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The Effects of Labetalol and Dilevalol on Isolated Cardiovascular Preparations of the Guinea-pig and Rat*

SHEILA A. DOGGRELL

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

Abstract—Differing effects of labetalol and dilevalol on cardiovascular preparations have been reported. I have studied the effects of labetalol and dilevalol on the contractile responses of the rat and guinea-pig left atria and rat portal vein. On the guinea-pig left atria low concentrations of labetalol ($\geq 10^{-8}$ M) and of dilevalol ($\geq 10^{-7}$ M) inhibited to a small extent the responses to electrical cardiac stimulation, which is indicative of membrane stabilizing activity. Labetalol ($\geq 3 \times 10^{-8}$ M) and dilevalol ($\geq 10^{-8}$ M) caused surmountable antagonism of the isoprenaline responses of the atria and the pA_2 values were 8·60 and 8·98 at the β_1-adrenoceptors of the rat left atria and 7·90 and 8·31, respectively, on the guinea-pig left atria which has functional β_1- and β_2-adrenoceptors. Labetalol and dilevalol (both at $\geq 10^{-7}$ M) attenuated the spontaneous contractile activity of the rat portal vein and the attenuation to labetalol at 10^{-6} M was abolished by ICI 118,551 which illustrates that the labetalol-induced attenuation is β_2-adrenoceptor mediated. The isoprenaline attenuation responses of the portal vein were inhibited by labetalol and dilevalol (both at $\geq 10^{-7}$ M) and the pA_2 value for the labetalol at β_2-adrenoceptors was 7·59. It is concluded that labetalol and dilevalol are β_1-adrenoceptor selective antagonists.

Racemic β-adrenoceptor antagonists (β-blockers) are commonly used in the treatment of hypertension, angina and cardiac arrhythmias. These drugs act as antagonists at β_1- and β_2-adrenoceptors and may also have ancillary properties. The properties of racemic drugs are not always shared equally between the stereoisomers. There have been many studies of racemic β-blockers but only a few studies of the individual stereoisomers.

Labetalol is a β-blocker that contains two asymmetric centres. Dilevalol is the *R,R* stereoisomer of labetalol. In the original comparison of labetalol and its stereoisomers (Brittain et al 1982), labetalol and dilevalol were classified as nonselective β-blockers. Thus labetalol had a pA_2 value of 7·68 at the β_1-adrenoceptors of the guinea-pig left atrium and a value of 7·40 at the β_2-adrenoceptors of guinea-pig trachea. Dilevalol was more potent than labetalol and had pA_2 values of 8·26 at the β_1-adrenoceptors of the guinea-pig atria and of 8·52 at the β_2-adrenoceptors of the guinea-pig trachea. Previously, I have investigated the effects of labetalol and dilevalol at β_1- and β_2-adrenoceptors in separate studies (β_1-adrenoceptors, rat right ventricle (Doggrell & Hughes 1985); β_2-adrenoceptors, rat aorta (Doggrell 1988a)) and have evidence that labetalol and dilevalol are selective β_1-adrenoceptor antagonists. Thus, labetalol had a pA_2 of 8·30 at the β_1-adrenoceptors of the rat right ventricle and 7·45 at the β_2-adrenoceptors of the rat aorta, and dilevalol had a pA_2 of 8·90 in ventricle and of 8·25 in aorta.

As an ancillary property, labetalol causes vasodilation (independent of α-adrenoceptor blockade). There is debate concerning the mechanism underlying this vasodilation. In the dog denervated limb (Baum et al 1981) the vasodilation with labetalol is reversed by high concentrations of propranolol and is considered to be due to β_2-adrenoceptor agonism. In isolated perfused gracilis muscle of the dog (Dage & Hsieh 1980) and in rat aorta (Doggrell 1988a) the vasodilatory action of labetalol appears not to be due to β_2-agonism as it is not blocked by β-blockers.

The aims of the present study were, firstly, to determine whether labetalol and dilevalol are nonselective or β_1-adrenoceptor selective antagonists and, secondly, to clarify the effects of labetalol and dilevalol alone on cardiovascular tissues. Thus, we report the effects of labetalol and dilevalol on the β_1-adrenoceptor mediated contractions of the rat electrically-driven left atria and the β_2-adrenoceptor mediated attenuations of the rat portal vein to isoprenaline. As the pA_2 values that we have obtained for labetalol and dilevalol at rat cardiac β_1-adrenoceptors are different from those previously reported using guinea-pig atria (Brittain et al 1982), I have also studied the effects of the labetalol and dilevalol on the responses of the electrically-driven left atria of guinea-pig to isoprenaline. Finally the effects of labetalol and dilevalol alone on the electrically-driven left atria of rat and guinea-pig and on the spontaneous contractile activity of the rat portal vein were determined.

Materials and Methods

General

Male Wistar rats, 250–350 g, were stunned and exsanguinated. Male and female adult guinea-pigs were killed by cervical dislocation. The rat or guinea-pig heart or rat portal vein was rapidly removed and placed in Krebs solution saturated with 5% CO_2–95% O_2. 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_2EDTA 0·04) at 37°C which was bubbled with 5% CO_2 –95% O_2. Contractile responses were measured isometrically with force displacement transducers (Grass model FTO3.C) and displayed on a polygraph (Grass model 79B). In each series of experiments, the individual values (percentages, slopes,

* A preliminary account of some of these findings has been presented to the New Zealand Section of the Australasian Society of Clinical and Experimental Pharmacologists (Doggrell 1991).

pD_2 values, concentration-ratios and pA_2 values) obtained were subject to Student's *t*-test. Differences were considered significant for $P<0.05$. Mean values ± s.e.m. were also obtained.

Contractile responses of the electrically-driven left atria of rat and guinea-pig (method described by Doggrell 1988a)

Left atria were removed from the heart and either halved (rat) or quartered (guinea-pig). Each atrial strip was mounted longitudinally between two platinum electrodes under 1 g tension in 5 mL organ baths containing Krebs solution (with 10^{-5} M guanethidine to prevent the release of noradrenaline from nerve endings, and atropine at 10^{-6} M) and allowed to equilibrate with washing for 60 min. Tissues were electrically stimulated at 4 Hz (5 ms, 10 V). After 9 min of stimulation, a cumulative challenge with isoprenaline was made on a 3 min cycle. This cycle was continued until a maximum response was obtained.

One of the tissues remained untreated while the other tissues from the same atrium were treated with drug for 60 min. During this 60 min, about 500 mL of drug-free or drug-containing Krebs buffer flowed over the tissue. The tissues were electrically stimulated and cumulatively challenged with isoprenaline until an isoprenaline maximal response was obtained. This procedure was repeated with the same tissue remaining untreated throughout and the other tissues being treated with higher concentrations of the same drug.

The contractile responses to cardiac stimulation just before the second and third challenges with isoprenaline were calculated as a percentage of the response to stimulation before the first challenge with isoprenaline. For each challenge with isoprenaline, the response to electrical stimulation just before challenge with isoprenaline was subtracted from the combined response to cardiac stimulation and isoprenaline. The maximal combined responses to cardiac stimulation and isoprenaline were calculated as a percentage of the maximum of the first challenge with isoprenaline. If the maximum response to cardiac stimulation and isoprenaline between treated and untreated tissues was not significantly different, response curves were calculated as a percentage of the maximum of the individual curves.

Attenuation responses of the rat portal vein (method described by Doggrell 1990b)

Each portal vein was cleared of surrounding tissue and mounted under 1 g tension in a 5 mL organ bath containing

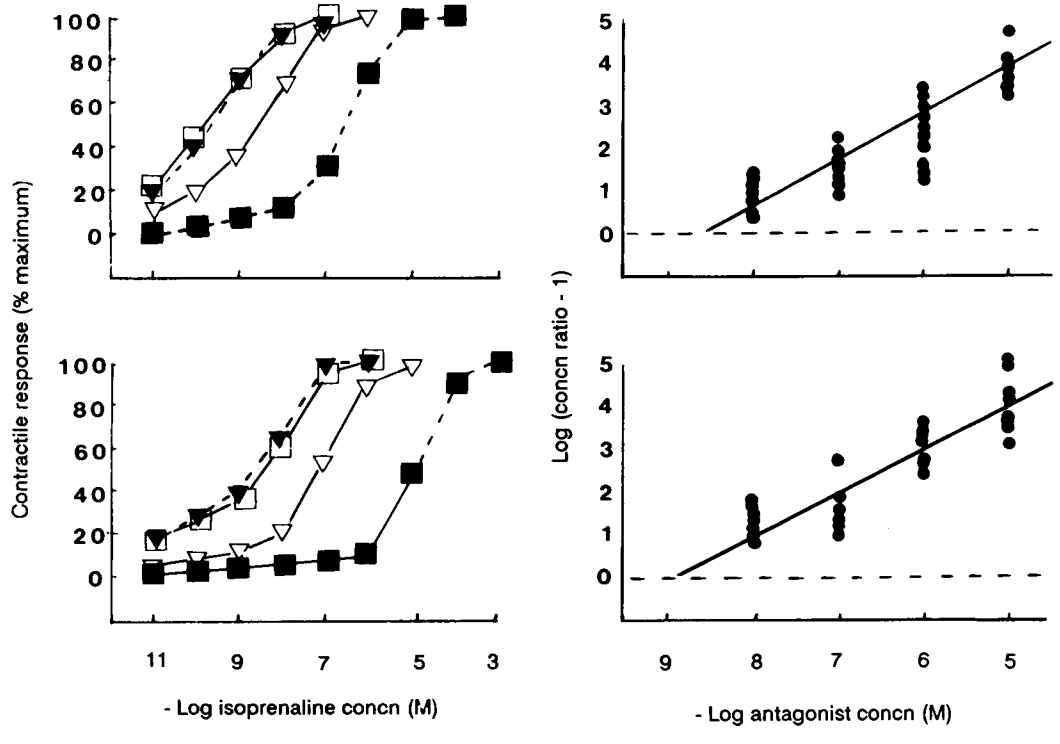

FIG. 1. Effects of labetalol and dilevalol on the contractile responses of the rat electrically-driven left atria to isoprenaline. Top left: responses in the absence (▼) and presence (▽) of labetalol at 10^{-7} M and in the absence (□) and presence (■) of labetalol at 10^{-5} M. Bottom left: responses in the absence (▼) and presence (▽) of dilevalol at 10^{-7} M and in the absence (□) and presence (■) of dilevalol at 10^{-5} M. Responses are calculated as a percentage of the maximum and plotted against the molar concentration of isoprenaline on a logarithmic scale. Each value is the mean from 5–8 tissues; s.e.m. are within the symbols. Right: Schild regression (logarithm of the concentration-ratio minus 1 against the logarithm of the molar concentration of antagonist) for labetalol (top) and dilevalol (bottom).

Krebs solution and allowed to equilibrate with washing for 30 min. To prevent isoprenaline from stimulating α-adrenoceptors, and to inhibit the extraneuronal uptake process, tissues were treated with phenoxybenzamine at 10^{-4} M for 45 min. Tissues were then rapidly washed for 20 min. The washing was then stopped, and the tissues were allowed to stabilize for 20 min. During this period, the amplitude of the spontaneous contractions became constant and then three series of experiments were performed.

Effect of labetalol and dilevalol on responses to isoprenaline. A cumulative challenge to isoprenaline (10^{-9}, 3×10^{-9}, 10^{-8} M) was made to each portal vein on a 5 min cycle. The cycle was continued until a maximum attenuation was obtained. Tissues were then rapidly washed in the presence of drug for 45 min. During this 45 min about 500 mL of drug-containing Krebs solution flowed over the tissue. Washing was stopped for 20 min before a second challenge to isoprenaline. Tissues were then treated with a higher concentration of the same drug in a rapid wash. After a 45 min/500 mL wash and a 20 min stabilization, a third challenge to isoprenaline was initiated.

Cumulative challenge to labetalol. A cumulative challenge to labetalol was made to each portal vein on a 10 min cycle.

Effect of ICI 118,551 on the attenuation responses to labetalol. Tissues were treated with either 450 mL of drug-free or 450 mL of labetalol-containing Krebs solution over 45 min. Washing was stopped for 20 min and then ICI 118,551 was added to each tissue.

On the portal vein, the measurement of the contractile response was taken as the average of the amplitude of the final three contractions in a 5 min period. The attenuation in the presence of a drug or drugs was calculated as a percentage of the contractile response in the first stabilization period.

Assessment of data

Slopes were determined for all isoprenaline response curves. In addition, when responses to isoprenaline were normalized, pD_2, concentration-ratio and pA_2 values were determined. The slope (difference in percentage maximum of the response/unit of log of molar concentration of isoprenaline) and pD_2 values were computed by regression line analysis. The regression line analysis was performed on the steepest part of the log concentration-response curve, which was usually over the range 20–80% of the maximum response. For each tissue, the concentration ratios (the antilog of the difference between the pD_2 values) were determined between each challenge with isoprenaline. Previous studies had shown that the sensitivity to isoprenaline decreased with successive challenges in the rat left atria (Doggrell 1988b) but not the rat portal vein (Doggrell 1990a). Consequently concentration ratios obtained in the presence of drugs had to be corrected for changes occuring in untreated left atria but not portal veins. Thus the difference in the mean pD_2 values from untreated left atria were subtracted from the difference in the individual pD_2 values from treated left atria. pA_2 values were determined for concentrations of drugs that had no effect on the slope of the isoprenaline response curves by Schild analysis. Thus the Schild plot [log (x − 1), where x is the concentration-ratio, ordinate, vs the logarithm of the molar concentration of drug, abscissa] was computed by regression line analysis of individual log (x − 1) values.

Drugs

The drugs used were labetalol hydrochloride† (Glaxo, UK), guanethidine hydrochloride† (Ciba-Geigy, Switzerland), dilevalol hydrochloride† (SCH 19930, Schering Corporation, USA), atropine sulphate (Serva, Germany), (−)-isoprenaline bitartrate (Sigma Chemical Co., USA) and phenoxybenzamine hydrochloride† (Smith, Kline and French, USA). Compounds marked with a dagger were donated.

Results

Rat left atria

Direct muscle stimulation (4 Hz, 5 ms, 10 V) contracts the rat left atria and the force of contraction is increased by isoprenaline acting at β_1-adrenoceptors. With successive challenges, the cardiac stimulation response and the sensitivity to isoprenaline decreases (Doggrell 1988b).

In the present study, the cardiac stimulation responses were not significantly altered by labetalol or dilevalol at 10^{-8}–10^{-6} M but were inhibited by labetalol and dilevalol at 10^{-5} M by 42% ± 10 (8) (mean % ± s.e.m., n = 8) and 39% ± 7 (8), respectively. The isoprenaline responses were inhibited by labetalol and dilevalol (Fig. 1) at 10^{-8}–10^{-5} M, there being parallel rightward shifts of the isoprenaline response curves (i.e. the slopes of isoprenaline response curves from treated and untreated tissues were not significantly different), no effect on isoprenaline maximum responses and reduced isoprenaline pD_2 values. The slopes of the Schild regression analysis for both labetalol and dilevalol (Fig. 1) were 0·98 and the mean pA_2 values were 8·60 ± 0·05 (18) and 8·98 ± 1·10 (14), respectively.

Guinea-pig left atria

Direct muscle stimulation (4 Hz, 5 ms, 10 V) contracted the guinea-pig left atria and the force of contraction was increased by isoprenaline. With successive challenges, the cardiac stimulation response decreased but the sensitivity to

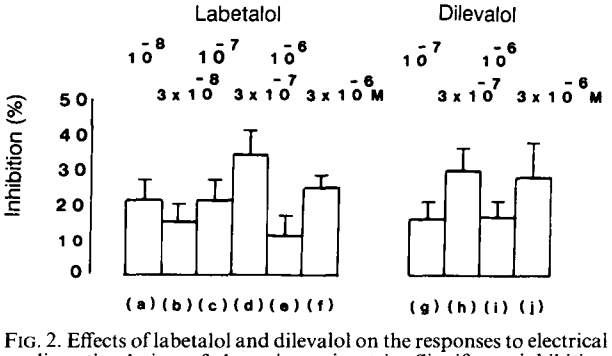

FIG. 2. Effects of labetalol and dilevalol on the responses to electrical cardiac stimulation of the guinea-pig atria. Significant inhibition ($P < 0.05$) was observed with labetalol at 10^{-8}–3×10^{-6} M and dilevalol at 10^{-7}–3×10^{-6} M. Percentage inhibition of responses to electrical cardiac stimulation in the presence of labetalol at 10^{-8} (a), 3×10^{-8} (b), 10^{-7} (c), 3×10^{-7} (d), 10^{-6} (e) and 3×10^{-6} M (f) and of dilevalol at 10^{-7} (g), 3×10^{-7} (h), 10^{-6} (i) and 3×10^{-6} M (j). Each value is the mean from six tissues; vertical lines show s.e.m.

isoprenaline was unchanged. Thus the second and third cardiac stimulation responses were 63% ±2 and 56% ±4 (6) of the first challenge and the isoprenaline pD_2 values were 7·98±0·05, 7·94±0·08 and 7·96±0·06 (6) for the first, second and third challenges to isoprenaline, respectively.

The responses to electrical cardiac stimulation were not significantly altered by dilevalol at 10^{-8}–3×10^{-8} M but were inhibited, to a similar extent, by labetalol at 10^{-8}–3×10^{-6} M and by dilevalol at 10^{-7}–3×10^{-6} M (Fig. 2). The isoprenaline responses were not altered by labetalol at 10^{-8} M but were inhibited by higher concentrations of labetalol (3×10^{-8}–3×10^{-6} M) and by dilevalol at 10^{-8}–3×10^{-8} M (Fig. 3). The inhibitory effect of labetalol and dilevalol on isoprenaline responses consisted of parallel rightward shifts of the response curves, no effect on maximum responses and reduced pD_2 values. The slopes of Schild regression analysis for labetalol and dilevalol were 0·91 and 0·97 which were not significantly different from unity and the mean pA_2 values were 7·90±0·04 (6) and 8·31±0·04 (6), respectively. The pA_2 values obtained for labetalol and dilevalol on the guinea-pig atria were significantly lower ($P < 0.001$) than those observed on the rat left atria.

Rat portal vein

The spontaneous contractile activity of the phenoxybenzamine-treated portal vein remains unchanged for 6 h (Doggrell 1990a). Following a rapid 45 min wash in Krebs solution containing labetalol or dilevalol, the spontaneous contractile activity of the rat portal vein was significantly ($P < 0.05$) attenuated. Thus the responses were reduced by 15, 29 and 14% by labetalol at 10^{-7}, 10^{-6} and 10^{-5} M and by 30, 39 and 36% by dilevalol at 10^{-7}, 10^{-6} and 10^{-5} M (Fig. 4).

Three successive challenges of the rat portal vein to isoprenaline produced identical attenuation curves (Doggrell 1990a). Labetalol and dilevalol antagonized the responses to isoprenaline. Labetalol at 10^{-7}–10^{-5} M caused parallel rightward shifts of isoprenaline log concentration response curves (Table 1) with no effect on isoprenaline maximal responses (Fig. 4). Schild analysis of this data (Fig. 4) produced a slope of 1·07 which was not significantly different from unity and a pA_2 of 7·59±0·04 (14) for labetalol. This pA_2 value obtained for labetalol on the rat portal vein was significantly lower ($P < 0.01$) than the pA_2 for labetalol on the rat left atria. On the portal vein, dilevalol (10^{-7}–10^{-5} M) caused non-parallel rightward shifts of isoprenaline response curves (Table 1) with no effect on isoprenaline maximal responses (Fig. 4). The data with dilevalol was unsuitable for Schild analysis.

Further experiments were performed in order to examine the effects of ICI 118,551 on the attenuating responses to

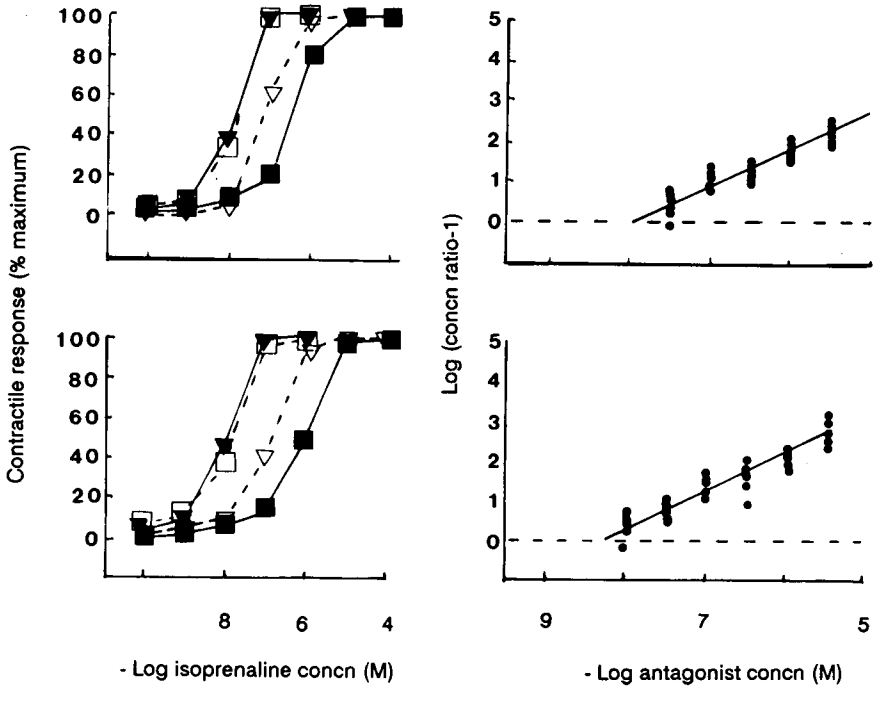

FIG. 3. Effects of labetalol and dilevalol on the contractile responses of the guinea-pig electrically-driven left atria to isoprenaline. Top left: responses in the absence (▼) and presence (▽) of labetalol at 10^{-7} M and in the absence (□) and presence (■) of labetalol at 10^{-5} M. Bottom left: responses in the absence (▼) and presence (▽) of dilevalol at 10^{-7} M and in the absence (□) and presence (■) of dilevalol at 10^{-5} M. Responses are calculated as a percentage of the maximum and plotted against the log of the molar concentration of isoprenaline. Each value is the mean from six tissues; s.e.m. are within the symbols. Right: Schild regression for labetalol (top) and dilevalol (bottom).

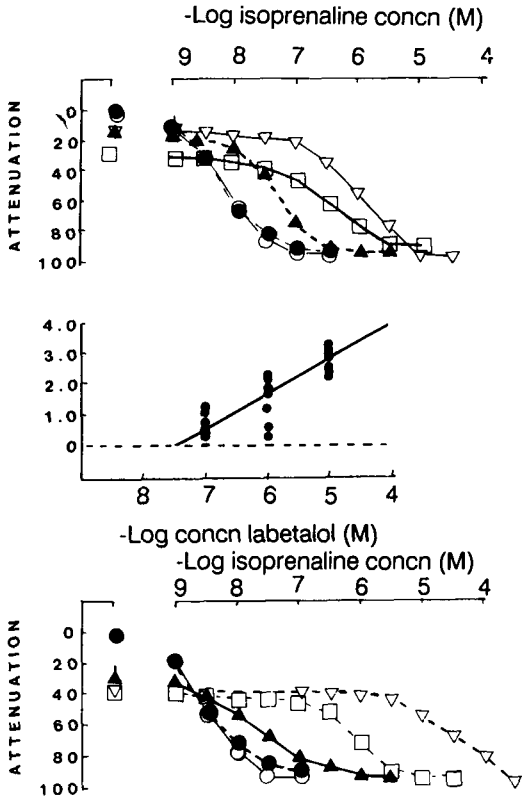

FIG. 4. Effects of labetalol and dilevalol alone and on the attenuation responses of the rat portal vein to isoprenaline. Top: responses in the absence (○) and presence of labetalol at 10^{-7} (▲) and 10^{-5} M (▽) and from other tissues, in the absence (●) and presence of labetalol at 10^{-6} M (□). Bottom: responses in the absence (○) and presence of dilevalol at 10^{-7} (▲) and 10^{-5} M (▽) and, from other tissues, in the absence (●) and presence of dilevalol at 10^{-6} M (□). Responses are calculated as a percentage attenuation and plotted against the log of the molar concentration of isoprenaline. Each value is the mean from 6–8 tissues; vertical lines show s.e.m. Middle: Schild regression for labetalol.

labetalol. In the first attempt at this, a cumulative challenge of the rat portal vein to labetalol was made by adding 5 and then 4·5 μL of a concentrated solution of the drug to the 5 mL organ bath on a 10 min cycle to produce final concentrations of 10^{-8}, 10^{-7}, 10^{-6} and then 10^{-5} M. Labetalol added in this manner did not attenuate the contractile activity of the rat portal vein (n=4, data not shown) and the effects of ICI 118,551 could not be determined. In order to produce attenuating responses to labetalol the protocol used in the previous study had to be repeated. Then, following a 45 min wash with 450 mL of Krebs solution containing labetalol at 10^{-6} M, the contractile activity of the rat portal vein was attenuated by 13%. ICI 118,551 at 10^{-6} M had no effect alone but reversed the labetalol attenuation.

Discussion

Labetalol and dilevalol have been classified as nonselective β-blockers on the basis of their pA_2 values at guinea-pig β-adrenoceptors. However, from the results of previous studies (Doggrell & Hughes 1985; Doggrell 1988a) and the present study it is concluded that labetalol and dilevalol are selective β_1-adrenoceptor antagonists in the rat. Thus it has been shown that labetalol has pA_2 values of 8·30 and 8·60 at the β_1-adrenoceptors of the rat right ventricle and left atria and of 7·45 and 7·59 at the β_2-adrenoceptors of the rat aorta and portal vein, respectively. Dilevalol is also β_1-selective in the rat having pA_2 values of 8·90 and 8·98 at the β_1-adrenoceptors of the ventricle and atria, respectively, and of 8·25 at the β_2-adrenoceptors of the aorta.

The pA_2 values for labetalol and dilevalol at rat β_2-adrenoceptors are consistent with those obtained by Brittain et al (1982) at the β_2-adrenoceptors of the guinea-pig trachea. There is, however, a major difference between the pA_2 values obtained in this study for labetalol and dilevalol at rat cardiac β_1-adrenoceptors and those of Brittain et al for the ability of labetalol and dilevalol to inhibit the isoprenaline responses of the guinea-pig atria. The values of Brittain et al (1982) on the guinea-pig atria were 4 times lower than those obtained in the present study on the rat heart. One of the possible explanations for the difference between studies is experimental technique. To test this possibility the experimental technique developed to use with the rat left atria (Doggrell 1988b) has also been used to determine the pA_2 values for labetalol and dilevalol in inhibiting the isoprenaline responses of the guinea-pig atria. The pA_2 values obtained on guinea-pig atria were in agreement with those of Brittain et al (1982). Thus the discrepancy between rat and guinea-pig heart studies is not related to experimental technique.

Another possible explanation for the different pA_2 values for labetalol and dilevalol in inhibiting isoprenaline responses in rat cardiac tissues and guinea-pig atria is that the population of cardiac β-adrenoceptors differs between the rat and guinea-pig. Previous studies have shown that the rat right ventricle (Doggrell 1989) and rat left atria (Doggrell 1990b) have functional β_1-adrenoceptors only. In contrast, the guinea-pig atria have a subpopulation of functional β_2-adrenoceptors (O'Donnell & Wanstall 1985). Thus the pA_2 values that were obtained for labetalol and dilevalol against isoprenaline responses on rat cardiac tissues, will be pA_2 values at β_1-adrenoceptors whereas those obtained on guinea-pig atria will be for a mixed population of β_1- and β_2-adrenoceptors and will be intermediate between the true values for β_1- and β_2-adrenoceptors. Accepting that the pA_2

Table 1. Effects of labetalol and dilevalol on the slopes of isoprenaline log concentration-response curves on rat portal vein.

	Slopes[a]
Control	65±5 (8)
Labetalol 10^{-7} M	63±10 (8)
10^{-5} M	66±10 (8)
Control	58±7 (8)
Labetalol 10^{-6} M	63±6 (7)
Control	58±5 (6)
Dilevalol 10^{-7} M	43±6 (6)*
10^{-5} M	34±6 (6)*
Control	64±4 (6)
Dilevalol 10^{-6} M	47±11 (6)*

[a] Mean±s.e.m. (n)=number of animals. *$P<0.05$ compared with the corresponding control.

values at β_1-adrenoceptors from the rat cardiac tissues are the correct values, it is concluded that labetalol and dilevalol are β_1-adrenoceptor selective antagonists.

With successive challenges, the cardiac stimulation responses of both the rat and guinea-pig atria decreased and there was greater variability in this effect on the rat than on the guinea-pig left atria. One unexpected finding of the present study was that low concentrations of labetalol and dilevalol decreased the cardiac stimulation responses of the guinea-pig left atria. This effect was probably not due to inhibition of the effects of noradrenaline released from noradrenergic nerves as it was observed in the presence of guanethidine. The inhibitory effect of labetalol and dilevalol on the responses to electrical cardiac stimulation may represent membrane stabilizing activity. Low concentrations of labetalol and dilevalol also caused similar small depressions of the cardiac stimulation responses of the rat left atria but this effect was not significant. Membrane stabilizing activity has not been reported with low, clinically relevant, concentrations of labetalol and dilevalol previously and the importance of this, if any, remains to be evaluated.

There is debate as to whether β_2-adrenoceptor agonism is the mechanism underlying the vasodilation with labetalol that is independent of α-adrenoceptor blockade. Baum et al (1981) demonstrated that the vasodilatory action of labetalol in dog denervated limbs was prevented by high doses of propranolol, a nonselective β-adrenoceptor antagonist, and suggested that labetalol caused vasodilation by acting as an agonist at β_2-adrenoceptors. However, Dage & Hsieh (1980) were unable to reverse the vasodilator action of labetalol on the isolated perfused gracilis muscle of the dog with propranolol and concluded that the vasodilatory action of labetalol was not related to β_2-adrenoceptor agonism. More recently it has been demonstrated that labetalol relaxes the KCl-contracted rat aorta and that this vasodilation is not antagonized by ICI 118,551 (Doggrell 1988a). In the present study prolonged, but not short, treatment with labetalol attenuated the contractile activity of the rat portal vein and this attenuation was reversed by the addition of ICI 118,551. Thus, in conclusion, labetalol causes vasodilation and in some tissues this is mediated by β_2-adrenoceptors and in other tissues (dog gracilis muscle, rat aorta) the mechanism underlying the vasodilatory action remains unknown.

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References

Baum, T., Watkins, R., Sybertz, E., Vemulapalli, S., Pula, K. K., Eynon, E., Neoson, S., Vliet, G. V., Glennon, J., Moran, R. M. (1981) Antihypertensive and hemodynamic actions of SCH 19927, the R_1R isomer of labetalol. J. Pharmacol. Exp. Ther. 218: 444–452

Brittain, R. T., Drew, G. M., Levy, G. (1982) The α- and β-adrenoceptor blocking potencies of labetalol and its individual stereoisomers in anaesthetized dogs and in isolated tisuses. Br. J. Pharmacol. 77: 105–114

Dage, R. C., Hsieh, C. H. (1980) Direct vasodilation by labetalol in anaesthetized dogs. Ibid. 70: 287–293

Doggrell, S. A. (1988a) 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. (1988b) Simultaneous assessment of membrane-stabilizing and β-adrenoceptor blocking activity of drugs with rat left atria. J. Pharmacol. Methods 19: 93–107

Doggrell, S. A. (1989) The effects of β-adrenoceptor antagonists on the force responses of the electrically driven rat right ventricle strip to isoprenaline. J. Auton. Pharmacol. 9: 265–277

Doggrell, S. A. (1990a) Assessment of the β_2 adrenoceptor and Ca^{2+} channel-blocking activity of drugs with the rat portal vein. J. Pharmacol. Methods 24: 145–156

Doggrell, S. A. (1990b) Effects of bromoacetylalprenololmenthane (BAAM), an irreversible β-adrenoceptor antagonist, on the rat isolated left atria and portal vein. J. Auton. Pharmacol. 10: 333–344

Doggrell, S. A. (1991) Pharmacodynamic profiles of labetalol, dilevalol and celiprolol on isolated cardiovascular preparation. N.Z. Med. J. 104: 47

Doggrell, S. A., Hughes, E. W. (1985) Comparison of the effects of labetalol and SCH 19927, the R_1R isomer of labetalol on the rat isolated right ventricle and aorta. J. Auton. Pharmacol. 5: 279–288

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