Acute thermoregulatory and cardiovascular effects of 6-hydroxydopamine administered centrally in rabbits and cats

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Central noradrenergic neurones have been implicated in the control of both thermoregulation (Hellon, 1972) and blood pressure (Chalmers & Reid, 1971). The administration of 6-hydroxydopamine (6-OHDA) into the c.s.f. of rats (Uretsky & Iversen, 1970) and rabbits (Chalmers & Reid, 1971) produces long-lasting depletion of brain noradrenaline (NA). However, recent studies suggest that 6-OHDA produces an initial release of endogenous NA both *in vitro* (Kuchii & Shibata, 1972) and *in vivo* (Breese & Howard, 1971). The acute effects of 6-OHDA on temperature and blood pressure in cats and rabbits after injection into a lateral cerebral ventricle have therefore been studied in order to elucidate the central noradrenergic control of these functions.

6-OHDA (750 μg) was administered intraventricularly to five conscious rabbits. Mean arterial blood pressure rose from 92 mmHg (S.E. of mean $\pm$2·0) before injection to a maximum of 124 mmHg (S.E. of mean $\pm$7·0) after 5 min; in the same animals, rectal temperature increased by 0·46°C (S.E. of mean $\pm$0·14) after 30 min and by 1·64°C (S.E. of mean $\pm$0·30) at 150 min following injection. Five rabbits were pre-treated with 400 μg/kg 6-OHDA by intracisternal injection to deplete brain NA (Chalmers & Reid, 1971). Eight days later, 750 μg 6-OHDA was administered intraventricularly. Although blood pressure and temperature rose significantly, the time courses of both responses were delayed. Thus mean arterial blood pressure rose from 85 mmHg (S.E. of mean $\pm$7·4) before injection to a maximum of 114 mmHg (S.E. of mean $\pm$5·9) after 15 min; rectal temperature increased by 0·03°C (S.E. of mean $\pm$0·16) after 30 min and by 1·1°C (S.E. of mean $\pm$0·39) and 150 min following injection. In 4 conscious cats intraventricular injections of 750 μg 6-OHDA caused a fall in temperature of 4·35°C (S.E. of mean $\pm$0·31) over the succeeding 240 min. Administration of the same dose of 6-OHDA intraventricularly into the same animals 9 days later produced a maximum temperature fall of 0·62°C (S.E. of mean $\pm$0·32). In these cats the hypothermic response to intraventricular NA (100 μg) was unaltered by the administration of 6-OHDA 7 days previously.

The temperature changes in rabbits and cats after intraventricular injections of 6-OHDA are further evidence to indicate that endogenous NA functions as a central neurotransmitter in thermoregulation. The effects of intraventricular 6-OHDA on blood pressure in rabbits adds support to the hypothesis that endogenous NA is a central transmitter in cardiovascular control.

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The effect of some synthetic analogues of ACTH on the metabolism of biogenic amines in the rat brain

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The present investigation consists of a study of the role of pituitary-adrenal hormones in avoidance conditioning of the rat. It was found that hypophysectomy markedly impaired the acquisition of a conditioned avoidance response in a shuttle-box. Treatment of hypophysectomized rats with ACTH restored the deficient performance almost to normal (De Wied, 1964).

It was later found that the synthetic analogues ACTH 1–10 and ACTH 4–10, which lack the endocrine and metabolic effects of ACTH, showed a similar facilitation of avoidance conditioning in hypophysectomized rats (De Wied, 1969). Treatment of intact rats with the same peptides delayed extinction of a conditioned avoidance response (Van Wimersma Greidanus & De Wied, 1971). It was also found that ACTH 4-10-7-D-Phe facilitated extinction of the avoidance behaviour in intact rats and failed to facilitate acquisition in hypophysectomized rats (De Wied, 1969).

Other investigators have shown that ACTH 4-10 in intact rats, increased the incorporation of ^{14}C-leucine into brain proteins; ACTH 4-10-7-D-Phe was without effect (Reading & Dewar, 1971). This suggests that the behavioural effects of some of the ACTH analogues might be a consequence of their action on the synaptosomal membrane. The present investigation was therefore undertaken to see if there was any correlation between the effects of these peptides on the metabolism of brain amines and their reported effects on behaviour.

Groups of 10 male Wistar rats, initially weighing 70–80 g, were injected daily for two weeks with 10 μg of ACTH 4-10 or ACTH 4-10-7-D-Phe. This was the same dose schedule as used in the behavioural studies. The animals were killed by decapitation, the brains dissected into cortical, mid-brain and brain stem regions and assayed for noradrenaline, dopamine, 5-hydroxytryptamine, their precursor amino acids and some of their metabolites by the fluorometric methods which have been described previously (Leonard, 1972; Leonard & Shallice, 1971). In some experiments, the effect of these peptides was also studied on the depletion of brain noradrenaline and 5-hydroxytryptamine by α-methyl tyrosine and p-chlorophenylalanine respectively. Both peptides were found to affect brain amine metabolism and their effects were qualitatively similar. ACTH 4-10 reduced the 5-hydroxytryptamine concentration and, in the brain stem, increased the 5-hydroxyindoleacetic acid concentration. ACTH 4-10-7-D-Phe had a similar action. Both peptides slightly increased the tryptophan concentration. Brain tyrosine and noradrenaline concentrations were slightly reduced by the peptide; normetanephrine levels were also reduced in the cortex and mid-brain, but slightly elevated in the