J. Pharm. Pharmacol. 1990, 42: 319–324
Received April 3, 1989

The Effects of (±)-, (+)- and (−)-Celiprolol and Bromoacetylalprenololmentane at the β-Adrenoceptors of Rat Isolated Cardiovascular Preparations

SHEILA A. DOGGRELL

Department of Pharmacology, School of Medicine, University of Auckland, Private Bag, Auckland, New Zealand

Abstract—The effects of (±)-, (+)- and (−)-celiprolol and of bromoacetylalprenololmentane (BAAM, an irreversible β-adrenoceptor antagonist) on the contractile responses of the electrically driven rat right ventricle strip to isoprenaline and on the relaxant responses of the rat aorta to procaterol, have been studied. Racemic and (−)-celiprolol or BAAM treatment of the ventricle produced non-parallel rightward shifts of the isoprenaline response curves with a reduction in the maximal response. Sotalol produced parallel rightward displacements of the procaterol response curves of the aorta with no effect on the maximal relaxations. Racemic and (+)- and (−)-celiprolol or BAAM treatment of the aorta produced non-parallel rightwards shifts of the procaterol relaxant curves with a reduction in the maximal relaxation. The BAAM data was used to demonstrate that the K_A (dissociation constant) for isoprenaline at β_1-adrenoceptors was $1{\cdot}46 \times 10^{-7}$ M and for procaterol at β_2-adrenoceptors was $2{\cdot}34 \times 10^{-5}$ M. Calculation of receptor occupancy demonstrated that to produce a maximal response of the rat right ventricle, isoprenaline had to occupy 87% of the β_1-adrenoceptors. Likewise, for a maximal response of the rat aorta, procaterol had to occupy 81% of the β_2-adrenoceptors. It is suggested that the use of tissues with small β-adrenoceptor reserves has shown that (±)- and (−)-celiprolol are slowly dissociating, rather than readily reversible, β-adrenoceptor antagonists.

(±)-Celiprolol (*N*-(3-acetyl-4-(3-t-butylamino-2-hydroxy) propoxy)-phenyl-1,1-diethylurea hydrochloride) lowers blood pressure in animals and is in clinical trial as an antihypertensive drug (Smith & Wolf 1984). Studies of the effects of (±)-celiprolol on isolated preparations have shown that it causes parallel rightward shifts of concentration response curves, and it has been assumed that it is a readily reversible β-adrenoceptor antagonist. Its pA_2 values have been determined and have demonstrated that it is a β_1-adrenoceptor selective antagonist having a pA_2 of 8·1 and 7·6 at the β_1-adrenoceptors of the left and right guinea-pig atria, respectively, and that it has a pA_2 value of 6·0 and 5·0 at the β_2-adrenoceptors of the calf tracheal muscle and rat uterus (Smith & Wolf 1984). The effects of (+)- and (−)-celiprolol at β-adrenoceptors has not been reported. I have compared the effects of (±)-, (+)- and (−)-celiprolol at β-adrenoceptors by investigating the effects of the drug on the responses of the electrically driven rat right ventricle to isoprenaline and on the relaxant responses of the rat aorta to procaterol (a potent and selective β_2-adrenoceptor agonist, O'Donnell & Wanstall 1985). I also report the ability of (±)- and (−)-celiprolol to cause non-parallel rightward shifts of isoprenaline and procaterol response curves, a finding which is compatible with slowly reversible or irreversible, rather than reversible, β-adrenoceptor antagonism. Therefore I have also examined the effects of an irreversible β-adrenoceptor antagonist, bromoacetylalprenololmentane (BAAM) on the responses to isoprenaline and procaterol. BAAM has been shown to cause irreversible blockade of isoprenaline response curves (Posner et al 1984) and of [^{125}I]pindolol binding to β-adrenoceptors in the rat brain (Minneman & Mowry 1986). A preliminary account of some of the data below has been presented to the Australasian Society of Clinical and Experimental Pharmacologists (Doggrell 1988a).

Materials and Methods

General

Male Wistar rats (250–350 g) were stunned and exsanguinated. The heart or thoracic aorta was rapidly removed and placed in Krebs solution saturated with 5% CO_2 in oxygen. All experiments were performed in the presence of a modified Krebs solution (composition (mM): NaCl, 116; KCl, 5·4; $CaCl_2$, 2·5; $MgCl_2$, 1·2; NaH_2PO_4, 1·2; $NaHCO_3$, 22·0; D-glucose, 11·2; Na_2 EDTA, 0·04) at 37°C which was bubbled with 5% CO_2 in oxygen. Contractile responses were measured isometrically with force displacement transducers (Grass model FTO 3.C) and displayed on a polygraph (Grass model 79B). In each series of experiments, the individual values obtained were subjected to Student's *t*-test. Differences were considered significant when $P < 0{\cdot}05$. Mean values ± s.e.m. were also obtained.

Contractile responses of the electrically driven rat right ventricle strip (method described by Doggrell & Hughes 1986)

Two strips (2 mm wide, 10 mm long and 1·5 mm thick) were prepared from each right ventricle. The individual strips were mounted longitudinally between two platinum electrodes under 1 g tension in 5 mL organ baths containing Krebs solution (with guanethidine at 10^{-5} M to prevent the release of noradrenline from nerve endings, and atropine at 10^{-6} M) and allowed to equilibrate for 60 min. In previous experiments it was shown that the threshold voltage (2 Hz, 5 ms duration) for contraction was 3–4 V and that the maximal force response of the electrically driven rat right ventricle strip occurred with isoprenaline at $10^{-6}/3 \times 10^{-6}$ M (Doggrell & Hughes 1986).

After 2 min of stimulation at 2 Hz (5 ms duration, 10 V) isoprenaline at 10^{-6} M was added, and stimulation was continued for a further 3 min or longer until a maximal

contractile response to isoprenaline had been obtained. The tissues were then allowed to recover for 25 min in a rapid flow of prewarmed Krebs solution. The tissues were challenged after 2 min of stimulation with isoprenaline at 3×10^{-6} M for 3 min. Stimulation was stopped and the tissues were washed in a rapid flow of prewarmed Krebs.

In studying the effects of procaterol and celiprolol on isoprenaline responses, one ventricle strip was treated with drug for the remainder of the experiment while the other strip of the pair remained untreated. In the study of the effect of BAAM on isoprenaline responses, one ventricle strip was treated with BAAM while the other strip of the pair was treated with vehicle ($\leq 0{\cdot}1\%$ ethanol) for 30 min. In all experiments, strips were washed rapidly for 30–60 min before the determination of non-cumulative isoprenaline response curves. Stimulation was stopped and the strips were rapidly washed in the absence of drug for 15–25 min between challenges to stimulation and isoprenaline. Untreated and treated tissues were challenged simultaneously with a single concentration of isoprenaline and only one concentration of one drug was used for each ventricle strip.

The increase in contractile force for each concentration of isoprenaline was measured and calculated as a percentage of the response obtained to the challenge with a maximum concentration of agonist at the beginning of the experiment. The slope of the response curve (difference in percentage maximum of the response/unit of logarithm of molar concentration of agonist) was computed by regression line analysis performed on the steepest part of the response curve which was usually between 20–80% of the maximum response of the individual curve.

Relaxant responses of the rat aorta (method of Doggrell 1988b)

Individual rings of rat aorta were suspended between stainless steel hooks under 1 g tension in 5 mL organ baths containing Krebs solution. Tissues were equilibrated for 30 min before exposure to phenoxybenzamine at 5×10^{-5} M for 30 min to block α-adrenoceptors. Tissues were washed for 20 min and then contracted by ≥ 150 mg by the addition of KCl to the organ bath to give a final concentration of $2\text{–}3 \times 10^{-2}$ M. When the contraction was constant, three series of experiments were performed.

(i) *The effects of drugs alone.* A cumulative challenge with procaterol, celiprolol or sotalol at $10^{-9}/10^{-8}$–10^{-4} M was made on a 4 min cycle.

(ii) *The effects of sotalol and celiprolol on responses to procaterol.* Three successive cumulative challenges of the KCl contracted rat aorta with procaterol produce identical relaxant curves (Doggrell 1988b). An initial cumulative challenge with procaterol was made to each aorta on a 4 min cycle in the absence of drugs. Tissues were then equilibrated for 45 min in the presence of a drug before recontracting the aorta and repeating the procaterol challenge. Tissues were then equilibrated for a further 45 min, in the presence of a higher concentration of the drug being tested before a third contraction with KCl and another procaterol challenge.

(iii) *The effects of BAAM on responses to procaterol.* A maximal response to procaterol was obtained at 10^{-5} M. Tissues were then washed for 60 min before one aorta of a pair was treated with BAAM at 3×10^{-6} M for 30 min while the other aorta of the pair remained untreated. Both tissues were then rapidly washed for 15 min before recontracting with KCl and a cumulative challenge with procaterol was made on a 4 min cycle to both aortas.

The maximal decrease in contractile response to each concentration of procaterol, celiprolol or sotalol was measured and calculated as a percentage of the KCl contraction. For the studies of the effects of drugs on responses to procaterol, the relaxant to procaterol were calculated as a percentage of the response obtained to the maximum concentration of agonist at the beginning of the experiment. Slopes of response curves and pD_2 values (the negative logarithm of the molar concentration of agonist producing 50% of the maximum response) were computed by regression line analysis of the steepest part of the response curve which was usually between 20–80% of the maximum response. For each tissue, the ability of a drug to alter responses was expressed as the concentration ratio (the antilogarithm of the difference between the pD_2 values in the presence and in the absence of the drug). When the effects of a drug were compatible with competitive antagonism (i.e. there was a reduction in the pD_2 value, but no effect on the slope of the concentration-response curve), pA_2 values were determined. pD_2 values were calculated for each tissue from the formula $pA_2 = pAx + \log(x - 1)$ where pAx is the negative logarithm of the molar concentration of drug and x is the procaterol concentration ratio.

Dissociation constants and fractional receptor occupancy

The dissociation constants (K_A) of isoprenaline (ventricle) and procaterol (aorta) were determined by the method of Furchgott & Bursztyn (1967). Isoprenaline or procaterol response curves were obtained from untreated tissues and from tissues that had been treated for 30 min with BAAM, an irreversible β-adrenoceptor antagonist. According to Furchgott & Bursztyn (1967) the following equation describes the relationship that exists between the response curves to an agonist before and after partial inactivation with an irreversible antagonist:

$$\frac{1}{[A]} = \frac{1-q}{qK_A} + \frac{1}{q[A']} \qquad (1)$$

where [A] and [A′] are corresponding equieffective concentrations of agonist before and after partial irreversible receptor inactivation, respectively, and q is the fraction of active receptors remaining after partial irreversible blockade. Plots of reciprocals of isoprenaline or procaterol concentration before fractional receptor inactivation (i.e. 1/[A]) against the reciprocals of the corresponding equieffective concentrations of isoprenaline or procaterol after receptor inactivation (i.e. 1/[A′]) yielded straight lines in accord with receptor theory (Furchgott & Bursztyn 1967). The K_A of isoprenaline or procaterol was then calculated from the slope and intercept of the resulting "double reciprocal" plots by the following equation (Furchgott & Bursztyn 1967):

$$K_A = (\text{slope} - 1)/\text{intercept} \qquad (2)$$

Fractional β-adrenoceptor occupancy by isoprenaline or

procaterol was calculated for each bath concentration studied ([A]) using the dissociation constants obtained from the interaction of isoprenaline or procaterol with β-adrenoceptors according to the procedure of Ruffolo (1982). Thus the following relationship between agonist concentration ([A]) and dissociation constant was used to calculate β-adrenoceptor occupancy by isoprenaline or procaterol:

$$\% \text{ receptor occupancy} = \frac{[A]}{K_A + [A]} \times 100 \qquad (3)$$

The occupancy-response relationships were constructed by plotting the calculated β-adrenoceptor occupancy for isoprenaline or procaterol, against the corresponding response from the concentration-response curve.

Drugs

The drugs used were sotalol hydrochloride (donated by Bristol), (±)-, (+)- and (−)-celiprolol hydrochloride (donated by Chemie Linz AG), guanethidine hydrochloride (donated by Ciba-Geigy), atropine sulphate, (−)-isoprenaline bitartrate (Sigma Chemicals), phenoxybenzamine hydrochloride (donated by Smith, Kline & French) and procaterol hydrochloride (donated by Warner-Lambert).

Results

Ventricle

Procaterol, (±)- and (−)-celiprolol at 10^{-6} M (+)-celiprolol at 10^{-5} M had no effect on the resting tone or on the force of contraction of the electrically driven rat right ventricle strip. Procaterol at 10^{-6} M had no effect on the responses of the electrically driven preparation to isoprenaline (n = 8, data not shown).

(±)-Celiprolol at 10^{-6} M produced a non-parallel rightward shift of the isoprenaline response curve with a reduction in the maximal response (Table 1, Fig. 1). (+)-Celiprolol at 10^{-6} M had no effect (data not shown) and at 10^{-5} M produced a parallel rightward shift of the isoprenaline response curve with no effect on the maximal response (Table 1, Fig. 1). (−)-Celiprolol at 10^{-6} M had a similar effect to (±)-celiprolol in causing a non-parallel rightward shift of the isoprenaline response curve with a reduction of the maximal response.

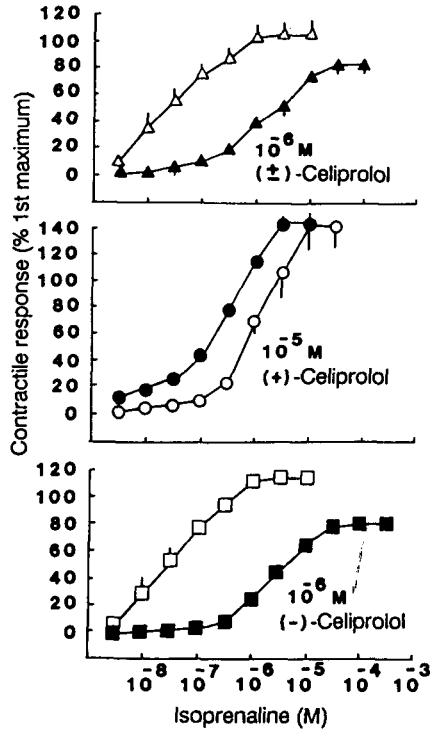

FIG. 1. Effects of (±)-, (+)- and (−)-celiprolol on the contractile responses of the electrically driven rat right ventricle strip to isoprenaline. Top: responses in the absence (△) and presence (▲) of (±)-celiprolol at 10^{-6} M. Middle: responses in the absence (●) and presence (○) of (+)-celiprolol at 10^{-5} M. Bottom: responses in the absence (□) and presence (■) of (−)-celiprolol at 10^{-6} M. Responses are calculated as a percentage of the first maximum and plotted against the log of the molar concentration of isoprenaline. Each value is the mean from 7–8 tissues; vertical lines show s.e.m.

Table 1. Effects of drugs on slopes of isoprenaline response curves (ventricle) and procaterol response curves (aorta).

	Isoprenaline slopes[a]	Procaterol slopes[a]
Control	ND	68±7 (7)
Sotalol, 10^{-8} M		80±21 (7)
Control	ND	57±6 (7)
Sotalol, 10^{-7} M		100±20 (7)
Control	70±11 (8)	44±4 (7)
(±)-Celiprolol, 10^{-6} M	45±5 (8)*	24±2 (7)*
Control	58±6 (7)	55±15 (6)
(+)-Celiprolol, 10^{-6} M	68±10 (7)	17±3 (6)*
Control	58±5 (7)	ND
(+)-Celiprolol, 10^{-5} M	74±11 (7)	
Control	66±7 (7)	46±6 (8)
(−)-Celiprolol, 10^{-6} M	50±3 (7)*	34±6 (8)*
Control	79±12 (5)	ND
BAAM, 3×10^{-7} M	40±6 (5)*	
Control	ND	37±5 (7)
BAAM, 3×10^{-6} M		21±4 (7)*

[a] Mean ± s.e.m.
ND = not determined.
(n) = number of animals.
* $P < 0.05$, paired t-test with own control.

BAAM, an irreversible β-adrenoceptor antagonist, produced a marked depression of the maximum responses to isoprenaline at 3×10^{-7} M for 30 min, and a non-parallel rightward shift of the isoprenaline response curves (Fig. 2, Table 1). The K_A (dissociation constant) was determined by the method of Furchgott & Bursztyn (1967). The reciprocals of the corresponding equieffective concentrations of isoprenaline obtained in untreated and BAAM treated tissues were plotted (Fig. 2) and the slope and intercept determined. The K_A for isoprenaline was calculated from equation (2) and was 1.46×10^{-7} M. Fractional β-adrenoceptor occupancy by isoprenaline was calculated by the procedure of Ruffolo (1982). For each concentration of isoprenaline, the % receptor occupancy was calculated from equation (3). A plot of the occupancy-response relationship (Fig. 2), shows that isoprenaline produced half-maximal response in the rat right ventricle strip by occupying 15% of those available. Further-

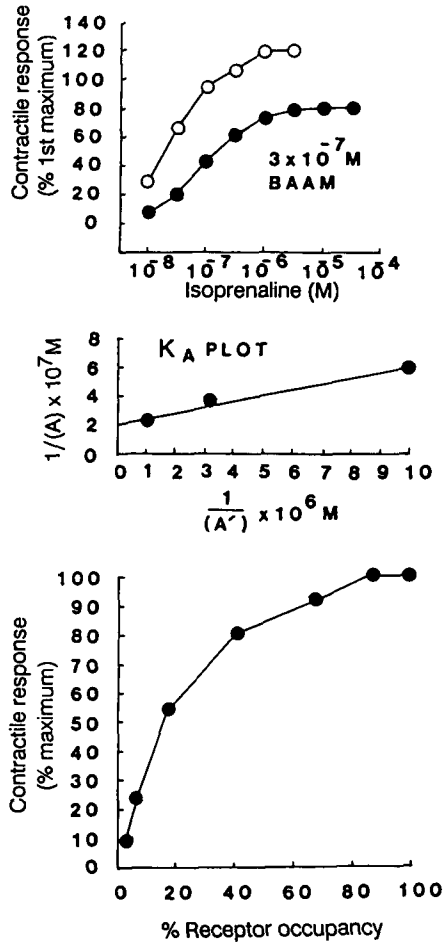

FIG. 2. Effect of BAAM on the contractile responses of the electrically driven rat right ventricle strip to isoprenaline. Top: responses from 5 untreated tissues (○) and responses from paired tissues treated with BAAM at 3×10^{-7} M for 30 min (●). Middle: Double-reciprocal plot (K_A plot) of equieffective concentrations of isoprenaline before (A^{-1}) and after (A'^{-1}) treatment with BAAM. Bottom: Contractile responses to isoprenaline plotted as a function of the calculated β-adrenoceptor occupancy. Responses are calculated as a percentage of the maximum response.

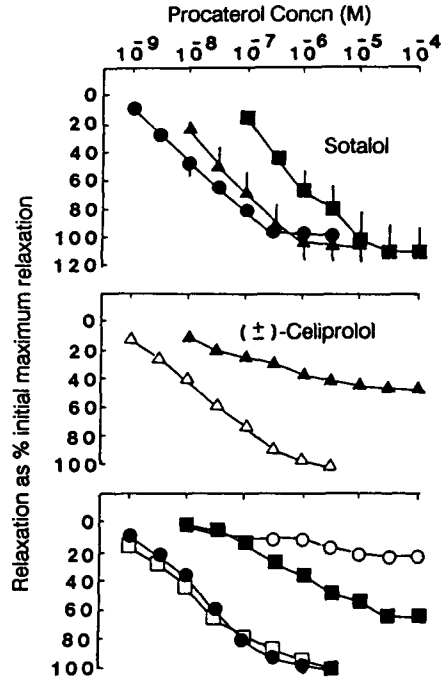

FIG. 3. Effects of sotalol, (±)-, (+)- and (−)-celiprolol on the relaxant responses of the rat aorta to procaterol. Top: responses in the absence (●) and presence of sotalol at 10^{-8} (▲) and 10^{-7} M (■). Middle: responses in the absence (△) and presence (▲) of (±)-celiprolol at 10^{-6} M. Bottom: responses in the absence (●) and presence (○) of (+)-celiprolol at 10^{-6} M and, from another group of animals, in the absence (□) and presence of (−)-celiprolol at 10^{-6} M (■). Responses are calculated as a percentage of the initial maximum relaxation and plotted against the log of the molar concentration of procaterol. Each value is the mean from 6–8 tissues; vertical lines show s.e.m.

more, to produce a maximal response, isoprenaline has to occupy 87% of the β-adrenoceptors available to it in the rat right ventricle.

Aorta

(i) *The effects of drugs alone.* When the rat aorta had been contracted by the addition of KCl, it was relaxed by procaterol, $\geq 10^{-9}$ M, but not by sotalol, $\leq 10^{-4}$ M, or by (±)-celiprolol at $\leq 10^{-5}$ M. (±)-Celiprolol at 10^{-4} M caused a small relaxation of the KCl contracted aorta.

(ii) *The effects of sotalol and celiprolol on responses to procaterol.* Sotalol at 10^{-8}–10^{-7} M produced parallel rightward displacements of the procaterol relaxant curves with no effect on maximal relaxation (Table 1, Fig. 3). The submaximal responses to procaterol were inhibited × 8 by sotalol at 10^{-8} M which gave a mean pA_2 value of 8·19 (n = 7) and they were inhibited × 28 by sotalol at 10^{-7} M (pA_2 value = 8·23, n = 7). The procaterol relaxant curves were not affected by (±)-, (+)- or (−)-celiprolol at 10^{-7} M. However, they each produced non-parallel rightward displacements of the procaterol relaxant curves with a reduction in the maximal relaxation at 10^{-6} M (Table 1, Fig. 3).

(iii) *The effects of BAAM on responses to procaterol.* BAAM produced a marked depression of the maximum relaxation to procaterol at 3×10^{-6} M for 30 min, and a non-parallel rightward shift of procaterol response curves (Fig. 4, Table 1). The K_A for procaterol at the β_2-adrenoceptors of the rat aorta was $2{\cdot}34 \times 10^{-5}$ M (see K_A plot in Fig. 4). The plot of the occupancy-response relationship (Fig. 4) showed that procaterol produced a half-maximal response in the rat aorta by occupying 1% of those available. However, to produce a maximal response, procaterol occupied 81% of the β_2-adrenoceptors available to it in the rat aorta.

Discussion

Procaterol is a potent β_2-adrenoceptor selective agonist which has been used to demonstrate a subpopulation of β_2-adrenoceptors in the guinea-pig atria (Johansson & Persson 1983) and a minor population of β_2-adrenoceptors in the rat atria (O'Donnell & Wanstall 1985). The results of the present study suggest that functionally, the rat right ventricle strip has only β_1-adrenoceptors. Thus procaterol had no effect

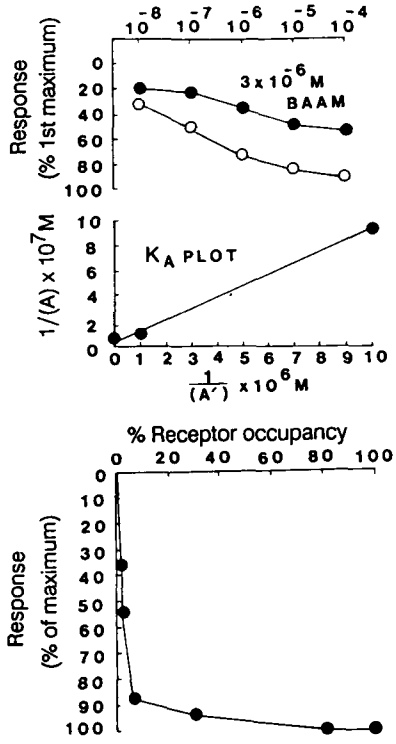

FIG. 4. Effect of BAAM on the relaxant responses of the rat aorta to procaterol. Top: responses from 7 untreated tissues (○) and responses from paired tissues treated with BAAM at 3×10^{-6} M for 30 min (●). Middle: Double reciprocal plot (K_A plot) of equieffective concentrations of procaterol before (A^{-1}) and after (A'^{-1}) treatment with BAAM. Bottom: Relaxant response to procaterol plotted as a function of the calculated β_2-adrenoceptor occupancy. Responses are calculated as a percentage of the maximum response.

alone and procaterol did not alter the responses to isoprenaline, a non-selective β-adrenoceptor agonist.

The effect of an irreversible antagonist on an agonist concentration-response curve can be used to determine the dissociation constant of the agonist (K_A) and the receptor reserve for the agonist on any tissue (discussed by Kenakin 1987). There have been many studies of the effects of α-agonists at α-adrenoceptors using phenoxybenzamine as the irreversible α-adrenoceptor antagonists (e.g Ruffolo & Reid 1985). Similar studies of the effects of β-agonists at β-adrenoceptors have been hampered until recently by the lack of truly irreversible β-adrenoceptor antagonists. BAAM is a newly developed β-adrenoceptor antagonist (Posner et al 1984; Minneman & Mowry 1986). The effect of BAAM presented here, on the responses of the rat right ventricle to isoprenaline, showed that to produce a maximal response, isoprenaline occupied 87% of the available β_1-adrenoceptors. The study of the effect of BAAM on the responses of the rat aorta to procaterol showed that to produce a maximal response, procaterol occupied 81% of the available β_2-adrenoceptors. Thus there is only a small β_1-adrenoceptor reserve in the ventricle for maximal isoprenaline responses and a small β_2-adrenoceptor reserve on the aorta for maximal procaterol responses.

Radioligand studies have shown that (±)-celiprolol has affinity for β-adrenoceptors (Van Ingwegen et al 1984). (±)-Celiprolol produces parallel rightward shifts of isoprenaline-response curves in atrial, tracheal and uterine preparations and is therefore considered to be a readily reversible β-adrenoceptor antagonist. In the present study (±)- and (−)-celiprolol did not act as readily reversible β-adrenoceptor antagonists on the ventricle strip or aorta; i.e. (±)- and (−)-celiprolol caused non-parallel rightward shifts of the isoprenaline (ventricle) and procaterol (aorta) response curves with a depression of the maximal responses.

One possible explanation of the non-competitive antagonoism with (±)- and (−)- celiprolol is that, in addition to being reversible β-adrenoceptor antagonists, (±)- and (−)-celiprolol are membrane stabilizers. Propranolol is a reversible β-adrenoceptor antagonist and membrane stabilizer (Fitzgerald 1984). However, the effects of propranolol and (±)- and (−)-celiprolol on the ventricle are not similar. Propranolol causes a parallel rightward shift of isoprenaline response curves which is compatible with reversible β-adrenoceptor antagonism and a depression of isoprenaline maximal responses which is probably due to membrane stabilization (Doggrell & Hughes 1986).

A more probable explanation of the non-parallel rightward shifts of the isoprenaline and procaterol response curves with (±)- and (−)-celiprolol is that these drugs are slowly dissociating antagonists at β-adrenoceptors. Slowly dissociating antagonists produce parallel rightward shifts of agonist response curves in tissues with spare receptors for the agonist. When the spare receptors are occupied or in tissues with few spare receptors, slowly dissociating antagonists cause non-parallel rightward shifts of agonist response curves. Such explanation requires that the preparations in which (±)-celiprolol has been shown to cause parallel rightward shifts of isoprenaline response curves have spare receptors for the maximum response to isoprenaline, and that the rat right ventricle and aorta (in which (±)-celiprolol cause non-parallel rightward shifts of response curves) have few spare receptors for a maximum response to isoprenaline and procaterol, respectively. Studies with guinea-pig atria and rat uterus (Nicholson & Broadley 1978; Kenakin 1982) do indicate that these tissues have spare receptors for the maximum responses to isoprenaline. The effects of irreversible β-adrenoceptor antagonists on the responses of the calf trachea to isoprenaline have not, to my knowledge, been studied. The present study has demonstrated that the rat right ventricle strip has a small β_1-adrenoceptor reserve for the maximum response to isoprenaline and that the rat aorta has a small β_2-adrenoceptor reserve for the maximum response to procaterol.

In conclusion, the use of tissues with small β-adrenoceptor reserves for maximal responses to isoprenaline/procaterol has revealed that (±)- and (−)-celiprolol are slowly dissociating, rather than readily reversible, antagonists at β-adrenoceptors.

Acknowledgement

This study was supported by a project grant from the national heart Foundation of New Zealand.

References

Doggrell, S. A. (1988a) (±) and (−)-Celiprolol do not act solely as competitive antagonists at β_1- or β_2-adrenoceptors. Clin. Exp. Pharmacol. Physiol. (Suppl.) 8: 11

Doggrell, S. A. (1988b) Relaxant and β_2-adrenoceptor blocking activities of labetalol, dilevalol, amosulalol and KF-4317 on the rat isolated aorta. J. Pharm. Pharmacol. 40: 812–815

Doggrell, S. A., Hughes, E. W. (1986) On the assessment of the β-adrenoceptor blocking activity of propranolol using the rat isolated right ventricle. J. Pharmacol. Method 15: 119–131

Fitzgerald, J. D. (1984) β-Adrenoceptor antagonists. In: van Zwieten, P. A. (ed.) Handbook of Hypertension. Volume 3. Pharmacology of Antihypertensive Drugs. Amsterdam, New York and Oxford, Elsevier, pp 249–306

Furchgott, R. F., Bursztyn, P. (1967) Comparison of the dissociation constants and of relative efficacies of selected agonists acting on parasympathetic receptors. Ann. N.Y. Acad. Sci. 144: 882–899

Johansson, L., Persson, H. (1983) β_2-Adrenoceptors in guinea-pig atria. J. Pharm. Pharmacol. 34: 804–807

Kenakin, T. P. (1982) Theoretical and practical problems with the assessment of intrinsic efficacy of agonists: Efficacy of reputed beta-1 selective adrenoceptor agonists for beta-2 adrenoceptors. J. Pharmacol. Exp. Ther. 223: 416–423

Kenakin, T. P. (1987) Pharmacological analysis of drug-receptor interaction. Raven Press, New York

Minneman, K. P., Mowry, C. B (1986) Interactions of putatively irreversible antagonists with β_1- and β_2-adrenoceptors. Biochem. Pharmacol. 35: 857–864

Nicholson, C. D., Broadley, K. J. (1978) Irreversible β-adrenoceptor blockade of atrial rate and tension responses. Eur. J. Pharmacol. 52: 259–269

O'Donnell, S. R., Wanstall, J. C. (1985) Responses to the β_2-selective agonist procaterol of vascular and atrial preparations with different functional β-adrenoceptor populations. Br. J. Pharmacol. 84: 227–235

Posner, P., Peterson, C. V., Pitha, J., Baker, S. P. (1984) The effect of bromoacetylalprenololmentane on rat atrial tension development and β-adrenoceptors. Eur. J. Pharmacol. 100: 373–376

Ruffolo, R. R. (1982) Important concepts of receptor theory. J. Auton Pharmacol. 2: 277–295

Ruffolo, R. R., Reid, R. L. (1985) Relationship between alpha adrenoceptor occupancy for the alpha-1 adrenoceptor agonist, cirazoline, and the alpha-2 adrenoceptor agonist B-HT 933, in canine saphenous vein. J. Pharmacol. Exp. Ther. 235: 636–643

Smith, R. D., Wolf, R. S. (1984) Celiprolol. In: Scriabine, A. (ed.) New Drug Annual: Cardiovascular Drugs. Raven Press, New York, pp 19–35

Van Inwegen, R. G., Khandwala, A., Weinryb, I., Pruss, T. P., Neiss, E., Sutherland, C. A. (1984) Effects of celiprolol (REV 5320), a new cardioselective beta-adrenoceptor antagonist, on in vitro adenylate cyclase alpha- and beta-adrenergic receptor binding and lipolysis. Arch. Int. Pharmacodyn. Ther. 272: 40–55