Two types of intrinsic sympathomimetic activity with β-adrenoceptor blocking drugs.

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The intrinsic sympathomimetic activity of β-adrenoceptor blocking drugs can be demonstrated by an increase in heart rate in rats depleted of catecholamines by pretreatment with syrosingopine. Thus dichlorisoprenaline, practolol, oxprenolol and pindolol produce a dose dependent tachycardia. The relationship between the dose requirements for intrinsic sympathomimetic activity and β-adrenoceptor blockade is not however uniform. Dichlorisoprenaline and practolol demonstrated intrinsic activity at all β-adrenoceptor blocking doses whereas the intrinsic activity of both oxprenolol and pindolol was evident only at high doses, relative to β-adrenoceptor blockade.

The haemodynamic effects of practolol and pindolol were compared in anaesthetized dogs with those of propranolol and 4-(2-hydroxy-3-isopropylaminopropoxy)phenylacetamide (ICI 66082), which are without intrinsic sympathomimetic activity. The depression of heart rate and atrio-ventricular conduction time, aortic flow and left ventricular dp/dt (during cardiac pacing) produced by practolol, was less than that resulting from either propranolol or ICI 66082. Pindolol however produced a biphasic response with depression of cardiac function of a similar order to that produced by propranolol at a dose of 0.025 mg/kg but a tendency to increase cardiac function at a dose of 1 mg/kg. These results therefore also support the conclusion from the work in rats that the intrinsic sympathomimetic activity of pindolol is only apparent at high doses relative to β-adrenoceptor blockade. The intrinsic activity of practolol is present at all β-adrenoceptor blocking doses and effectively reduces the haemodynamic depressant effects of β-adrenoceptor blockade.

An interaction between the α and β actions of catecholamines in guinea-pig liver slices

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Catecholamines have been shown to increase glucose release and potassium efflux from guinea-pig liver slices (Haylett & Jenkinson, 1972). The membrane potential of cells within the slice also rises, and this, together with the change in potassium efflux, can be accounted for as a consequence of an increase in the potassium permeability of the liver cells. The effect on potassium permeability is normally mediated by an α-adrenoceptor-like receptor. However, low doses of isoprenaline (50 nM), which generally have little effect on the membrane potential, have been found to cause hyperpolarization if applied up to 20 min after application of the selective α-adrenoceptor agonist amidephrine (Haylett & Jenkinson, 1973). For convenience this phenomenon has been termed potentiation.

The aim of the present work was to examine the pharmacological characteristics of the potentiated response, and the results to be described are based on comparisons of the effects of drugs on the continuously recorded membrane potentials of individual cells in guinea-pig liver slices (for methods see Haylett & Jenkinson, 1972).

The main series of experiments was designed to test whether potentiation could be observed with other α- and β-adrenoceptor agonists. Cyclic AMP and its dibutyryl derivative were also examined, in view of the possible role of cyclic AMP in responses mediated by β-adrenoceptors.

The following agents were found to cause hyperpolarization and potentiation in the dose range 5-50 μM, and both effects could be reversibly abolished by phentolamine (10 μM), suggesting that these actions are α-mediated and related: amidephrine, methoxamine, naphazoline, noradrenaline, oxymetazoline, phenylephrine, tetrahydrozoline, tramazoline, xylometazoline.

The additional finding that α-adrenoceptor agonists potentiated the responses not only to isoprenaline and salbutamol but also to cyclic AMP (Figure 1a and 1b) and dibutyryl cyclic AMP suggests that potentiation of β-mediated responses occurs at a step subsequent to β-adrenoceptor activation. In keeping with this idea, 10 μM propranolol reversibly abolished the potentiated response to isoprenaline and salbutamol but had no effect on that to cyclic AMP.

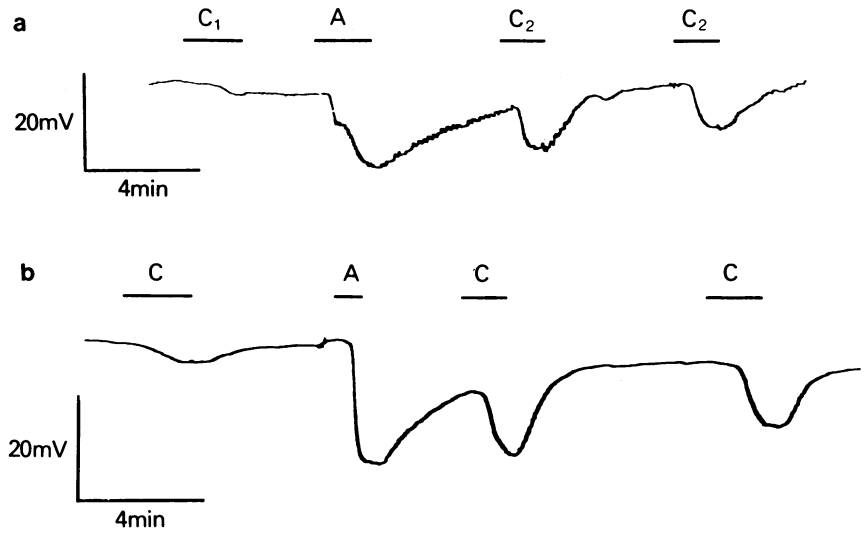

Figure 1 Figure *1a* shows responses to cyclic AMP (1 mM at 'C_1' and 0.25 mM at 'C_2') before and after an application of the α-agonist (−)amidephrine (10 μM at 'A'). Figure *1b* is from another experiment where the chloride in the bathing fluid had been replaced by isethionate, and shows that potentiation of cyclic AMP (0.5 mM at 'C') by (−)amidephrine (10 μM at 'A') is not chloride-dependent.

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Alterations to vasodilator effects of isoprenaline in the dog following intra-arterial infusions with isoprenaline, salbutamol and orciprenaline

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Recently there has been much interest in the possible development of tolerance to sympathomimetic bronchodilator drugs (Conolly, Davies, Dollery & George, 1971; Minatoya & Spilker, 1975).

In the present studies the effects of infusions of three sympathomimetic drugs on the blood flow response to isoprenaline have been investigated in twenty anaesthetized dogs.

Heart rate, arterial blood pressure and blood flow in the external iliac artery were recorded. In each dog, isoprenaline (0.001, 0.002, 0.004 and 0.008 μg/kg) was injected into the external iliac artery and the increase in blood flow noted. The maximum dose of isoprenaline injected was such that changes in heart rate and arterial blood pressure were minimal.

In group 1, four successive dose response curves were constructed allowing 40 min between each. The remaining three groups received an infusion into the external iliac artery for 30 min between successive dose response curves. Group 2 was infused with isoprenaline 0.002 $\mu g\ kg^{-1}\ min^{-1}$ between dose response curves 1 and 2, 0.006 $\mu g\ kg^{-1}\ min^{-1}$ between dose response curves