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

and (±)-amphetamine on efflux by inhibiting the efflux of amine across the neuronal plasma membrane. In other studies, we have demonstrated that the increases in noradrenaline efflux produced by ouabain, omission of K^+ or metabolic inhibition are similarly inhibited by cocaine or desipramine.

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Some actions of bradykinin on mouse isolated ileum

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Superfusion techniques are used to detect or assay many biologically active substances; the choice of donor species and tissue depending on the sensitivity of response to the agent in question. In studying the suitability of mouse tissues for bioassay purposes we found that bradykinin produced biphasic responses in the isolated ileum and that the contractile component was reduced by AH 5158, a drug which blocks both α- and β-adrenoceptive receptors (Farmer, Kennedy, Levy & Marshall, 1972). Experiments were undertaken to assess whether the release of endogenous materials by bradykinin might be responsible for its actions in this tissue.

Isotonic or isometric recordings were made from 1·5 cm lengths of mouse distal ileum, under 0·5 g tension, over which McEwen's solution at 32° C, saturated with a mixture of 95% O_2 and 5% CO_2, flowed at a rate of 1 ml/min. Agonist drugs were applied for 30 s (optimal contact time) generally on a 4 min cycle. When the actions of antagonists were assessed they were present continuously in the superfusing medium except during the 30 s agonist contact period.

Bradykinin caused an initial decrease in the tone and the pendular movements of the ileum followed within 12 s by a contraction. The threshold concentration for this biphasic effect was about 1·0 ng/ml; the maximum relaxation occurred with 82 ± 11 ng/ml and maximum contraction with 670 ± 48 ng/ml (means ± S.E. of means). The inhibitory action of AH 5158 (10 to 100 μg/ml) on submaximal contractions was confirmed and no antagonism of the bradykinin-induced relaxation was seen in this concentration range. This action of AH 5158 would appear to be non-selective since it caused similar reductions in the intestinal contractions produced by furmethide, 5-HT or PGE_2. Neither propranolol (up to 10 μg/ml) nor phentolamine (up to 30 μg/ml) produced a selective inhibition of the bradykinin-induced responses and we concluded that it was unlikely that released catecholamines were responsible for the peptide's actions.

Non-steroidal anti-inflammatory drugs can reduce some of bradykinin's effects (Collier, Dinneen, Johnson & Schneider, 1968; Collier, James & Piper, 1968) and it has recently been shown that members of this group of drugs may also prevent the biosynthesis and/or release of prostaglandins, or like materials, from certain tissues (Piper & Vane, 1969; Gryglewski & Vane, 1972a, 1972b). Using sodium meclofenamate as an example, we found that this drug had dose-dependent anti-bradykinin activity (0·1 to 10 μg/ml) while leaving unchanged the responses to other agonists. Both the relaxant and contractile components of the bradykinin response were reduced by this drug. If sodium meclofenamate owes its anti-bradykinin activity to an inhibition of prostaglandin production then it would be necessary to demonstrate the release of two, or more, prostaglandin-like substances having opposite effects on the mouse ileum.