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THE EFFECTS OF INTRAVENTRICULAR 6-HYDROXYDOPAMINE ON BODY TEMPERATURE AND ARTERIAL BLOOD PRESSURE IN CATS AND RABBITS

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1 In unanaesthetized cats, the administration of 6-hydroxydopamine (6-OHDA), 750 μg, via the lateral cerebral ventricle produced a pronounced fall in rectal temperature but only a slight fall when repeated 7 days later. At this time hypothalamic noradrenaline concentration had diminished to 4% of control.

2 In these animals, the hypothermic response to exogenous noradrenaline, 100 μg, given via the same route was uninfluenced by pretreatment with 6-OHDA.

3 In unanaesthetized rabbits, intraventricular noradrenaline, 100 μg, produced a rise in rectal temperature and a biphasic effect on arterial pressure, a rise lasting 30 min followed by a fall.

4 Intraventricular 6-OHDA, 750 μg, in unanaesthetized rabbits produced a rise in body temperature and a rise in arterial pressure. The same dose given to rabbits depleted of central noradrenaline with central 6-OHDA produced rises in body temperature and arterial pressure of similar magnitude, but of slower onset.

5 These results suggest that intraventricular 6-OHDA releases noradrenaline from central neurones and that these neurones subserve thermoregulatory functions in both species. In the rabbit, central noradrenergic neurones can raise arterial pressure.

Introduction

The regional distribution of noradrenaline within the central nervous system (Vogt, 1954; Bertler, 1961) and its histochemical localization to nerve terminals (Dahlstrom & Fuxe, 1965) indicates that this catecholamine may act as a synaptic transmitting substance within the brain. In particular it has been suggested that central noradrenergic neurones are involved in the control of body temperature (Feldberg & Myers, 1964; Feldberg, 1968; Hellon, 1972), arterial blood pressure and heart rate (Chalmers & Reid, 1972).

The evidence implicating central noradrenergic mechanisms in the control of these peripheral autonomic functions is derived principally from the results of experiments in which exogenous noradrenaline is introduced directly into the lateral cerebral ventricle or cisterna magna. Thus in the cat (Feldberg & Myers, 1963), dog and monkey (Feldberg, Hellon & Lotti, 1967), intraventricular noradrenaline produces a fall in body temperature while in the mouse (Brittain & Handley, 1967), rabbit (Cooper, Cranston & Honour, 1965) and sheep (Bligh, 1966) there is a rise. Furthermore, the ox (Findlay & Thompson, 1968) is unresponsive to intraventricular noradrenaline, while the rat has a biphasic temperature response (Feldberg & Lotti, 1967). Arterial blood pressure and heart rate of anaesthetized rabbits (Toda, Matsuda & Shimamoto, 1969) and dogs (McCubbin, Kaneko & Page, 1960) are reduced by intraventricular noradrenaline, although in the unanaesthetized rabbit there is an initial pressure rise lasting 20-40 min (Toda *et al.*, 1969). Such studies are clearly complicated not only by the interspecies differences in the temperature response to centrally administered noradrenaline, but also by the apparent influence of anaesthesia on the cardiovascular effects. Furthermore, relatively large amounts of exogenous noradrenaline must be administered to elicit both the thermoregulatory and cardiovascular responses.

An alternative method of approaching these problems is to employ agents which increase the effective concentration of endogenous noradrenaline within the synaptic cleft. This can be done using substances which release noradrenaline from the presynaptic nerve terminals or which prevent its re-uptake. The latter approach has been utilized in studies of temperature regulation (Cranston, Hellon, Luff & Rawlins, 1972) by

administering desipramine and imipramine into the lateral central ventricles of cats and rabbits; changes in body temperature resulted which were different for the two species but nevertheless closely resembled those following intraventricular injection of relatively large amounts of exogenous noradrenaline.

There is evidence to suggest that 6-OHDA, a synthetic dopamine analogue which causes long-lasting destruction of adrenergic neurones (Thoenen & Tranzer, 1968) produces an initial release of noradrenaline from nerve terminals (Simmonds & Uretsky, 1970; Howard, Leahy & Breese, 1971). The present study was undertaken to investigate whether injections of 6-OHDA into the cerebral ventricles resulted in effects on body temperature and arterial pressure similar to those of exogenous noradrenaline and whether animals which have been depleted centrally of noradrenaline become refractory to attempts to release noradrenaline with further doses of 6-OHDA.

Methods

Experiments were performed using male New Zealand white rabbits weighing 2.3-2.8 kg and cats weighing 2.8-3.2 kg of either sex. In both species, rectal temperature was measured every 160s with a Kent multichannel recorder, with a thermistor inserted 8-10 cm.

Cats

In four cats, Collison cannulae (Feldberg & Sherwood, 1954) were inserted into one lateral cerebral ventricle under general anaesthesia (pentobarbitone sodium, 30 mg/kg) at least one week prior to any further procedure. At the start of each experiment, the animals were placed in individual cages measuring 300 x 400 x 600 mm. When rectal temperature had been stable for at least 30 min, injections of noradrenaline, 100 μg, or 6-hydroxydopamine (6-OHDA), 750 μg, were made intraventricularly in a total volume of 100 μl and temperature recorded for at least 4 h thereafter. Each animal received noradrenaline first, followed 2 days later by 6-OHDA. Seven days were allowed to elapse before each animal received further injections of noradrenaline and 6-OHDA again separated by 2 days. These cats, together with four normal control animals were sacrificed by intraperitoneal pentobarbitone overdosage and the brains rapidly removed and dissected over ice. Tissues were frozen at -70°C and assayed fluorimetrically for noradrenaline (von Euler & Lishajko, 1961) and dopamine (Carlsson & Waldeck, 1958) following alumina column chromatographic extraction.

Rabbits

The blood pressure and temperature responses of rabbits to intraventricular injections of noradrenaline, 100 μg, and 6-OHDA, 750 μg, were studied in different groups. Intraventricular injections were made using modified Monnier-Gangloff head plates (Cooper *et al.*, 1965) which had been affixed under pentobarbitone anaesthesia at least one week previously. At the start of each experiment animals were placed in conventional headstocks. Blood pressure was measured directly via a polypropylene catheter inserted into the central artery of one ear and connected to a Devices strain gauge transducer. When blood pressure and temperature had remained stable for at least 30 min, intraventricular injections of noradrenaline (6 rabbits) and 6-OHDA (5 rabbits) were made in a volume of 100 μl and recordings performed for 4 h thereafter. In a further group of four animals, the responses of blood pressure and temperature to intraventricular 6-OHDA were studied 8 days after pretreatment with 6-OHDA, 500 μg/kg, administered intracisternally under light pentobarbitone anaesthesia as described previously (Chalmers & Reid, 1972). In an additional group of experiments, the acute effects on arterial blood pressure of intravenous 6-OHDA at doses of 25, 250 and 2,500 μg/kg in a volume of 1 ml were studied in five rabbits. Intravenous injections were made into the marginal vein of the ear through an indwelling 23G butterfly needle.

Drugs

(−)-Noradrenaline bitartrate (1 μg/ml) was used directly from commercially available capsules (Levophed: Bayer Products Ltd). 6-OHDA hydrobromide (Sigma Chemical Co.) was freshly dissolved in 0.9% (w/v) sodium chloride solution containing 0.1% (w/v) ascorbic acid.

Results

Cats

The mean body temperature response of cats to intraventricular noradrenaline 100 μg is shown in Figure 1. A mean maximum fall of 1.33°C (s.e. mean ± 0.12) was observed in normal animals. Seven days after intraventricular 6-OHDA, the hypothermic response to noradrenaline was unaltered (at 60 min, $P > 0.05$).

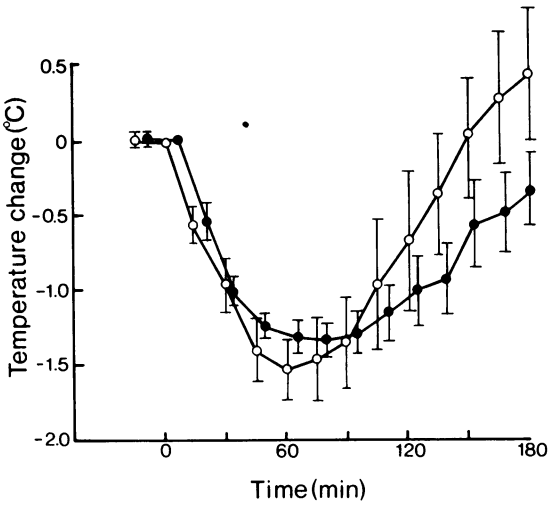

Fig. 1 Change in rectal temperature (mean ± s.e. mean) in four cats after noradrenaline, 100 μg, intraventricularly. Before (●) and 7 days after (○) 6-hydroxydopamine, 750 μg, intraventricularly.

The mean temperature response of these cats to intraventricular 6-OHDA, 750 μg, is shown in Figure 2. A profound fall in temperature (mean maximum fall 4.35 ± 0.31°C) resulted after the first injection. However, when this dose was repeated 9 days later in the same animals there was a maximum temperature fall of only 0.62 ± 3.2°C, significantly less than the first response (at 180 min, $P < 0.01$).

The degree of depletion of noradrenaline in different brain regions achieved with intraventricular 6-OHDA administered 9 days previously, is shown in Table 1. Hypothalamic noradrenaline content was reduced to 4% of control. Telencephalic dopamine concentration was reduced to 65% of control levels.

Rabbits

Noradrenaline (100 μg; administered by intraventricular injection) increased body temperature in rabbits by 0.94 ± 0.33°C at 150 min (Figure 3). Arterial blood pressure showed a biphasic response to this dose of intraventricular noradrenaline with an initial short lasting rise in pressure followed by a more persistent fall (Figure 3). Intraventricular 6-OHDA, 750 μg, caused a rise in rectal temperature in rabbits (Fig. 4) and an acute rise in mean arterial pressure lasting 20-40 min (Figure 5). Unfortunately, four out of five of these animals died within 24 h of this procedure. In a further group of four animals, pretreated 8 days previously with intracisternal 6-OHDA, 500 μg/kg, subsequent intraventricular administration of 6-OHDA, 750 μg, still caused a rise in temperature although the time course was delayed (Figure 4). Thus the average rise in temperature at 30 min in normal and pretreated rabbits was 0.46 ± 0.14°C (s.e. mean ± 0.14) and 0.03 ± 0.14°C respectively while at 150 min the corresponding values were 1.64 ± 0.30°C and 1.10 ± 0.39°C. Similarly, although in the 6-OHDA pretreated animals a rise in arterial pressure was still observed after intraventricular 6-OHDA, the onset was delayed (Figure 5). The depletion of noradrenaline achieved by pretreatment with intracisternal 6-OHDA is shown in Table 1. Telencephalic dopamine was reduced to 56% of control.

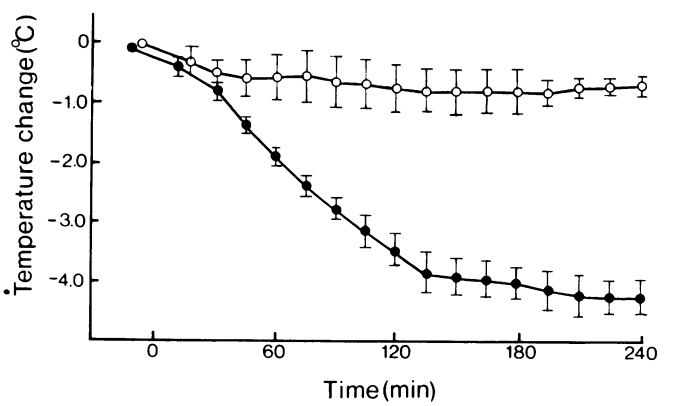

Fig. 2 Change in rectal temperature (mean ± s.e. mean) in four cats following 6-hydroxydopamine, 750 μg, intraventricularly; first dose (●) and second dose 9 days later (○).

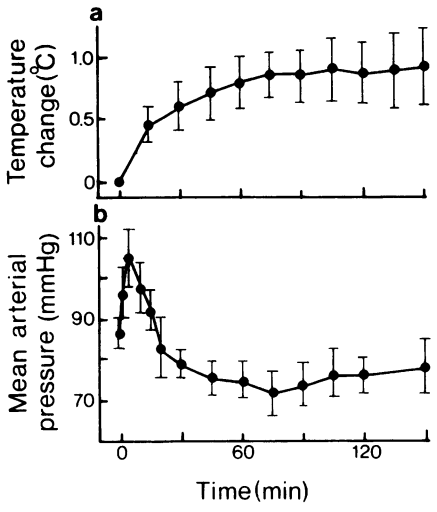

Fig. 3 Effect of intraventricular noradrenaline, 100 μg, on rectal temperature (a) and mean arterial blood pressure (b) in five unanaesthetized rabbits. Vertical bars indicate ± s.e. mean.

In view of the possibility that the cardiovascular effects of intraventricular 6-OHDA were mediated by a peripheral action of the compound which had leaked from the cerebrospinal fluid, the effects of intravenous 6-OHDA on arterial blood pressure were examined in four conscious rabbits. Single intravenous injections of 75 μg and 750 μg were without effect on arterial pressure, but a rise in mean arterial pressure occurred from 98.8 ± 7.2 mmHg to a maximum of 127.5 ± 7.2 mmHg at 1 min after intravenous injection of 3 mg. At 10 min mean arterial pressure had fallen to 101.3 ± 7.2 mmHg.

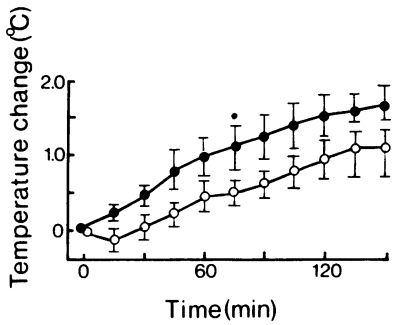

Fig. 4 Effect of intraventricular 6-hydroxydopamine, 750 μg, on rectal temperature in conscious rabbits. Normal rabbits (•) and rabbits pretreated with intracisternal 6-hydroxydopamine 7 days previously (○). Vertical bars indicate ± s.e. mean.

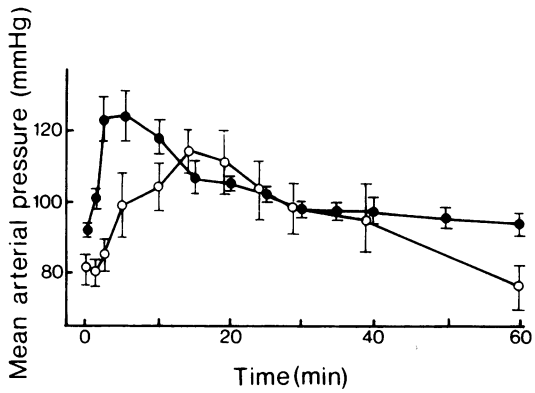

Fig. 5 Effect of intraventricular 6-hydroxydopamine, 750 μg on mean arterial pressure in conscious rabbits. Normal rabbits (•) and rabbits pretreated with intracisternal 6-hydroxydopamine 7 days previously (○). Vertical bars indicate ± s.e. mean.

Table 1 Endogenous brain noradrenaline content in cats and rabbits pretreated with central 6-hydroxydopamine (6-OHDA). Cats (n = 4) pretreated 9 days earlier with intraventricular 6-OHDA, 750 μg, compared with a control group of normal cats (n = 4). Rabbits (n = 6) pretreated 8 days earlier with intracisternal 6-OHDA, 500 μg/kg, and a control group of normal rabbits (n = 6). Mean values ± s.e. are given

	Cats			*Rabbits*		
	Control (ng/g)	*6-OHDA*		*Control (ng/g)*	*6-OHDA*	
		(ng/g)	*% control*		*(ng/g)*	*% control*
Telencephalon	150 ± 11	20 ± 5*	13	172 ± 8	77 ± 4*	45
Hypothalamus	529 ± 22	23 ± 4*	4	1377 ± 132	740 ± 88*	54
Mid brain	279 ± 35	188 ± 27	68	367 ± 15	140 ± 14*	38
Medulla-pons	197 ± 16	80 ± 14*	41	465 ± 38	285 ± 31*	61
Cerebellum	170 ± 59	6 ± 1*	3	132 ± 6	27 ± 5*	20

* $P < 0.01$, when compared by Student's t test.

Discussion

The temperature responses of normal cats to intraventricular noradrenaline observed in the present study (Fig. 1) were both qualitatively and quantitatively similar to those reported previously (Feldberg & Myers, 1963, 1964; Cranston *et al.*, 1972). In these animals intraventricularly administered 6-OHDA also produced profound hypothermia (Fig. 2) which was largely abolished when the compound was readministered in the same dose and by the same route 9 days later. At this time, although the hypothalamic noradrenaline content was reduced to 4% of control, the hypothermic response to intraventricular noradrenaline was unimpaired. In normal rabbits, both intraventricular noradrenaline and 6-OHDA produced similar increases in temperature. Pretreatment with 6-OHDA intracisternally resulted in a lowering of hypothalamic noradrenaline content to 54% of control levels, and intraventricular injection of 6-OHDA in those animals produced a delayed rise in temperature.

The most likely explanation of these results is that the acute effects of 6-OHDA on body temperature are caused indirectly by release of endogenous catecholamine. It is unlikely that 6-OHDA produces these effects by a direct postsynaptic action since the response to intraventricular noradrenaline was not affected by pretreatment with 6-OHDA, indicating the presence of intact postsynaptic receptors. It is probable that the failure to abolish the hyperthermic 6-OHDA response in the rabbit as completely as the hypothermic response in the cat, is related to the different depletion of hypothalamic noradrenaline achieved in the two species.

A similar delay, but not abolition of the hypothermic response of rabbits to intraventricular desmethylimipramine after comparable depletion of endogenous noradrenaline by pretreatment with α-methyl-*p*-tyrosine has been observed by Cranston *et al.* (1972). Simmonds & Uretsky (1970) suggested that dopamine may be implicated in the hypothermic action of intraventricular 6-OHDA in rats. However, Breese & Howard (1971) found that while preferential depletion of brain noradrenaline impaired the response to subsequent doses of 6-OHDA, preferential depletion of dopamine did not. In our studies, the response to 6-OHDA in the cat was largely abolished by 6-OHDA when hypothalamic noradrenaline was 4% and telencephalic dopamine was 65% of control. By contrast, the hyperthermic response in the rabbit was still present when the concentrations of noradrenaline and dopamine were reduced to only 54% and 56% respectively. Although Myers & Yaksh (1968) noted little effect of intraventricular dopamine on body temperature in the rat, a dose dependent hypothermic action of intraventricular dopamine in this species has been recently reported (Kruk, 1972). It is possible that the temperature changes in the rabbit following 6-OHDA are mediated by release of both noradrenaline and dopamine, but the data here presented from the cats imply that, in large part, the action of 6-OHDA is due to its effect on noradrenergic neurones.

The intraventricular injection of both noradrenaline and 6-OHDA in unanaesthetized rabbits produced similar increases in arterial blood pressure. The possibility that the response to noradrenaline was mediated by a peripheral action of this amine due to leakage from the subarachnoid space cannot be excluded. It seems unlikely, however, that such a mechanism could account for the response to 6-OHDA since the dose which produced a rise in blood pressure after intraventricular injection had no effect when given intravenously. Furthermore, if, as we have suggested, 6-OHDA produced its effects on arterial pressure by release of noradrenaline, then it seems reasonable that the effect might be delayed if noradrenaline concentration were diminished.

The acute effects of 6-OHDA when given by the intracisternal route have not been investigated in conscious rabbits. In rabbits under pentobarbitone anaesthesia, intracisternal 6-OHDA produces a transient fall in arterial pressure which lasts 1-3 h (Chalmers & Reid, 1972). These different results may be due to the effect of pentobarbitone anaesthesia on central cardiovascular control (Korner, Uther & White, 1968). Alternatively, 6-OHDA may exert its effect on different regions of the brain and spinal cord when administered by these two routes.

The present studies suggest that central noradrenergic neurones influence arterial blood pressure and that hypothalamic noradrenergic neurones have a pressor action. The hypotensive action of (−)-propranolol when administered intracerebroventricularly in the conscious rabbit (Dollery, Lewis, Myers & Reid, 1973) is consistent with these findings, as are the observations that pretreatment of rabbits with intracisternal 6-OHDA will prevent the onset of neurogenic (Chalmers & Reid, 1972) or renal (Lewis, Reid, Chalmers & Dollery, 1973) hypertension in this species.

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