mitter NA. At the same time, the released dopamine acts post-junctionally to increase the sensitivity of the effector cells. Thus, despite a reduction in transmitter release, there is a compensatory effect which tends to maintain transmission.

Although there is evidence in accord with this hypothesis for adrenergic transmission in the rabbit ear artery, the mechanism does not appear to operate in the guinea-pig atria or vas deferens.

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Effect of tricyclic antidepressants on the cardiovascular responses of the rat

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Moir, Crooks, Cornwell, O'Malley, Dingwall-Fordyce, Turnbull & Weir (1972), using a hospital-based drug information system, confirmed a possible correlation between the administration of amitriptyline and the incidence of sudden and unexpected death in patients with a diagnosis of cardiac disease. They found the incidence to be 13 such cases in 119 amitriptyline treated patients compared with only 3 in a matched control group. There were only 4 such deaths in a group of 87 patients receiving imipramine compared with 2 in the control group.

One or more of the following factors, acting alone or in combination, could contribute to the cardiotoxic effect of this group of drugs: potentiation of the effects of catecholamines by inhibition of their uptake; an atropine-like effect, or a direct effect on the myocardium.

This investigation was designed to compare the catecholamine potentiating and anticholinergic activity of 5 tricyclic antidepressant drugs (imipramine, desmethylimipramine, amitriptyline, nortriptyline and chlorimipramine) in the rat. This was done by determining the cardiovascular response to intravenously injected noradrenaline, isoprenaline, carbachol and to vagal stimulation in urethane anaesthetized rats after acute or chronic pretreatment with one of the above antidepressants. Chronic treatment with all 5 drugs was at the rate 10 (mg/kg)/day for 14 days via the drinking water; acute administration of 20 mg/kg or 40 mg/kg by intraperitoneal injection 1 h before the start of the experiment was carried out with 2 compounds only, amitriptyline and desmethylimipramine. Blood pressure, ECG and heart rate were monitored throughout the experiment.

After chronic administration, the pressor effect of noradrenaline was potentiated and was of longer duration; the carbachol depressor effect was slightly reduced but the effect of vagal stimulation on blood pressure was almost completely abolished compared with the control group. Imipramine and desmethylimipramine antagonized the increase in heart rate caused by isoprenaline.

After acute administration the pressor effect of noradrenaline was potentiated though the smaller of the two doses had the greater potentiating effect, possibly due to the α-adrenoceptor blocking action of high doses of tricyclic compounds (Asberg, Cronholm,

Sjoqvist & Tuck, 1971); the larger dose was more effective in inhibiting the carbachol depressor response than smaller doses. The effect of vagal stimulation was reduced to approximately that produced by an intraperitoneal injection of 1·6 mg/kg atropine sulphate. Both doses of desmethylimipramine blocked the effect of isoprenaline on the heart rate.

The present results provide no indication as to why amitriptyline should be particularly cardiotoxic.

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Effect of sympathomimetic amines on the efflux of noradrenaline from adrenergic nerves in rabbit atria

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The efflux of [^{3}H]-noradrenaline (NA) from adrenergic nerves in rabbit atria was accelerated by tyramine, metaraminol and NA; these findings are consistent with accelerative exchange diffusion (Paton, 1973). In the present study, the effects on efflux of additional phenethylamines have been examined.

As described previously (Paton, 1973), atria, from reserpine pre-treated rabbits, were exposed to pargyline and tropolone, and thereafter to $5{\cdot}8\times10^{-7}$M [^{3}H]-(−)-NA for 60 min. Phenethylamine derivatives (5×10^{-6}M or 5×10^{-5}M) were added between 60–100 min of efflux.

β-Phenethylamine, (+)- and (−)-amphetamine were the most potent compounds studied. The addition of phenolic hydroxyl groups greatly reduced their ability to increase efflux, relative potencies being: β-phenethylamine>*p*-tyramine>dopamine; and, (±)-amphetamine>(±)-hydroxyamphetamine>(±)-α-methyldopamine. β-Hydroxylation also reduced activity: β-phenethylamine>(±)-phenylethanolamine; and, (±)-amphetamine>(±)-phenylpropanolamine.

Introduction of α-methyl or β-hydroxyl groups to *m*-and/or *p*-hydroxyphenethylamines produced small changes in activity. *N*-methylation of such compounds resulted in significant and consistent reductions in activity: (±)-NA>(±)-adrenaline; (±)-norphenylephrine>(±)-phenylephrine; and, (±)-octopamine>(±)-synephrine.

The structural requirements for acceleration of [^{3}H]-NA efflux differ markedly from those for inhibition of NA influx into adrenergic nerves (Burgen & Iversen, 1965; Muscholl & Weber, 1965). In these latter studies, introduction of phenolic hydroxyl groups or α-methylation increased activity. (±)-Amphetamine was about 20 times more potent an inhibitor of influx than (−)-amphetamine (Burgen & Iversen, 1965), but, in the present study, the enantiomers were approximately equipotent. Metaraminol was the most potent inhibitor of influx studied by Burgen & Iversen but, in the present study, was much less active than either β-phenethylamine or (±)-amphetamine.

If all the compounds studied increased efflux by accelerative exchange diffusion, it might be anticipated that the structural requirements would be similar to those for affinity for influx. This was not, however, the case. It seems likely that the ability of phenethylamines to accelerate noradrenaline efflux is influenced by their affinities for carrier influx sites, their lipid solubilities and possibly their abilities to displace noradrenaline from reserpine-resistant intraneuronal binding sites.

The acceleration of efflux produced by β-phenethylamine and (±)-amphetamine was inhibited by cocaine. Previous studies showed that the uptake of these compounds was not however inhibited by cocaine (Thoenen, Hürlimann & Haefely, 1968; Ross & Renyi, 1971). It is thus possible that cocaine prevents the accelerative effect of phenethylamine