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THE SELECTIVITY OF β-ADRENOCEPTOR ANTAGONISTS ON CARDIOVASCULAR AND BRONCHODILATOR RESPONSES TO ISOPRENALINE IN THE ANAESTHETIZED DOG

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1 The actions of five β-adrenoceptor antagonists, chosen because of reported differences in their selectivities, were compared using the positive chronotropic, vasodepressor and bronchodilator responses to isoprenaline in anaesthetized dogs.

2 Propranolol was a potent antagonist of the isoprenaline responses in all three systems.

3 Practolol and acebutolol (M & B 17,803) blocked the positive chronotropic responses to isoprenaline to a greater extent than the vasodepressor or bronchodilator responses.

4 Butoxamine and α-methyl dichloroisoprenaline showed the opposite selectivity, blocking the vasodepressor and bronchodilator responses to isoprenaline to a greater extent than positive chronotropic responses. However, both drugs were considerably less potent than the other antagonists studied and their selectivities were less clear-cut than those of practolol or acebutolol.

5 All the antagonists lowered the resting heart rate and to a lesser extent the diastolic blood pressure. The effects of propranolol, practolol and acebutolol on heart rate probably result from cardiac β-adrenoceptor blockade. With butoxamine and α-methyl dichloroisoprenaline, however, the effects on heart rate probably result from a direct cardiodepressant action.

6 The relevance of the results to the problem of the sub-classification of β-adrenoceptors is discussed.

Introduction

β-Adrenoceptor antagonists are now widely used in the therapy of angina pectoris, hypertension and cardiac arrhythmias (Lewis, 1971). The ability to block β-adrenoceptors in cardiac muscle has been considered to be the basis of their therapeutic effect (Fitzgerald, 1969). Some of these drugs, notably propranolol, frequently induce respiratory distress in asthmatic subjects, an effect thought to result from block of β-adrenoceptors in airways smooth muscle (McNeill, 1964; Richardson & Sterling, 1969). This disadvantage is avoided by the use of the 'cardioselective' β-adrenoceptor antagonist, practolol (Dunlop & Shanks, 1968). In clinical trials with asthmatic subjects practolol caused a much lower incidence of respiratory side effects than propranolol (MacDonald & McNeill, 1968; Bernecker & Roetscher, 1970). Pharmacological results with other cardioselective β-adrenoceptor antagonists, for example, acebutolol (M & B 17,803) have been reported more recently (Basil, Jordan, Loveless & Maxwell, 1973).

The cardioselectivity of practolol and similar agents probably results from differences in the nature of the β-adrenoceptors in cardiac and airways smooth muscle. Lands and co-workers suggested that the β-adrenoceptors in cardiac muscle (β_1) differ from those in peripheral vascular and airways smooth muscle (β_2) (Lands, Arnold, McAuliff, Luduena & Brown, 1967; Lands, Luduena & Buzzo, 1967). Subsequent studies with both agonists and antagonists have added support to the concept of β-adrenoceptor sub-types (see Furchgott, 1972).

In the present study, the actions of five β-adrenoceptor antagonists are compared against isoprenaline positive chronotropic, vasodepressor and bronchodilator responses in the anaesthetized dog. The antagonists, chosen because of reported differences in their selectivities, were propranolol, practolol, acebutolol, butoxamine and α-methyl dichloroisoprenaline (α-methyl DCI).

Methods

Preparation of animals

Beagles of either sex weighing 7-13 kg were used. Anaesthesia was induced with thiopentone sodium (25 mg/kg i.v.) and was maintained with barbitone sodium (250 mg/kg i.p.). Animals were respired artificially with room air through a cuffed endotracheal tube using a stroke-volume of 13 ml/kg and a rate of 33/minute. Bilateral vagotomy was performed in all animals. Drugs were administered intravenously through a cannula in a femoral vein. Bilateral vagotomy and the use of a barbiturate anaesthetic reduce or eliminate the influence of autonomic reflexes which can otherwise significantly modify the positive chronotropic and bronchodilator responses to isoprenaline (Boissier, Advenier, Giudicelli & Viars, 1971; Vaughan Williams, Bagwell & Singh, 1973).

Interaction between isoprenaline and β-adrenoceptor antagonists on pulmonary airways resistance

As a first requirement it was necessary to establish a suitable method for measuring the effects of β-adrenoceptor antagonists on isoprenaline 'bronchodilator' responses. In initial experiments the direct effect of isoprenaline on pulmonary airways resistance was measured. Boissier *et al.* (1971) obtained dose-related decreases in pulmonary airways resistance in response to isoprenaline, but in our preliminary experiments the responses obtained were small and dose-response relations were inadequate. This may have been because resting pulmonary resistance was low, as has also been observed in anaesthetized animals by other workers (Lulling, Prignot & Lievens, 1968). Since satisfactory dose-response curves to isoprenaline are obtained by measuring the inhibitory effect of the drug against acetylcholine-induced increases in pulmonary resistance (Daly, Farmer & Levy, 1971), this method was adopted for use in the present experiments.

Pulmonary resistance was measured as described by Daly *et al.* (1971). A dose of acetylcholine, selected to give a submaximal increase of approximately 3-fold in pulmonary resistance, was administered intravenously at 5 min intervals until constant responses were obtained. Isoprenaline was injected intravenously 1 min before the next dose of acetylcholine and further doses of acetylcholine were given repeatedly until constant responses were again obtained. Isoprenaline produced a dose-dependent inhibition of the response to acetylcholine, the maximum effect observed being at the 1 min interval. Responses to isoprenaline, expressed as the percentage inhibition at 1 min of the acetylcholine-induced increase in pulmonary resistance, were plotted against log isoprenaline dose (e.g. Figure 1) in each experiment. Isoprenaline 'bronchodilator' dose-response relations were redetermined, commencing 15 min after each of 3 or 4 intravenous doses of a β-adrenoceptor antagonist, the determination of each set of values taking about 45 min to complete. A cumulative dosing schedule was used; for example, to increase the antagonist dose-level from 0.1 mg/kg to 1 mg/kg a further dose of 0.9 mg/kg was administered.

Whenever possible, quantitative analysis was carried out using the method of Arunlakshana & Schild (1959). The results for each experiment were plotted as log (isoprenaline dose-ratio-1) against log dose antagonist. The regression line was fitted by eye. The slope of the regression and the dose of antagonist (mg/kg) to produce an isoprenaline dose-ratio of 10 were estimated. Providing experimental conditions are satisfactory (Furchgott, 1972), evidence of competitive antagonism is provided by a parallel displacement to the right of the agonist dose-response curve and a slope of unity for the regression line (Arunlakshana & Schild, 1959).

Interaction between isoprenaline and β-adrenoceptor antagonists on heart rate and blood pressure

Arterial blood pressure (1 mmHg ≈ 133 Pa) was measured from a femoral artery with a Bell and Howell physiological pressure transducer connected to a Devices M4 recorder. The pulse pressure was used to trigger a heart rate meter for display. The experimental design was similar to that described above. Isoprenaline dose-response relations for increase in heart rate (beats/min) and decrease in diastolic blood pressure (mmHg) were determined by the sequential intravenous injection of increasing doses of the agonist before and from 15 min after intravenous administration of the antagonist. Each set of determinations took about 45 min to complete. Absolute changes in heart rate and blood pressure were used for analysis as recommended by Vaughan Williams *et al.* (1973). The magnitude of each response was usually estimated by comparing the peak level with the immediately preceding resting level. However, a difficulty arose in experiments with the cardioselective antagonists practolol and acebutolol. In these, the large doses of isoprenaline required to re-establish positive chronotropic responses caused

falls in diastolic blood pressure that persisted between isoprenaline doses. In these instances the resting level immediately before the first dose of antagonist was used for comparison. Quantitative analysis of these results was performed as in the preceding section.

The effects of the β-adrenoceptor antagonists on resting heart rate and blood pressure were assessed at 15 min after injection i.e. immediately before determining sensitivity to isoprenaline.

Drugs

The following drugs were used: acebutolol hydrochloride (May & Baker Ltd), acetylcholine chloride (BDH Chemicals Ltd), barbitone sodium (BDH Chemicals Ltd), butoxamine (Wellcome Research Laboratories), α-methyl dichloroisoprenaline (A.B. Hassle), (±)-isoprenaline sulphate (Burroughs Wellcome and Co.), (±)-practolol (Imperial Chemical Industries), (±)-propranolol hydrochloride (Imperial Chemical Industries), thiopentone sodium (Abbott Laboratories Ltd).

Unless stated otherwise, dosages are expressed in terms of free base.

Results

Effects on sensitivity to isoprenaline

In control experiments, determinations of positive chronotropic, vasodepressor and bronchodilator dose-response relations to isoprenaline at hourly intervals for 6 h showed that the sensitivity of individual dogs to isoprenaline varied by less than 3-fold over this period. Representative experiments using propranolol are illustrated in Figure 1 and results using various antagonists are summarized in Table 1.

Propranolol. Propranolol (0.01, 0.1 and 1 mg/kg) produced parallel displacements to the right of the positive chronotropic, vasodepressor and bronchodilator dose-response curves for isoprenaline. Small differences in the potency of propranolol were noted in the three tissues. Thus, propranolol was about four times more potent in blocking vasodepressor than positive chronotropic responses to isoprenaline ($P < 0.02$) and tended to be more potent in blocking bronchodilator than cardiac responses ($P > 0.05$).

Practolol. Practolol (0.3, 3 and 30 mg/kg) produced parallel displacements to the right of the isoprenaline positive chronotropic dose-response curve, but in the same experiments had little or no effect on vasodepressor responses to isoprenaline in doses of 0.3 or 3 mg/kg. At 30 mg/kg practolol produced a 3-fold displacement to the right of the isoprenaline vasodepressor dose-response curve in three out of four experiments, but was ineffective in the fourth experiment.

Practolol also had low potency against isoprenaline bronchodilator responses. Thus, there was little or no effect in doses up to and including 10 mg/kg. Higher doses of practolol (30 and 100 mg/kg) displaced the isoprenaline bronchodilator dose-response curve to the right. Practolol was approximately 80 times more potent in blocking positive chronotropic responses to isoprenaline than bronchodilator responses.

Acebutolol. Acebutolol (0.03, 0.3 and 3 mg/kg) produced parallel displacements to the right of the positive chronotropic dose-response curve to isoprenaline. It had no effect on vasodepressor responses to isoprenaline at 0.03 and 0.3 mg/kg but at 3 mg/kg displaced the curve to the right by 2 to 4-fold in three out of four experiments; the fourth experiment showed no antagonism. Bronchodilator responses to isoprenaline were not impaired by acebutolol, 0.3 mg/kg but 3 and 30 mg/kg displaced the dose-response curve to the right. Acebutolol was approximately 60 times more potent in blocking positive chronotropic responses to isoprenaline than bronchodilator responses.

Butoxamine. Butoxamine, in contrast to the above antagonists, had no effect on isoprenaline positive chronotropic responses in doses up to and including 10 mg/kg and was lethal at 30 mg/kg. It had no effect on isoprenaline vasodepressor responses in doses up to and including 1 mg/kg but at 3 mg/kg reduced the sensitivity to isoprenaline by 7-fold in one experiment, while producing no effect in two other experiments. At 10 mg/kg the isoprenaline dose-response curve was displaced to the right in all three dogs by factors of 10-60-fold. The low doses of isoprenaline (0.1-1 μg/kg) that previously had produced depressor responses now produced small pressor responses (10 mmHg). Butoxamine had no effect on isoprenaline bronchodilator responses at 0.1 and 1 mg/kg but at 10 mg/kg reduced the sensitivity by 7-10-fold in each of three experiments.

α-Methyl DCI. Only a small amount of this drug was available for study. It had no effect on positive chronotropic responses to isoprenaline at 0.3 and 3 mg/kg but at 30 mg/kg reduced the sensitivity by 5-fold in one experiment and by

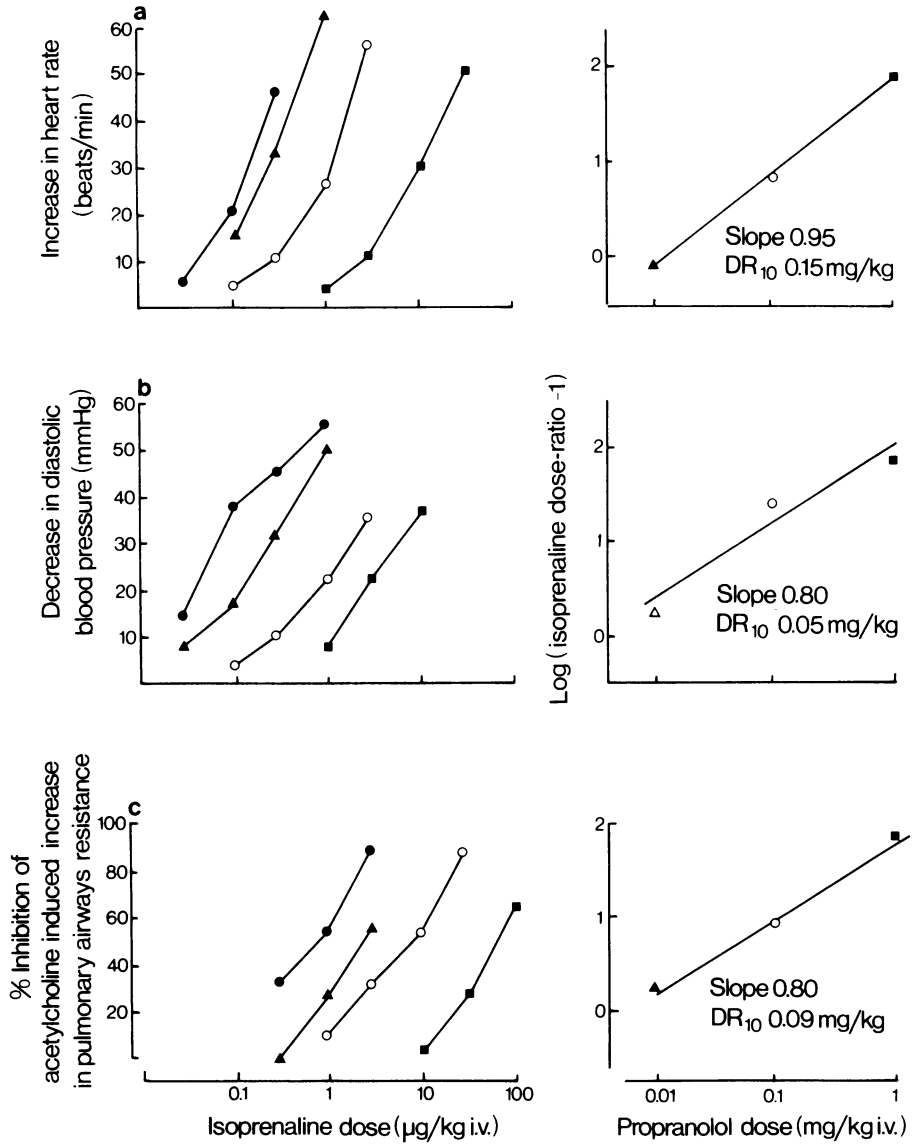

Figure 1 Effects of propranolol on responses of (a) heart rate, (b) blood pressure and (c) pulmonary airways resistance to isoprenaline in the anaesthetized dog. (●) Pre-dose; (▲) 0.01 mg/kg; (○) 0.1 mg/kg; (■) 1 mg/kg propranolol i.v. (a) and (b) determined in the same animal. DR_{10} — as in Table 1.

10-fold in another. There was no effect on the vasodepressor responses at 0.3 mg/kg, but reduced sensitivity to isoprenaline at 3 and 30 mg/kg. Reversal of the isoprenaline vasodepressor responses was not observed. Sensitivity to the bronchodilator responses was unaffected by 1 mg/kg and reduced by 3 and 10 mg/kg.

Effects on resting heart rate, diastolic blood pressure and pulmonary resistance

All the antagonists tested lowered resting heart rate and diastolic blood pressure (Table 2), effects on heart rate being the more pronounced. Propranolol, practolol and acebutolol each

Table 1 Effects of β-adrenoceptor antagonists on positive chronotropic, vasodepressor and bronchodilator responses to isoprenaline in the anaesthetized dog

	Positive chronotropic response			*Vasodepressor response*			*Bronchodilator response†*		
Antagonist	DR_{10}	*Slope*	n	DR_{10}	*Slope*	n	DR_{10}	*Slope*	n
Propranolol	0.13 (0.09-0.17)	1.18 (0.85-1.51)	4	0.03 (0.01-0.04)	1.03 (0.73-1.33)	4	0.06 (0.03-0.15)	0.83 (0.70-0.96)	4
Practolol	0.54 (0.35-0.82)	0.94 (0.74-1.14)	4	>30 (3-fold displacement at 30 mg/kg in 3 of 4 expts.)	–	4	44 (range 28-56)	1.25 (range 0.83-1.58)	3
Acebutolol	0.30 (0.24-0.39)	0.91 (0.81-1.01)	4	>3 (2-4-fold displacement at 3 mg/kg in 3 of 4 expts.)	–	4	18.6 (range 12-35.5)	1.14 (range 1.05-1.22)	3
Butoxamine	>10 (No block at 10 mg/kg; lethal at 30 mg/kg)	–	3	Blocks at 10 mg/kg (Responses to low doses of isoprenaline reversed; responses to higher doses reduced)	–	3	c. 10 (No block at 1 mg/kg; 7-10-fold displacement at 10 mg/kg in 3 expts.)	–	3
α-Methyl DCI	c. 30 (No block at 3 mg/kg; 5 and 10-fold displacement at 30 mg/kg in 2 expts.)	–	2	13.0 13.5	0.60 0.65	1 1	9 (range 3-13)	1.00 (range 0.75-1.40)	3

DR_{10} – dose of antagonist (mg/kg i.v.) to produce an isoprenaline dose-ratio of 10
Slope – of regression obtained from plot of log (isoprenaline dose-ratio−1) on log (antagonist dose, mg/kg i.v.)
n – number of experiments
Figures in parentheses are 95% confidence limits unless otherwise indicated
† – inhibition by isoprenaline of the acetylcholine-induced increase in pulmonary airways resistance

Table 2 Effects of β-adrenoceptor antagonists on heart rate and diastolic blood pressure in the anaesthetized dog

Antagonist	*Dose (mg/kg i.v.)*	*Decrease in heart rate (beats/min)*	*Change in diastolic blood pressure (mmHg)*
Propranolol		[Pre-dose, 133(110-150)]	[Pre-dose, 90(70-120)]
(*n* = 4)	0.01	14(5-20)	+1 (+10 to −10)
	0.1	31(10-45)	−2.5(+5 to −20)
	1	46(15-70)	−7.5(−5 to −20)
Practolol		[Pre-dose, 143(135-155)]	[Pre-dose, 101(87-115)]
(*n* = 4)	0.3	26(25-30)	−8 (0 to −15)
	3	42(40-45)	−7 (0 to −22)
	30	57(55-59)	−11(−5 to −20)
Acebutolol		[Pre-dose, 147(116-170)]	[Pre-dose, 98(55-115)]
(*n* = 4)	0.03	20(3-35)	−2.5(0 to −10)
	0.3	38(15-60)	−15 (−5 to −30)
	3	54(31-75)	−26 (−15 to −40)
Butoxamine		[Pre-dose, 172(150-185)]	[Pre-dose, 122(110-135)]
(*n* = 3)	1	8(5-10)	0
	3	26(20-35)	−5 (0 to −10)
	10	68(50-75)	−30(−15 to −45)
	30	Lethal	
α-Methyl DCI		[Pre-dose, 150-155]	[Pre-dose, 77-115]
(*n* = 2)	0.3	5-11	−2 to −5
	3	23-25	+1 to −15
	30	55-58	−5 to −15

Pre-dose—level of heart rate or diastolic blood pressure immediately before first dose of β-adrenoceptor antagonist
n-number of experiments
Values in brackets are ranges
Data in this Table and Table 1 obtained from the same experiments.

lowered heart rate in dose ranges found to block isoprenaline positive chronotropic responses. In contrast, butoxamine and α-methyl DCI lowered heart rate in doses that had little or no effect on positive chronotropic responses to isoprenaline. None of the antagonists had any significant effect on resting pulmonary airways resistance.

Discussion

The present work involved two series of experiments—one measuring antagonist potency against isoprenaline bronchodilator responses and the other against isoprenaline positive chronotropic and vasodepressor responses. This was necessary because the doses of acetylcholine used to produce bronchoconstriction also caused pronounced cardiovascular effects. Comparisons of drug potency from one animal to another are complicated by individual variations in sensitivity but variation was relatively small in the present experiments (Table 1). The main advantage of the methods used is that accurate determinations of antagonist potency could be obtained in each of the three systems examined.

The results with propranolol confirm that the drug is a potent antagonist of positive chronotropic, vasodepressor and bronchodilator responses to isoprenaline. The observation that vasodepressor responses were blocked to a slightly greater degree than positive chronotropic responses is in agreement with previous findings (Shanks, 1966; Boissier *et al.*, 1971; Vaughan Williams *et al.*, 1973).

We found practolol to be about four times less potent than propranolol in antagonizing isoprenaline positive chronotropic responses, in accord with previous estimates in animals and in man (Barrett, Crowther, Dunlop, Shanks & Smith, 1968; Brick, Hutchison, McDevitt, Roddie & Shanks, 1968; Wale, Pun & Rand, 1969; Boissier *et al.*, 1971; Burden & Parkes, 1971; Basil *et al.*,

1973). In contrast, practolol had low antagonist potency against isoprenaline vasodepressor and bronchodilator responses. Although there is agreement in the literature that practolol has a relatively greater potency on cardiac than on vascular responses (Barrett, *et al.*, 1968; Dunlop & Shanks, 1968; Wale *et al.*, 1969; Boissier *et al.*, 1971; Vaughan Williams *et al.*, 1973), there is conflicting evidence regarding its relative effects on cardiac and pulmonary responses. Thus, whereas there are reports that practolol has no specificity in this respect in guinea-pigs (Burden & Parkes, 1971) and dogs (Boissier *et al.*, 1971) it has also been claimed that practolol has a relatively greater effect on cardiac responses in both guinea-pigs (Baird & Linnell, 1972) and cats (Parkes, 1973). The reasons for these differences are not known; the degree of selectivity could vary somewhat depending on the species and the method of assessment used (Basil *et al.*, 1973). However, our results and the other reports showing a significant cardiac to pulmonary selectivity with practolol would seem to be in accord with findings in asthmatic subjects (see Introduction). The observed cardio-selectivity of acebutolol was comparable with that of practolol as in other studies using anaesthetized dogs (Briant, Dollery, Fenyvesi & George, 1971; Basil *et al.*, 1973) but Baird & Linnell (1972) found this drug to be much less cardioselective in guinea-pigs and there is doubt about its selectivity in man (see Basil *et al.*, 1973; Briant, Dollery, Fenyvesi & George, 1973).

Butoxamine was found to be a weak β-adrenoceptor antagonist, but with some degree of selectivity. Thus, it prevented isoprenaline vasodepressor responses at 10 mg/kg without modifying positive chronotropic responses. After butoxamine, small doses of isoprenaline exerted a pressor effect attributed to its cardiac stimulant action not being masked by vasodilatation. These results confirm previous reports that butoxamine blocks vasodepressor, but not cardiac responses to isoprenaline (Levy, 1966; Wilkenfeld & Levy, 1968; Parratt & Wadsworth, 1970). The present experiments show for the first time that butoxamine blocks isoprenaline bronchodilator responses in the dose-range required to block the vasodepressor responses. The examination of butoxamine was limited to a relatively narrow dose-range because the drug was lethal at 30 mg/kg. This may derive from a direct cardiodepressant action, suggested by the finding that butoxamine caused large decreases in heart rate and has previously been shown to markedly decrease cardiac contractility (Levy, 1966; Wilkenfeld & Levy, 1968; Wastila, Su, Friedman & Mayer, 1972).

Like butoxamine, α-methyl DCI was more effective in blocking isoprenaline vasodepressor and bronchodilator responses than positive chronotropic responses. The vascular to cardiac selectivity of α-methyl DCI has been reported previously (Moran, 1966). α-Methyl DCI also resembled butoxamine in that doses that decreased resting heart rate failed to block positive chronotropic responses to isoprenaline, indicating a direct cardiodepressant action.

Different profiles of selectivity are apparent in the β-adrenoceptor antagonists examined. Several workers have related similar data, also obtained in the anaesthetized dog, to differences in the β-adrenoceptors mediating the observed responses. Levy & Wilkenfeld (1969) concluded that cardiac and intestinal smooth muscle β-adrenoceptors belong in one category (β_1) and peripheral vascular β-adrenoceptors in another (β_2), in accord with Lands and co-workers dual β-adrenoceptor classification (see Introduction). Other findings (Boissier *et al.*, 1971; Levy, 1973a, b, c; Wasserman & Levy, 1974), would seem to indicate that β-adrenoceptors in peripheral vascular and airways smooth muscle are different, which is not in accord with the Lands classification.

Experiments in intact animals have undoubtedly been helpful in receptor classification, but there are certain drawbacks to their use, especially when attempting to differentiate between receptors within a single class. Particularly rigorous control of experimental conditions is then necessary and this cannot be achieved in the intact animal (Furchgott, 1972). For example, it is not possible to control the distribution and disposition patterns of the administered drugs. Conclusions from the above publications are further complicated because some of the antagonists used had only low potency in the tissues concerned (Levy, 1973c; Wasserman & Levy, 1974) or because some results were inconsistent with competitive antagonism (Boissier *et al.*, 1971). With these potential drawbacks in mind, it is appropriate to consider the relevance of the present results to the sub-classification of β-adrenoceptors.

Propranolol was shown to be a potent but non-selective antagonist. Practolol and acebutolol showed selectivity for cardiac compared with peripheral vascular and airways smooth muscle. Butoxamine and α-methyl DCI showed the opposite selectivity, although this was less clear-cut. These findings provide strong support for the idea that β-adrenoceptors in cardiac muscle differ from those in peripheral vascular and airways smooth muscle. The question of the relationship between β-adrenoceptors in the latter two tissues is more difficult to answer because of

the low potency of butoxamine and α-methyl DCI. A potent antagonist of this type would be a useful aid in the sub-classification of β-adrenoceptors. However, the results do show that although there were clear differences in the potencies of the five antagonists examined, the potency of each was similar in peripheral vascular and airways smooth muscle. This tends to favour the idea that the β-adrenoceptors in these tissues are of the same type. A similar conclusion was drawn from a corresponding study with the selective β-adrenoceptor agonist salbutamol (Daly *et al.*, 1971). Thus, these findings, unlike some cited above, are consistent with the Lands dual β-adrenoceptor classification.

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