Studies have been undertaken in two patients and three volunteers using specially prepared " medihalers " loaded with ^{3}H-isoprenaline, designed to deliver 500 μg per dose. Arterial blood samples were taken in four of the studies, at timed intervals immediately after the inhalation. Urine was collected for 48 h after administration of the ^{3}H-isoprenaline.

In no subject was a pharmacological response detected. In three subjects no radioactivity was found in the arterial blood. In the other, radioactivity equivalent to isoprenaline 0·3 ng/ml was detected 5 min after inhalation.

Two of the normal subjects excreted 96 and 97·25% of the total dose in the urine over 48 h. In a third subject, in whom collections were incomplete, only 48% of the dose was recovered, but the pattern of metabolite excretion was the same.

The urinary radioactivity comprised conjugated isoprenaline (81–95%) conjugated 3-O-methyl isoprenaline (4–6%), free isoprenaline (1–2%) and free 3-O-methyl isoprenaline (1–2%).

The pattern of metabolism following administration of isoprenaline from the " medihaler " is similar to that seen after small oral doses (0·5 mg isoprenaline) administered to three other subjects in which the urinary radioactivity was mainly conjugated isoprenaline (68–94%). The remainder of the radioactivity was conjugated 3-O-methyl isoprenaline (2–8%), free isoprenaline (4%) and free 3-O-methyl isoprenaline (0–1%). The pattern of metabolism in both studies differs from that seen after intravenous administration, in which up to 30% of the isoprenaline is excreted as 3-O-methyl isoprenaline, and none as the conjugate of isoprenaline.

The conclusion from this study is that most of the isoprenaline taken from a pressurized aerosol is swallowed.

The effects of dopamine, L-dopa, L-tyrosine, and pyridoxine on sympathetic nerve endings in man

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The normal human eye has been used as a model for investigating the mechanism of action of L-dopa and related substances in volunteer subjects. Eye drops of L-dopa (1·0% w/v in borate buffer) and dopamine (10% w/v in bicarbonate:sulphite buffer) produce marked mydriasis. Solutions of L-tyrosine (0·06% w/v in borate buffer) have no detectable effects. Prior treatment with 5% guanethidine eye drops (Ismelin eye drops; Ciba) reduced or abolished the mydriatic response to L-dopa or dopamine in five out of twelve subjects. Persisting response to dopamine or L-dopa after guanethidine pre-treatment in the remaining seven subjects was associated with preservation of the mydriatic response to tyramine (2% w/v in borate buffer). These results suggest that the mydriatic action of dopamine and L-dopa, like that of tyramine, is indirect, depending on release of noradrenaline from sympathetic nerve endings. Probable depletion of noradrenaline in the sympathetic nerve endings of the iris by guanethidine eye drops inhibits the action of all these drugs. In six out of forty subjects, mydriasis produced by dopamine or L-dopa waned gradually despite continued instillation of the drug into the conjunctival sac. This decreasing mydriasis may reflect depletion of available noradrenaline stores.

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.