHODS

Male mice of the Swiss albino strain (20–30 g) were used. The rectal temperature was checked at regular intervals with an electrothermometer before and after intraperitoneal injection of various drugs.

Apomorphine was administered in doses of 5, 10 or 30 mg/kg.

Haloperidol was injected in a dose of 0·5 mg/kg 30 min before saline or apomorphine, respectively. This drug blocks both central dopamine and noradrenaline receptors in the doses used (Carlsson & Lindqvist, 1963; Corrodi, Fuxe & Hökfelt, 1967b).

Phenoxybenzamine was injected in a dose of 20 mg/kg 30 min before apomorphine. This drug blocks noradrenaline but not dopamine receptors in brain (Andén, Corrodi & others, 1967).

Pimozide (1 or 5 mg/kg) was injected 4 h before apomorphine (5 mg/kg). Pimo-

* After this study had been completed, Dr. Barnett informed us about his brief report of a hypothermic action of apomorphine (Barnett, Taber & Peschel, 1969).

zide is one of the most selective blockers of dopamine receptors in brain so far known (Andén, Butcher & others, 1970).

Protriptyline and *desipramine*, both in doses of 10–20 mg/kg, were injected 30 min before apomorphine. These drugs are potent blockers of amine uptake at the nerve cell membrane of peripheral and central noradrenaline neurons (Carlsson, Fuxe & others, 1966; Carlsson, Corrodi & others, 1969b).

Chlorimipramine in a dose of 10–20 mg/kg was injected 30 min before apomorphine. This drug is mainly a blocker of amine uptake in central 5-HT neurons (Carlsson, Corrodi & others, 1969a).

Atropine in a dose of 20 mg/kg was injected 30 min before apomorphine.

RESULTS

Apomorphine (5–10 mg/kg) caused a sharp decrease (3 to 4°) in the body temperature of mice (Table 1). Pretreatment of mice with haloperidol (0·5 mg/kg) but not with phenoxybenzamine (10 mg/kg) partially blocked the effect of apomorphine. Haloperidol (0·5 mg/kg) had no effect by itself on body temperature (Table 1). After pretreatment with pimozide in a dose of 1 mg/kg apomorphine elicited no hypothermic effect but rather a slight increase in body temperature (Table 2).

Desipramine and protriptyline in doses of 10 mg/kg also blocked the hypothermic action of apormorphine (Fig. 1). In fact, the temperature in these mice increased slightly after the injection of apomorphine. Chlorimipramine had a less marked blocking effect (Table 2). Atropine had no effect on the hypothermia induced by apomorphine (Fig. 1).

Table 1. *Apomorphine-induced hypothermia in mice—effect of pretreatment with phenoxybenzamine and haloperidol*.*

Pretreatment			Apomorphine mg/kg	Rectal temperature °C (means of 5–6 mice)									
Time	Drug	Dose		Before pretreatment	15′ after	0′	15′	30′	45′	60′	90′	150′	180′	s.e.†
30 min	Saline	10 ml/kg	5	38·9	—	38·5	35·3	34·2	37·4	37·0	37·7	37·1	37·3	0·1–0·3
30 min	Saline	,,	10	38·2	—	38·4	35·4	33·2	33·4	35·5	37·7	37·3	37·4	0·2–0·5
30 min	Phenoxybenzamine	10 mg/kg	10	38·3	37·1	37·3	35·0	33·3	33·0	34·3	36·3	36·4	36·8	0·1–0·4
30 min	Haloperidol	0·5 mg/kg	—	38·5	39·2	38·5	38·8	38·7	38·7	38·3	38·1	37·3	37·5	0·2–0·4
30 min	,,	0·5 mg/kg	10	37·8	38·8	38·3	36·0	37·3	37·7	38·2	38·2	36·7	37·1	0·2–0·3

* Room temperature 22°.
† Standard error of the mean.

Table 2. *Apomorphine-induced hypothermia in mice—effect of pretreatment with pimozide or chlorimipramine.*

Pretreatment			Apomorphine mg/kg	Before	Rectal temperature ° (means of 5 mice) After pretreatment				After apomorphine					
Time	Drug	Dose			15′	30′	75′	165′	15′	30′	45′	60′	90′	s.e.
4 h	Saline	10 ml/kg	5	37·7	—	37·5	37·4	37·1	36·7	35·4	36·3	37·0	—	0·2–0·3
4 h	Pimozide	1 mg/kg	5	37·8	—	37·7	37·7	37·1	37·7	37·8	37·6	38·0	—	,,
30 min	Saline	10 ml/kg	10	36·3	36·9	36·9	—	—	35·0	34·5	34·2	35·1	35·7	,,
30 min	Chlorimipramine	5 mg/kg	10	36·2	37·0	37·0	—	—	36·6	36·1	35·1	35·6	36·2	,,
30 min	,,	10 mg/kg	10	36·4	36·7	37·0	—	—	37·2	36·2	35·3	35·1	35·2	,,

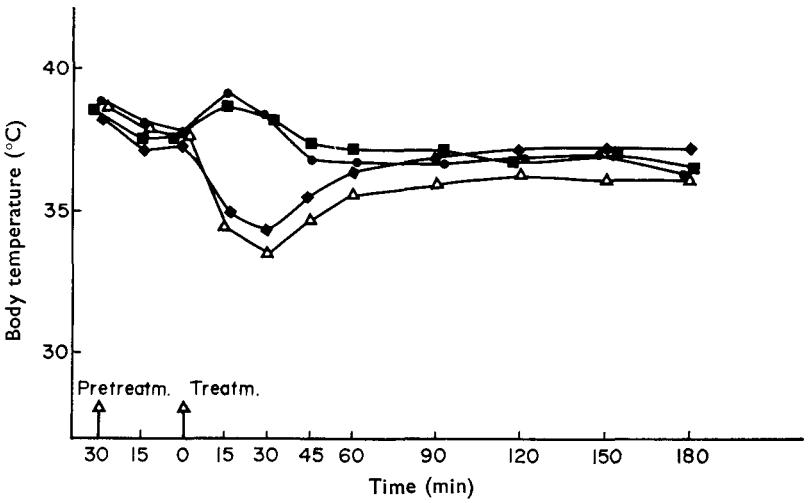

FIG. 1. Hypothermic effect of apomorphine in mice. This is unaffected by pretreatment with atropine but completely blocked by pretreatment with desipramine and protriptyline (PT) (*cf.* Table 2).

△ Saline and apomorphine (10 mg/kg, i.p.). ◆ Atropine (20 mg/kg) + apomorphine (10 mg/kg, i.p.). ■ Protriptyline (10 mg/kg) + apomorphine (10 mg/kg, i.p.). ● Desipramine (10 mg/kg) + apomorphine (10 mg/kg, i.p.).

DISCUSSION

The mechanism of action of apomorphine is thought to be a direct stimulation of dopamine receptors in brain, because it can increase dopamine receptor activity independent of dopamine in the nerve terminals (Ernst, 1967; Andén & others, 1967; Ungerstedt, 1971) as revealed in several behavioural tests (Randrup & Munkvad, 1968; Fuxe & Ungerstedt, 1970). The hypothermic action of apomorphine in mice was antagonized by haloperidol and especially by the specific dopamine-receptor blocking agent pimozide, but not by phenoxybenzamine, a blocker of noradrenaline receptors. These observations suggest that the hypothermic action is mediated by dopamine receptors in the central nervous system. The novel anti-parkinsonian drug amantadine has recently been reported to exert a hypothermic action in mice (Zetler, 1970). This is of interest in relation to its supposed dopamine releasing effect in brain (Grelak, Clark & others, 1970; Scatton, Cheramy & others, 1970; Strömberg, Svensson & Waldeck, 1970; Farnebo, Fuxe & others, 1971; Von Voigtlander & Moore, 1971). On the other hand, dopa treatment of parkinsonian patients does not result in hypothermic effects. This fact may be related to the simultaneous increase of peripheral and central noradrenaline release induced by dopa treatment resulting *inter alia* in increased peripheral vasoconstriction. The finding that pimozide can counteract amphetamine hyperthermia (Hill & Horita, 1971) may be explained along similar lines. The amphetamine-induced peripheral and central noradrenaline release may dominate dopamine release in the brain, and pimozide by its ability to block the motor hyperactivity induced by amphetamine, could reduce heat production and in this way counteract the hyperthermia.

Desipramine and protriptyline, which block the neuronal uptake of noradrenaline and to a lesser extent 5-HT, also counteracted the hypothermic action of apomorphine. This indicates that central noradrenaline and dopamine neurons have antagonistic

functions in body temperature control. Chlorimipramine, which predominantly inhibits 5-HT uptake, was less effective in antagonizing apomorphine hypothermia.

Cholinergic mechanisms do not seem to be involved in apomorphine-induced hypothermia, since atropine failed to antagonize the effect.

The results may indicate the existence of a critical balance between central dopamine and noradrenaline neurons in thermo-regulation. It appears that, at least in the mouse, a selective direct stimulation of dopamine receptors will elicit a decrease in body temperature, whereas a stimulation of noradrenaline (and perhaps 5-HT) receptor activity will tend to increase body temperature. It is well known that neuroleptic drugs in higher doses lower body temperature both in animals and man. It is tempting to suggest that this effect is partly mediated by their noradrenaline receptor blocking property. Thus, the hypothermic action of apomorphine must be allowed for in its use as a pharmacologic tool in elucidating the mechanism of action of other drugs or neuronal mechanisms in the central nervous system.

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