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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

brain stem. The concentration of dopamine was unaffected in any of the regions, but γ-aminobutyric acid levels were reduced throughout the brain. Both the peptides slightly increased the depletion of brain noradrenaline and dopamine caused by α-methyl tyrosine, but decreased the reduction in the 5-hydroxytryptamine concentrations caused by p-chlorophenylalanine.

They may act by slightly increasing the release of noradrenaline, but decreasing that of 5-hydroxytryptamine possibly by reducing the synthesis of this amine. However, as these peptides have different effects on the conditioned avoidance behaviour, but qualitatively similar effects on brain amine metabolism, it seems unlikely that these biochemical effects can explain the behavioural changes.

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The role of catecholamines in the reversal of reserpine-induced hypothermia in mice by desipramine and chlorpromazine

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Whittle (1967) has suggested that the reversal of reserpine-induced hypothermia in mice by desipramine and chlorpromazine is mediated by catecholamines. The present study was designed to test this hypothesis.

Groups of 6 male, albino mice (body weight, 18–20 g) were injected subcutaneously with reserpine 2 mg/kg, and maintained at an environmental temperature of 20 ± 1°C. Seventeen h later, the test drug or control vehicle was administered. Oesophageal temperatures were measured every hour using an orally-inserted probe.

Subcutaneous injection of L-dopa (125–500 mg/kg) produced a dose-dependent increase in the body temperature of reserpinized mice, confirming the results of Barnett & Taber (1968) and reversed some of the other symptoms of reserpinization.

Intraventricular and subcutaneous injection of catecholamines induced a hyperthermic effect in reserpinized mice. In addition, intraventricularly injected dopamine

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