Characterization of the β-adrenoceptors of guinea-pig tracheobronchial, skeletal and cardiac muscle

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Certain selective β_2-adrenoceptor stimulants given systemically produce effective bronchodilatation in man with minimal cardiovascular effects (Beumer, 1971; Legge, Gaddie & Palmer, 1971) but enhancement of physiological tremor is obvious in many patients. Studies in anaesthetized cats indicate that the tremor-inducing and bronchodilating actions of these drugs are mediated through similar β-adrenoceptors (Bowman & Nott, 1970). We now wish to report results of experiments designed to characterize the β-adrenoceptors in guinea-pig tracheobronchial, skeletal and cardiac muscles by using selective and non-selective β-adrenoceptor agonists and antagonists.

Experiments were performed using preparations of tracheal segments (James, 1969) and soleus muscles in pentobarbitone-anaesthetized guinea-pigs. Cumulative dose-response curves were determined for the agonists, (-)-isoprenaline being used as a reference drug in each experiment. (-)-Isoprenaline (0.001-3.0 μg/kg i.v.) had a similar potency in decreasing tracheal segment pressure, in decreasing the tension of submaximal tetanus of a soleus muscle and in increasing heart rate. However, the selective β_2-adrenoceptor agonists salbutamol (0.01-1000 μg/kg i.v.), terbutaline (0.1-1000 μg/kg i.v.) and fenoterol (0.01-300 μg/kg i.v.) were each less effective on heart rate than on tracheal pressure or muscle tension. The results are summarized in Table 1.

Propranolol (0.01-10 mg/kg i.v.) blocked responses to (-)-isoprenaline in the same dose range in all three tissues. Practolol (0.1-10.0 mg/kg i.v.) was more effective in blocking heart rate responses to isoprenaline than tracheal segment or soleus muscle responses. H35/25 (dl-erythro-4'-methyl-α(1-isopropylaminoethyl)-benzylalcohol hydrochloride) (0.1-10.0 mg/kg i.v.) was more effective in blocking tracheal segment and soleus muscle responses than heart rate responses to (-)-isoprenaline (Table 1).

No evidence was obtained with the drugs used to indicate that the β-adrenoceptors in guinea-pig tracheobronchial muscle differed from those in skeletal muscle.

Table 1 Activity of selective and non-selective β-adrenoceptor agonists and antagonists on tracheobronchial, skeletal and cardiac muscle of the anaesthetized guinea-pig

AGONISTS	*Equipotent dose (95% confidence limits) for*		
	Decrease in intratracheal segment pressure	*Decrease in tension of submaximal tetanus*	*Increase in heart rate*
(−)-Isoprenaline	1.0	1.0	1.0
Fenoterol	7.8 (4.7-13.2)	5.9 (3.7-9.5)	158.9 (121.4-207.9)
Salbutamol	9.5 (5.9-15.4)	9.4 (5.6-15.7)	73.9 (48.5-112.5)
Terbutaline	28.7 (20.5-40.1)	34.4 (22.1-53.7)	257.2 (172.8-382.9)

ANTAGONISTS	*Dose (mg/kg i.v.) (95% confidence limits) for 50% inhibition of (−)-isoprenaline responses on*		
	Tracheal segment	*Soleus muscle*	*Heart rate*
Propranolol	0.05 (0.02-0.14)	0.04 (0.01-0.09)	0.06 (0.04-0.09)
Practolol	8.2 (2.8-24.0)	12.8 (4.8-34.2)	0.9 (0.5-1.9)
H35/25	0.2 (0.1-0.4)	0.3 (0.2-0.4)	>10 (17-47% inhibition at 10 mg/kg; lethal at 30 mg/kg)

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Inhibition of constrictor responses of the rabbit ear artery by a mixture of oxytetracycline and ascorbic acid

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Powis (1973) reported marked potentiation of constrictor responses of the isolated perfused rabbit ear artery by oxytetracycline, 10^{-4} mol/l. In attempting to confirm this finding, a brand of oxytetracycline was used which consists of a mixture of oxytetracycline and ascorbic acid powder. When this is made up to a solution containing oxytetracycline 10^{-4} mol/l, ascorbic acid is present at a concentration of 1.3×10^{-3} mol/l. Addition of this mixture to the perfusing fluid of the artery had no appreciable effect on its pH, but caused a progressive and marked reduction in responses to noradrenaline so that after 30 min perfusion average responses (rise in perfusion pressure) in six experiments to 5, 10 and 20 ng of noradrenaline were reduced from 25 ± standard error 3 to 11 ± 3, from 40 ± 6 to 15 ± 3 and from 57 ± 9 to 23 ± 6 mm Hg respectively. ($P < 0.01$ – paired t test – in each case) – Figure 1. Addition of the oxytetracycline alone caused a small, non-significant increase in responses (Figure 1).

In a further series of six experiments, ascorbic acid alone at a concentration of 1.1×10^{-3} mol/l caused only slight reduction of responses to noradrenaline. Responses to 5, 10 and 20 ng of noradrenaline were reduced from 29 ± 6 to 25 ± 5 ($P < 0.05$), from 42 ± 8 to 37 ± 7 ($P < 0.02$) and from 60 ± 13 to 53 ± 11 mm Hg ($P > 0.05$) after 30 min perfusion.

Constrictor responses to histamine (0.5, 1.0, 2.0 μg) showed a similar marked depression in the presence of the mixture of oxytetracycline and ascorbic acid. This depressant action of the mixture on arterial constrictor responses appears to be another example of the unexpected effects of tetracyclines when mixed with stabilizing agents (Sulkowski & Haserick, 1964).

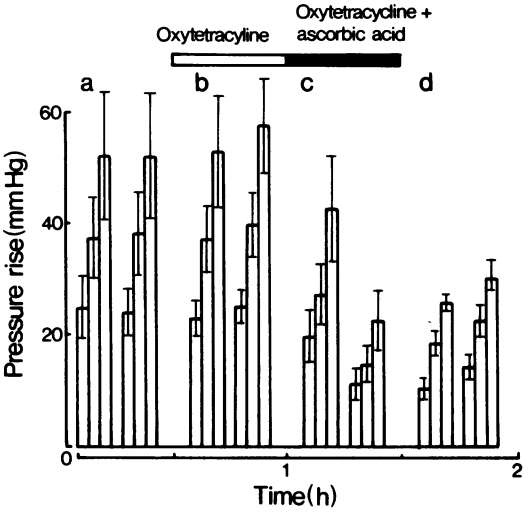

Figure 1 Effect on responses (rise in perfusion pressure) to noradrenaline of oxytetracycline, 10^{-4} mol/l and oxytetracycline 10^{-4} mol/l plus ascorbic acid 1.1×10^{-3} mol/l in the perfusate. Graded responses to noradrenaline, 5, 10 and 20 ng are shown. Results are means with standard errors from six experiments: (a) under control conditions, (b) with oxytetracycline present, (c) with the mixture present and (d) after a return to the control perfusate.

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