Stimulation in the presence of phenoxybenzamine (10 μg/ml.) resulted in a marked increase in the outflow of ^{3}H-NA. This effect was observed at both frequencies of stimulation, but was more pronounced for the lower frequency. In the presence of phenoxybenzamine no increase in outflow of ^{3}H-NA metabolites was observed when the nerves were stimulated. This effect of phenoxybenzamine appears to be due to prevention of access of the released transmitter to the metabolizing enzymes and not to an inhibitory effect on enzyme activity (Eisenfeld, Axelrod & Krakoff, 1967). The increase in outflow of transmitter observed in the presence of phenoxybenzamine was so large, however, that only a fraction could be accounted for by the prevention of the metabolism of the released ^{3}H-NA. The release of ^{3}H-NA and its metabolism were also studied in the presence of phentolamine (3 μg/ml.) and in the presence of cocaine (0.3 μg/ml.).

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Some pharmacological effects of noradrenaline and its metabolites injected into the cerebral ventricles in mice

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In recent years there have been many reports of changes in the urinary excretion patterns of catecholamine metabolites in patients suffering from some forms of mental disorders. We have been interested, therefore, in investigating the possibility that some of these metabolites might themselves influence the activity of the central nervous system.

Using an intracerebroventricular injection route we have started by measuring the effects of noradrenaline, normetanephrine, 3-4 dihydroxymandelic acid and vanillylmandelic acid on barbiturate sleeping time, spontaneous locomotor activity and motor co-ordination, in mice.

Because of the obvious limitations of these preliminary experiments, the results obtained are difficult to interpret; nevertheless some tentative conclusions are possible. All doses used are expressed in terms of base/20 g mouse.

On barbiturate sleeping time, noradrenaline (15 μg) caused a 50% increase, whereas all of the metabolites were inactive. These findings would support the conclusions of the many workers investigating peripheral mechanisms that the metabolism of noradrenaline results in deactivation.

In contrast the severe akinesia resulting from the administration of noradrenaline (5–20 μg) was also apparent following injections of normetanephrine (20–80 μg), whereas the deaminated metabolites were still without effect. Similar results were obtained on the accelerating rotarod, although in this case the dose of normetanephrine needed to produce a similar degree of inco-ordination was ten times that of noradrenaline (5–20 μg).

The relatively low doses of normetanephrine needed to produce marked effects in these tests might be taken to indicate that *O*-methylation in the central nervous system is not a deactivating process. The observations that the activity of noradrenaline in these tests is uninfluenced by pretreatment with pyrogallol (100 mg/kg intraperitoneally) but is potentiated by (as are the effects of normetanephrine) pretreatment with iproniazid (100 mg/kg intraperitoneally) are in accord with this suggestion.

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