Br. J. Pharmac. (1979), **67**, 367–370

THE SUBDIVISION OF β-ADRENOCEPTORS IN THE CARDIOVASCULAR SYSTEM OF THE RAT

F.J. IMMS, R.L.B. NEAME*[1] & D.A. POWIS*[1]

M.R.C. Environmental Physiology Unit, London School of Hygiene and Tropical Medicine, Keppel St., London WC1E 7HT and
Department of Physiology*, St. Bartholomew's Hospital Medical College, Charterhouse Square, London EC1M 6BQ

1 The antagonism by the β-adrenoceptor blocking drugs, propranolol (non-selective) and practolol (β-selective), of the cardiovascular actions of isoprenaline has been investigated in the rat.

2 All doses of practolol (0.1, 1 and 3 mg/kg) blocked the cardio-accelerator action of isoprenaline but only the largest dose blocked the vasodilator effect.

3 All doses of propranolol (0.01, 0.03 and 0.1 mg/kg) blocked the vasodilator effect of isoprenaline but only the largest dose diminished the tachycardia.

4 It is concluded that in the rat, as in other species, β-adrenoceptors may be subdivided into β_1 (cardiac) and β_2 (peripheral vascular) types.

Introduction

Both α- and β-adrenoceptors mediate the responses of the cardiovascular system to noradrenaline. In the rat the β-adrenoceptors appear to play a more dominant role than in other species (Imms, Neame & Powis, 1977a), mediating a marked increase in cardiac output while at the same time completely masking the vasoconstriction induced by α-adrenoceptor stimulation, with the result that total peripheral vascular resistance does not change. Since β-adrenoceptors play such a pronounced role in the cardiovascular response of the rat, it was considered of interest to establish whether they are homogeneous or whether they can be subdivided into β_1 (cardiac) or β_2 (peripheral vascular) types (Lands, Arnold, McAuliff, Luduena & Brown, 1967). Some previous experiments suggest two such populations of β-adrenoceptors in the rat (Debreczeni & Fenyvesi, 1971; Lewis, 1974) but the hypothesis was not rigidly tested.

Methods

Male albino rats of a Wistar derived strain, weighing 400 to 550 g, were anaesthetized with pentobarbitone sodium (70 mg/kg i.p.). They were prepared for determination of cardiac output by the thermal dilution technique, for recording of arterial blood pressure and heart rate, and for intravenous infusion of drugs. This preparation has been previously described in detail (Imms *et al.*, 1977a, b).

Two groups each of ten animals were studied. In group 1 the cardiovascular responses to an infusion of isoprenaline (50 ng/min) were recorded. This dose has been shown to produce changes in the measured cardiovascular variables of approximately 50% of maximum (Imms *et al.*, 1977b). Following β-adrenoceptor blockade with propranolol (0.01 or 0.03 mg/kg) the responses to isoprenaline were again measured. Additional propranolol was then administered to bring the total dose given to either 0.03 or 0.1 mg/kg and the response to isoprenaline was again tested.

In group 2 a similar protocol was followed but in this case β-adrenoceptor blockade was induced with practolol in doses of either 0.1 and 1.0 mg/kg or 1.0 and 3.0 mg/kg.

Drugs used were: isoprenaline sulphate (Macarthy); propranolol hydrochloride (Inderal, ICI); practolol (Eraldin, ICI).

Results

The control values for both the measured and derived cardiovascular variables were similar for the two groups of animals, suggesting that the animals belonged to a homogeneous population (Table 1). The

[1] Present address: Division of Clinical Practice, University of Newcastle, NSW 2308, Australia.

0007-1188/79/110367-04 $01.00

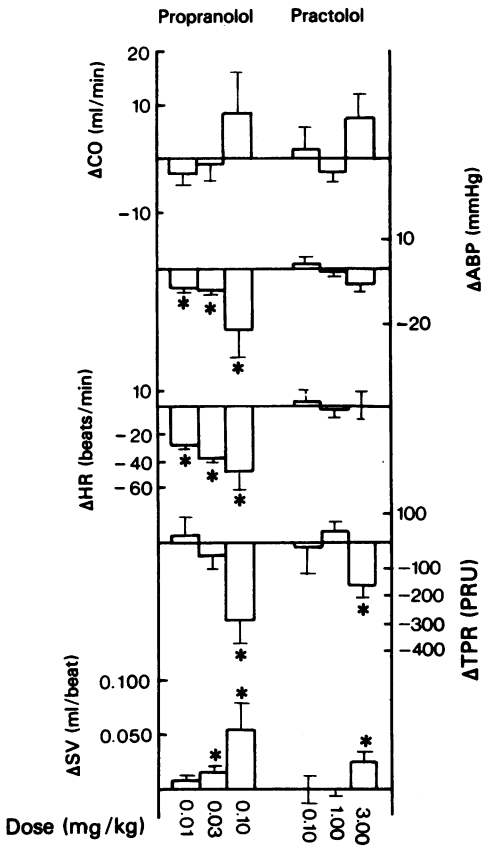

Figure 1 The effects of propranolol (0.01, 0.03 and 0.10 mg/kg) and practolol (0.1, 1.0 and 3.0 mg/kg) on the cardiovascular system of the rat. The histograms (means) indicate absolute changes from pre-treatment data; vertical lines show s.e. mean. Co = cardiac output; HR = heart rate; SV = stroke volume; ABP = arterial blood pressure, TPR = total peripheral resistance. Statistical significance determined by paired *t* tests (*$P < 0.05$).

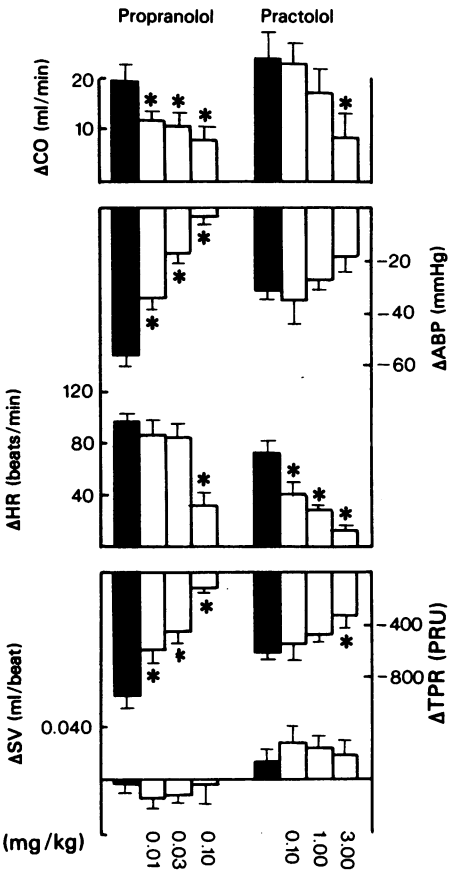

Figure 2 Changes in cardiovascular variables caused by infusion of isoprenaline (50 ng/min, filled columns). The open columns represent the effects of isoprenaline infusion following administration of either propranolol or practolol. *Indicates a significant reduction of the effects of isoprenaline ($P < 0.05$) by the blocking agent. Other details as in Figure 1.

values are similar to those which we obtained previously (Imms *et al.*, 1977a, b) and to those obtained by other workers using different techniques for measuring cardiac output (see Imms & Neame, 1974).

In none of the doses given did propranolol alter cardiac output but there was a dose-related slowing of heart rate with a concomitant increase in stroke volume (Figure 1). Practolol in doses which had

Table 1 Control values for cardiovascular variables for two groups of animals used in these experiments

Group	n	*Cardiac output (ml/min)*	*Mean arterial blood pressure (mmHg)*	*Heart rate (beats/min)*	*Total peripheral vascular resistance (PRU)*	*Stroke volume (ml/beat)*
1	10	81.9 ± 17.0	142 ± 11	390 ± 25	1788 ± 349	0.209 ± 0.047
2	10	81.7 ± 15.1	133 ± 12	402 ± 15	1663 ± 246	0.194 ± 0.034

Values are means ± s.d.

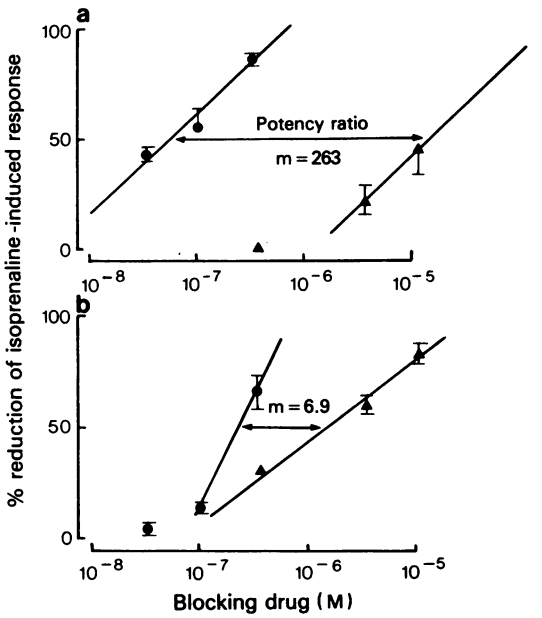

Figure 3 Log dose-response curves for propranolol (●) and practolol (▲) on (a) the peripheral vascular, and (b) the heart rate responses of the rat to infusions of isoprenaline (50 ng/min).

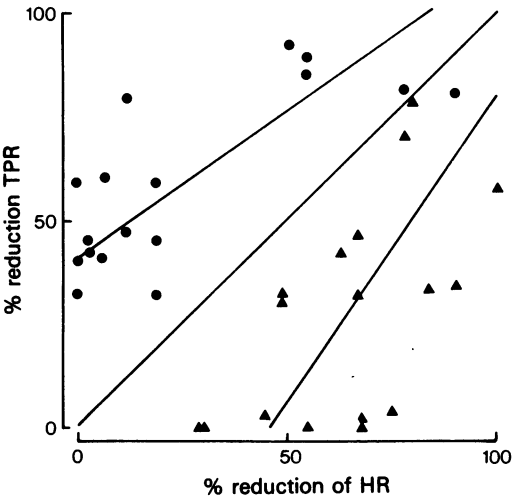

Figure 4 Comparison of the effects of propranolol (●) and practolol (▲) as blockers of the actions of isoprenaline on heart rate (HR) and on total peripheral resistance (TPR).

marked β-adrenoceptor blocking effects (see below) also had no significant effect on cardiac output, but in contrast to propranolol had no effect on heart rate. The largest dose of each blocker reduced total peripheral resistance. In the case of propranolol this caused a significant fall in arterial blood pressure (21 ± 9 mmHg).

Infusion of isoprenaline caused a marked reduction in total peripheral resistance which, despite a considerable increase in cardiac output, resulted in a fall in mean arterial blood pressure (Figure 2). The increase in cardiac output was due to an increase in heart rate with a maintained stroke volume.

The effects of propranolol and practolol on the cardiovascular responses to isoprenaline were different (Figure 2). The fall in total peripheral resistance evoked by isoprenaline was reduced following administration of every dose of propranolol, whereas only the largest dose of practolol significantly attenuated the response. By contrast, all doses of practolol reduced the heart rate response to isoprenaline, whereas the response of this variable was attenuated only by the largest dose of propranolol.

Discussion

It has been shown in this study that over the range of doses used, propranolol and practolol themselves had only minor effects on the measured circulatory variables of the anaesthetized rat (Figure 1), except for heart rate. Propranolol caused a significant fall in heart rate at each dose used whereas practolol did not. Langslet (1970; 1971) has shown that propranolol has a powerful membrane stabilizing effect which could reduce the spontaneous discharge rate of the pacemaker and thereby account for the fall in heart rate. However, since either the administration of hexamethonium, which has no reported quinidine-like action (Imms *et al.*, 1977a) or a depletion of catecholamines (Barrett & Carter, 1970) reduces heart rate to the levels seen with the highest dose of propranolol, it seems likely that the cardiac slowing observed in these experiments is due to reduction in β-adrenoceptor-mediated positive chronotropic drive. The failure of practolol, in doses known to have marked β-adrenoceptor blocking effects, to lower the heart rate may be due to the compound having partial β-adrenoceptor stimulating properties that would tend to offset the concomitant blockade of the sympathetically mediated positive chronotropic drive. In unpublished studies we have noted that atendol (Tenormin, ICI), which has no intrinsic sympathomimetic activity (Harry, Knapp & Linden, 1974), slows heart rate of the rat whereas pindolol (Visken, Sandoz), which does have such activity (Barrett & Carter, 1970), does not cause bradycardia.

The failure of propranolol and practolol to increase total peripheral resistance suggests a lack of tonic vasodilator discharge in the rat. In contrast, the ad-

ministration of phentolamine, an α-adrenoceptor blocking drug, caused a marked fall in total peripheral resistance (Imms *et al.*, 1977a). Chronic administration of both propranolol and practolol causes a reduction in total peripheral resistance probably by central depression of sympathetic vasoconstrictor tone (Esler & Nestel, 1973; Dollery, Lewis, Myers & Reid, 1973; Day & Roach, 1974).

To explore the differences between propranolol and practolol as antagonists of isoprenaline on the circulation, log dose-response curves have been separately plotted for an effect mediated predominantly by β_1 receptors (heart rate) or by β_2 receptors (total peripheral resistance). The effect of a blocker is calculated as the percentage reduction it causes in isoprenaline-induced changes (Figure 3). Regression lines have been calculated for the linear portion of the dose-response curves. With respect to heart rate, propranolol is less than 10 times as effective as practolol although the lines were not parallel; but as a blocker of the peripheral vascular effects of isoprenaline it is over 250 times as effective.

The selectivity may be further demonstrated by plotting the effect of the blocker on heart rate changes induced by isoprenaline against the effect on peripheral vascular changes induced by this agonist, as suggested by Hainsworth, Karim & Stoker (1974). Figure 4 shows that practolol, in doses which cause a marked reduction of the cardio-accelerator responses to isoprenaline, has little effect on its vasodilator action. This suggests that at low doses the agent has a more selective effect on the heart. On the other hand, low doses of propranolol cause marked attenuation of the vasodilator actions of isoprenaline but have little effect on the heart rate increment produced by the amine.

The evidence suggests that β-adrenoceptors affecting the cardiovascular system of the rat are not of a single type. As in other species, they appear to be divisible into β_1 and β_2 types.

References

BARRETT, A.M. & CARTER, A.J. (1970). Comparative chronotropic activity of β-adrenoceptor antagonists. *Br. J. Pharmac.*, **40**, 373–381.

DAY, M.D. & ROACH, A.G. (1974). Central α- and β-adrenoceptors modifying arterial blood pressure and heart rate in conscious cats. *Br. J. Pharmac.*, **51**, 325–335.

DEBRECZENI, L. & FENYVESI, T. (1971). Effect of β-adrenoceptor blocking compounds on isoprenaline induced changes in regional blood flow in the rat. *Br. J. Pharmac.*, **41**, 171–176.

DOLLERY, C.T., LEWIS, P.J., MYERS, M.G. & REID, J.L. (1973). Central hypotensive effect of propranolol in the rabbit. *Br. J. Pharmac.*, **48**, 343P.

ESLER, M.D. & NESTEL, P.J. (1973). Evaluation of practolol in hypertension. *Br. Heart J.*, **35**, 469–474.

HAINSWORTH, R., KARIM, F. & STOKER, J.B. (1974). Blockade of peripheral vascular responses to isoprenaline by three β-adrenoceptor antagonists in the anaesthetised dog. *Br. J. Pharmac.*, **51**, 161–168.

HARRY, J.D., KNAPP, M.F. & LINDEN, R.J. (1974). The actions of a new β-adrenoceptor blocking drug ICI 66082 on the rabbit papillary muscle and on the dog heart. *Br. J. Pharmac.*, **51**, 169–177.

IMMS, F.J. & NEAME, R.L.B. (1974). Circulatory changes following adrenalectomy in the rat. *Cardiovascular Res.*, **8**, 268–275.

IMMS, F. J., NEAME, R. L. B. & POWIS, D. A. (1977a). Responses of the cardiovascular system of the rat to noradrenaline infusions and their modification by adrenoceptor blocking agents. *Br. J. Pharmac.*, **60**, 115–121.

IMMS, F.J., NEAME, R.L.B. & POWIS, D.A. (1977b). Responses of the cardiovascular system of the rat to α- and β-adrenoceptor agonists. *Br. J. Pharmac.*, **60**, 107–114.

LANDS, A. M., ARNOLD, A., MCAULIFF, J.P., LUDUENA, F.P. & BROWN, T.G. (1967). Differentiation of receptor systems activated by sympathomimetic amines. *Nature*, **214**, 597–598.

LANGSLET, A. (1970). Membrane stabilization and cardiac effects of d, L-propranolol, d-propranolol and chlorpromazine. *Eur. J. Pharmac.*, **13**, 6–14.

LANGSLET, A. (1971). Effects of chlorpromazine, d, L-propranolol and d-propranolol in the isolated rat heart: modification of the response to isoprenaline and glucagon. *Eur. J. Pharmac.*, **15**, 164–170.

LEWIS, M.J. (1974). Effect of acute and chronic treatment with practolol on cardiovascular responses in the pithed rat. *J. Pharm. Pharmac.*, **26**, 783–788.

(Received December 18, 1978.)