ileum in the pithed rat. The cord was stimulated supraximally via the pithing rod in the thoracic region of the guinea-pig and totally in the rat; responses other than β-adrenoceptive were blocked by tubocurarine, phenoxybenzamine, and in the rat, atropine.

The range of stimulus pulse frequencies giving responses matching those to injected catecholamines differed from one organ to another; the relationship between frequency and equi-effective dose also differed (Fig. 1a).

When the effectiveness of β-adrenoceptor blocking agents against cord stimulation was expressed by displacement of the stimulus frequency-response relationship, the relation of this to dose of blocking agent was found to differ for different organs (Fig. 1b). Comparison of relative blocking activity for different organs may be made from the doses corresponding to the frequency ratio that is equivalent, for each organ, to a reference dose ratio for injected amine.

REFERENCE

BURDEN, D. T., PARKES, M. W. & GARDINER, D. G. (1971). Effect of β-adrenoceptive blocking agents on the response to bronchoconstrictor drugs in the guinea-pig air overflow preparation. *Br. J. Pharmac.*, **41**, 122–131.

Effects of β-adrenoreceptor blocking drugs on isolated skeletal and cardiac muscle

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Propranolol, oxprenolol and practolol produce differential effects on the chronotropic and inotropic actions of isoprenaline in the denervated dog heart (Harry, Kappagoda, Linden & Snow, 1971). An explanation of these results may be that these drugs have a negative inotropic action on the dog heart over and above their activity as β-adrenoceptor antagonists. In an attempt to test this hypothesis the actions of propranolol, oxprenolol and practolol on the isolated rat diaphragm and the isolated rabbit papillary muscle were investigated.

The isolated muscles were bathed in Krebs solution maintained at 32·5°C bubbled with 95% CO_2 and 5% CO_2 and containing tubocurare (10^{-5} g/l.). Supramaximal stimulation was used to produce a maximal isometric twitch tension from a constant resting tension of about 1 g. Each muscle was subjected to increasing concentrations of the drugs (0·2–1000 μg/ml) for 10 min after which the twitch tension was recorded. The relationship between isometric tension produced by the muscles and the concentration of β-blocking agents in the bath fluid was obtained. A separate group of control muscles was examined over the same periods of time but with no drugs added to the bathing fluids.

Each blocking agent was tested on at least five muscles. The results are summarized in Table 1.

TABLE 1. *Lowest bath concentrations (μg/ml) of propranolol, oxprenolol and practolol which produce statistically significant depression of isometric twitch tensions*

	Propranolol	Oxprenolol	Practolol
Rat diaphragm	20	100	1000
Rabbit papillary muscle	20	100	1000

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Thus propranolol, oxprenolol and practolol reduce the isometric tension induced by electrical stimulation in both isolated skeletal and cardiac muscle. However, the concentrations used to produce these effects are consistent with the concentrations of the drugs known to produce non-specific effects *in vitro*. These concentrations are greater than those used by Harry *et al.* (1971) in the intact dog and suggest that the actions of these three β-adrenoreceptor blocking agents on the effects of isoprenaline on the intact dog heart are not related to the effects reported here on isolated muscle preparations.

REFERENCE

HARRY, J. D., KAPPAGODA, C. T., LINDEN, R. J. & SNOW, H. M. (1971). Effects of β-adrenoceptor blocking drugs on the chronotropic and inotropic actions of isoprenaline on the acutely denervated dog heart. *Br. J. Pharmac.*, **41**, 387*P*.

Effects of several muscarinic agonists on cardiac performance and the release of noradrenaline from the sympathetic nerves of the rabbit heart

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There are on the terminal adrenergic fibres of the rabbit heart muscarinic receptors which, upon excitation, can inhibit the release of noradrenaline evoked both by nicotinic drugs and electrical stimulation of the sympathetic nerves (Muscholl, 1970). The specificity of these receptors has been investigated by comparing the potencies of several compounds with different muscarinic intrinsic activities on systolic atrial tension development, ventricular frequency and neuronal noradrenaline release.

Atrial and ventricular tensions (Fozard & Muscholl, 1971), ventricular frequency and coronary flow were measured in Langendorff rabbit hearts perfused at 60 cm water and 35·5°C. Concentration-effect curves to acetylcholine, oxotremorine, pilocarpine, N-methyl-1,2,5,6, tetrahydro-nicotinic acid propylyl ester (MH-1, Mutschler & Hultzsch, 1971), N-benzyl-3-pyrolidyl acetate methobromide (AHR 602) and 4-(m-chlorophenylcarbamoyloxy)-2-butyryltrimethylammonium chloride (McNeil-A-343) were established by perfusion with increasing concentrations of each compound for 1 min at 10 min intervals. In separate experiments, noradrenaline release into the perfusates was induced by postganglionic sympathetic nerve stimulation -NS- (Hukovic & Muscholl, 1962) (600 rectangular pulses, 1 ms, 10 Hz, supramaximal voltage) and 1,1-dimethyl-4-phenylpiperazinium-DMPP- ($9{\cdot}5 \times 10^{-5}$ M). Muscarinic agents were perfused 1 min before and during the 3 min collection period for NS or DMPP. Noradrenaline was estimated fluorimetrically after absorption on, and elution from, alumina. The results are summarized in Table 1.

TABLE 1. *pD_2 values (Ariëns, 1964) with potencies relative to acetylcholine (100) for inhibition of:*

					Noradrenaline release by			
Compound	Atrial tension	n_1	Ventr. rate	n_1	NS	n_2	DMPP	n_2
MH-1	8·01 (316)	5	6·91 (1098)	5	6·22 (417)	7	5·68 (186)	9
Oxotremorine	7·88 (234)	5	6·78 (813)	5	6·04 (275)	6	5·38 (93)	7
Acetylcholine	7·51 (100)	6	5·87 (100)	6	5·65 (100)	10	5·41 (100)	10
Pilocarpine	5·52 (1·0)	4	4·42 (2·2)	4	3·09 (0·3)	6	3·45 (1·1)	8
McNeil-A-343	4·46 (0·09)	4	<3·31 (<0·28)	4	facilitation†	8	5·25 (69)†	6
AHR 602	<3·30 (<0·006)	4	<3·30 (<0·27)	4	facilitation†	7	4·25 (6·9)†	6

n_1 = number of individual concentration-effect curves. n_2 = number of individual estimations used o calculate regression lines. † = effect not antagonized by atropine ($7{\cdot}2.10^{-7}$ M).