No evidence was found of direct interaction between L-dopa or dopamine and α-adrenoceptors Thus guanethidine, while capable of blocking the mydriatic action of L-dopa and dopamine, does not decrease the mydriatic response to direct α-adrenoceptor stimulating drugs such as phenylephrine (Sneddon & Turner, 1967). The waning of mydriasis produced by L-dopa or dopamine might suggest an α-adrenoceptor blocking action of these drugs. However, treatment of the eye for several hours with L-dopa or dopamine, with or without prior treatment with guanethidine eye drops, does not prevent a brisk mydriatic response to 10% phenylephrine drops (B.P.C.). Although prolonged exposure to high concentrations of drug is particularly favourable for the demonstration of adrenoceptor-blocking activity, no such activity was detectable in this test system.

It is uncertain whether the pharmacological activity of L-dopa is intrinsic or due to its principal metabolite, dopamine. Pyridoxal phosphate is an active coenzyme in the decarboxylation of L-dopa to dopamine, but in high concentrations inhibits his conversion (Lovenberg *et al.*, 1963). Pyridoxine eye drops (5% w/v in boratet buffer) have no effect on pupillary diameter. Administration of pyridoxine by mouth or intravenously (100–400 mg), or addition of 5% pyridoxine to dopamine eye drops (10%) does not affect the mydriatic response to dopamine. However, inclusion of 5% pyridoxine in 1% L-dopa eye drops decreases their mydriatic effect, while oral administration of pyridoxine may alter the mydriatic response to L-dopa eye drops in occasional subjects. Chromatographic studies suggest that pyridoxine does not interact with dopamine or L-dopa *in vitro*. The pharmacological effects of L-dopa may be due wholly or in part to its rapid conversion to dopamine *in vivo*.

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## Release by amphetamine in man of growth hormone and corticosteroids: the effects of thymoxamine and propranolol

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Methylamphetamine induces secretion of ACTH and growth hormone in man (Besser, Butler, Landon & Rees, 1969). The effect on ACTH is greater at night than in the morning, suggesting that the drugs may influence the mechanisms responsible for the nyctohemeral rhythm of ACTH secretion. We now report the influence of thymoxamine, an antagonist at α-adrenoceptors for catecholamines, and propranolol, a β-adrenoceptor antagonist, on these hormonal changes.

Twelve normal male volunteers, aged 21 to 34, were studied on three occasions at 18.00 h. Six subjects were present in the same room at each experimental session. An intravenous cannula was inserted into each subject. Thirty minutes later either thymoxamine (0·1 mg/kg body weight), propranolol (0·15 mg/kg body weight) or saline as a placebo was given intravenously, followed 5 min later in every subject by 15 mg methylamphetamine. The blocking drugs and the placebo were allocated by a random, double-blind, cross-over method. Blood was sampled immediately before the administration of methylamphetamine and then at 15 min intervals for 1 h in order to determine plasma fluorogenic corticosteroids (Mattingly, 1962) and immunoreactive growth hormone and ACTH concentrations (Hunter & Greenwood, 1964; Landon & Greenwood, 1968).

After the placebo, methylamphetamine caused a maximum rise in the plasma corticosteroids of 9·5±1·23 (mean±standard error of mean) μg/100 ml at 30 min, and in growth hormone of 13·4±3·68 ng/ml at 45 min. Increased ACTH levels preceded the rise in corticosteroids in both subjects in whom it was measured. This methylamphetamine-induced rise in plasma corticosteroids and ACTH was completely inhibited by thymoxamine, but after propranolol the maximum increase in corticosteroids (12·7±1·44 μg/100 ml) was significantly greater than after the placebo ($P<0·01$). The maximum increases in concentration of plasma growth hormone were, however, significantly greater after both thymoxamine (25·5±7·69 ng/ml, $P<0·01$) and propranolol (36·4±7·85 ng/ml, $P<0·01$).

By contrast thymoxamine given in the same manner and dose before intravenous insulin (0·15 u./kg body weight) did not alter the rise in plasma corticosteroids and growth hormone seen in six normal male volunteers in response to the induced hypoglycaemic stress.

Thymoxamine, propranolol or methylamphetamine did not alter the rate of disappearance of cortisol given intravenously (1 mg/kg). These results, together with the measured changes in plasma ACTH concentrations, suggest that the alterations in circulating levels of corticosteroids were not due to variation in the peripheral metabolic clearance of cortisol but rather to changes in ACTH secretion.

Thus, pharmacologically distinct pathways may be involved in the corticosteroid responses to methylamphetamine and hypoglycaemia, although both are thought to be mediated via hypothalamic-pituitary mechanisms. Amphetamine-sensitive control mechanisms for growth hormone secretion are influenced by blockade of catecholamine receptors in a manner which is probably different from those involved in ACTH release.

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