Finally we have shown that even large doses of normetanephrine (2 mg) injected intraperitoneally are without effect on spontaneous locomotor activity.

Degeneration of adrenergic nerves produced by 6-hydroxydopamine

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6-Hydroxydopamine (6-OH-DA) has been shown to deplete adrenergic nerves of endogenous noradrenaline (NA) (Porter, Totaro & Stone, 1963; Laverty, Sharman & Vogt, 1965; Thoenen, Hurlimann & Haefely, 1968). Several explanations for this depleting effect have been reported. Degenerative changes of sympathetic nerves in the cat have been observed in the electron microscope after injection of 6-OH-DA (Tranzer & Thoenen, 1967).

The purpose of this study was to investigate the action of 6-OH-DA on the adrenergic nerves by means of the histochemical fluorescence method of Falck and Hillarp for demonstration of catecholamines. Irides and atria from mice were prepared as stretch preparations and superior cervical ganglia and vas deferens were freeze dried. All tissues were treated with formaldehyde gas at 80° C for 1 hr, before examination by the fluorescence microscope. After the intravenous administration of 6-OH-DA (HBr, 20 mg/kg) the fluorescence of the adrenergic nerves of the iris underwent a general reduction within 15 min; after 1–2 hr there were no nerves visible in most animals. After about 8 hr strongly fluorescent parts of non-terminal axons terminating in a bulge could be seen. A complete restoration was not seen in 14–16 days.

The effect of 6-OH-DA at this dose level was not so pronounced on the other organs studied. Desmethylimipramine (25 mg/kg, 30 min beforehand) prevented the effect of 6-OH-DA. Reserpine (10 mg/kg, 30 min beforehand) did not delay the effect of 6-OH-DA, while nialamide (100 mg/kg, 1 hr beforehand) delayed the disappearance of NA somewhat and bretylium tosylate (50 mg/kg 30 min beforehand) even more.

There was no restoration of specific fluorescence after administration of α-methyl-NA (0.2 mg/kg I.V.) as long as the specific fluorescence from endogenous NA was lacking. This was not explained by blocking of the axon membrane pump by 6-OH-DA. These data support the assumption that 6-OH-DA or some metabolite causes a degenerative destruction of the sympathetic nerves, and that 6-OH-DA could be useful tool for achieving a chemical sympathectomy.

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The effect of tyramine, reserpine and other drugs on catecholamine metabolism in man

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There may be at least two forms of bound noradrenaline in the tissues; one appears to be liberated by nerve stimulation and by tyramine directly into the bloodstream, where

it is predominantly inactivated by catechol-*O*-methyltransferase, whilst the other is predominantly degraded by monoamine oxidase (MAO) in the tissue itself (Kopin, 1966). Some of the animal data drawn on to reach this conclusion have, however, been criticized (Smith, 1966) on the grounds that the tyramine dosage used was excessive and might have acted as a competitive MAO inhibitor. The present study was carried out to establish whether data compatible with the hypothesis could be obtained in man, using comparatively low drug dosage.

At intervals, six adult male volunteers were injected intravenously and with suitable precautions, with placebo, tyramine (2 mg), (+)-amphetamine (10 mg), prenylamine (30 mg) and reserpine (1.25 mg). Urine collections made at 1, 3, 6, 9, 12 and 24 hr were analysed for total metadrenalines, 4-hydroxy-3-methoxymandelic acid (VMA) and 4-hydroxy-3-methoxyphenylglycol (HMPG) by methods previously employed (Sandler & Ruthven, 1966).

Compared with placebo, tyramine provoked a significant general increase of urinary catecholamine metabolite output during the first 3 hr of urine collection. There was a relatively greater proportion of *O*-methylated metabolites (total metadrenalines) compared with the more prolonged but also highly significant increase in excretion noted after reserpine, where the oxidatively deaminated *O*-methylated metabolites (VMA and HMPG) predominated. These data mirror the findings in certain human catecholamine-secreting tumours (Sandler & Ruthven, 1966). The increase of HMPG at the expense of VMA observed after reserpine (Sandler & Youdim, 1968) could not be detected after prenylamine although the comparatively low ratio of *O*-methylated to oxidatively deaminated metabolites was similar after each drug. Amphetamine seemed to have little effect on metabolite output.

These observations in man and their implications are compatible with those summarized by Kopin (1966).

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Studies on the uptake and accumulation of ^{3}H-noradrenaline in adrenergic nerves after pretreatment with reserpine, nialamide and a tyrosine-hydroxylase inhibitor

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The uptake and accumulation *in vitro* of ^{3}H-noradrenaline in adrenergic nerves of rat iris during various experimental conditions has been studied. The rats were pretreated with reserpine (10 mg/kg I.P., 16 hours beforehand) and/or nialamide (100 mg/kg I.P., 2 hours beforehand) or with the tyrosine-hydroxylase inhibitor H 44/68 (the methylester of α-methyl-*p*-tyrosine; 500 mg/kg I.P., 16 hours beforehand). The irides were dissected out and incubated *in vitro* in a Krebs-bicarbonate buffer containing different concentrations