Fifty-two cells have been tested so far with both noradrenaline and isoprenaline. The profiles of activity were similar for the two amines and in no case did a cell respond in opposite directions to the two; isoprenaline had about one third the excitant potency of noradrenaline. The effects of isoprenaline, however, persisted for twice as long as noradrenaline; following a contact time of 75 sec the excitant effects of isoprenaline (100 nA) lasted a further 10 min compared with about 5 min for noradrenaline.

Previously, we showed that dibenamine applied locally from another barrel of the multibarrelled micropipette would, on some occasions, selectively abolish noradrenaline excitations. A further antagonist at α-receptors for adrenaline has now been used. In all the nine cells tested, phentolamine (22 nA) produced a complete block of noradrenaline excitations within 6 min and this effect was reversible. At the height of the block, the response of the cell to other excitatory agonists (for example, acetylcholine or L-glutamate) was unaffected.

Two β-receptor antagonists, propranolol and 2-isopropylamino-1-(*p*-nitrophenyl) ethanol HCl (INPEA) have also been tested against noradrenaline excitations. Propranolol was more difficult to use than INPEA, for it was depressant ("local anaesthetic") in fifteen out of eighteen cells tested, and, because of this, it was often impossible to demonstrate a specific block of a noradrenaline response. INPEA (25 nA) produced a complete and specific block of noradrenaline excitations in seven out of nine cells tested within 2 min.

The block of noradrenaline excitations by α or β receptor blocking agents was similar in each of the three types of preparation used.

These results indicate that neuronal excitation by noradrenaline involves either a population of mixed α and β receptors or a different type of receptor.

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The effects of phenoxybenzamine on metabolism of ^{3}H-noradrenaline released from the isolated nictitating membrane

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When the noradrenaline (NA) stores of isolated nictitating membrane of the cat were labelled with ^{3}H-NA, stimulation of the nerves resulted in an increased outflow of ^{3}H-NA and metabolites, mainly ^{3}H-normetanephrine (NMN) and ^{3}H-4-hydroxy-3-methoxy-mandelic acid (Langer, 1968).

When the nerves were stimulated at 25 shocks/sec only about 35% of the total increase in radioactive products was due to ^{3}H-NA. The remaining 65% were accounted for by ^{3}H-NA metabolites.

When the frequency of stimulation was reduced to 4 shocks/sec, the ^{3}H-NA metabolites amounted to as much as 80% and ^{3}H-NA to only 20% of the total increase in outflow of labelled compounds.

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.