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The β_1- and β_2-adrenoceptor stimulatory effects of alprenolol, oxprenolol and pindolol: a study in the isolated right atrium and uterus of the rat

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1 The rat isolated right atrium (frequency response) and progesterone-treated rat uterus (relaxation) were used to examine the β_1- and β_2-adrenoceptor stimulatory effects of alprenolol, oxprenolol and pindolol. In addition, the β_1-adrenoceptor stimulatory effect of practolol was studied in the right atrium.

2 All the compounds studied caused a concentration-dependent increase in atrial frequency and relaxation of the uterus. The atrial response to pindolol was competitively inhibited by the β_1-selective blocker pafenolol (10^{-7} M), while the β_2-selective blocker ICI 118551 (10^{-8} M) was without effect. Pafenolol (10^{-7} M) was also shown to inhibit the atrial frequency effect of alprenolol and oxprenolol. In the uterus, ICI 118551 (3×10^{-9} M, 3×10^{-8} M, 3×10^{-7} M) blocked the pindolol effect with a pK_B of 9.28. In addition, ICI 118551 (10^{-8} M) competitively inhibited the relaxation of the uterus induced by alprenolol and oxprenolol.

3 For alprenolol (right atrium and uterus), oxprenolol (right atrium), and pindolol (right atrium), the concentrations needed for half-maximal response were significantly greater than those required for occupation of half the receptors. This dissociation was most pronounced for pindolol in the right atrium. In this tissue, 80–85% of the β_1-adrenoceptors had to be occupied by pindolol to initiate a tissue response corresponding to 50% of the maximal effect generated by the compound.

4 The intrinsic activities of alprenolol, oxprenolol and pindolol (expressed as % of the maximal tissue response to isoprenaline) were significantly higher in the uterus than in the right atrium. The intrinsic activity of the compounds varied between individual preparations and, particularly in the uterus, correlated with the sensitivity of the tissue to β-adrenoceptor stimulation by isoprenaline.

5 Calculation of efficacy, relative to isoprenaline, of the partial β-agonists revealed a β_2-adrenoceptor selectivity for alprenolol (2.0), oxprenolol (1.4) and pindolol (3.0).

6 It is concluded that weak partial agonists such as alprenolol, oxprenolol and pindolol possess complex β_1- and β_2-adrenoceptor stimulatory properties in relation to β-adrenoceptor occupancy and tissue sensitivity to β-adrenoceptor stimulation.

Introduction

Several β-adrenoceptor blockers possess intrinsic activity, i.e. they are partial agonists. Earlier studies suggested that their action may be complex. Thus, Kaumann & Blinks (1980) reported a dissociation between β-adrenoceptor occupation and β-adrenoceptor activation for a number of partial β-agonists, the concentrations required for activation being greater than those required for occupation. A positive correlation was found between the maximal tissue response obtained with a partial β-agonist and the sensitivity of the tissue to β-adrenoceptor stimulation by isoprenaline (Kenakin & Beek, 1980; 1984; Mattsson *et al.*, 1983). This suggests that tissue-related factors, such as receptor density and the efficiency of receptor coupling, strongly influence the tissue response generated by a partial agonist (Kenakin, 1984). Furthermore, it has been proposed that some weak partial β-agonists, e.g. pindolol are more active on β_2- than on β_1-adrenoceptors (Clark, 1984).

The purpose of this study was to investigate the β_1- and β_2-adrenoceptor stimulatory effects of the partial β-agonists alprenolol, oxprenolol and pindolol. In

addition, the β_1-adrenoceptor stimulatory effect of practolol was examined. Special attention was paid to comparing the stimulatory and blocking concentrations of the compounds on β_1- and β_2-adrenoceptors, calculating relative efficacy of the compounds, and relating the stimulatory effect of the partial agonist to the tissue sensitivity to isoprenaline.

Methods

Uteri were obtained from Sprague-Dawley rats (200–300 g) treated with progesterone (10 mg kg^{-1} day^{-1} i.m.) for 6 days. Uteri taken from rats treated with progesterone are known to contain a 100% β_2-adrenoceptor population (Nahorski, 1981). The right atrium was isolated from male Sprague-Dawley rats (230–350 g). All rats were treated with reserpine (2 mg kg^{-1} i.p.) 16–20 h before the experiment. This was done in order to avoid release of endogenous noradrenaline caused by phenoxybenzamine and, in the uterus experiments, by high potassium. The animals were killed by a blow to the neck.

Isolated uterus

The uterine horn was cut longitudinally to obtain one or, in some experiments, two strips. The strip was mounted in an organ bath (volume 50 ml) with one end fixed and the other end sutured to a force displacement transducer (Grass model FT03). The experiments were carried out at 37°C in an aerated (97% O_2, 3% CO_2) buffer (pH 7.4) composition (mM): NaCl 122, KCl 4.7, $CaCl_2$ 2.5, $MgCl_2$ 1.2, $NaHCO_3$ 15.5, KH_2PO_4 1.2, disodium calcium EDTA 0.5, and glucose 11.5. The preparation was stretched to a baseline tension of 0.5 g. The approximate length of the strips was 15 mm and the width ~2 mm. To block neuronal and extraneuronal uptake and α-adrenoceptors, the preparation was incubated with phenoxybenzamine (10^{-6} M) for 30 min (Furchgott, 1966). After repeated washing the uterus was contracted by a high potassium buffer. The potassium concentration was increased to 60 mM by substituting KCl for equimolar amounts of NaCl.

Isolated right atrium

The hearts were rapidly removed and washed in buffer (for composition, see above), equilibrated with 97% O_2 and 3% CO_2. A strip including the sinus node was prepared from the right atrium and mounted for recording of (isometric) contraction. The atrial strip was pre-stretched to a baseline tension of 0.4 g (length ~15 mm and width 1–2 mm). The frequency of contraction was measured on a separate channel by a cardiotachometer (Grass model 7P4F). The experiments were performed at 37°C. The preparation was incubated with phenoxybenzamine as described above.

Concentration-response curves and calculations

In order to establish the sensitivity to β-adrenoceptor stimulation, a concentration-response curve to isoprenaline was constructed for each tissue. Starting

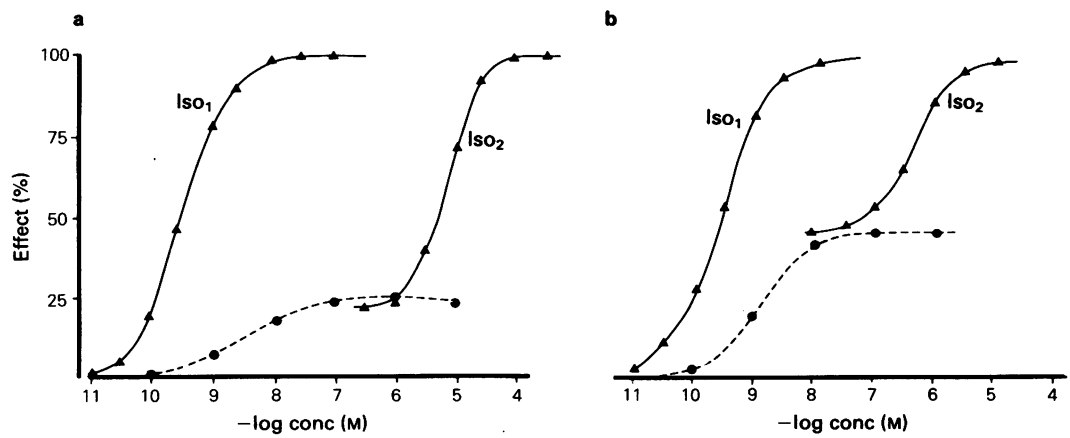

Figure 1 Concentration-response curves of (a) right atrial strip (frequency response) and (b) uterus strip (relaxation) to isoprenaline (▲———▲) and pindolol (●– – –●). After recording of the first isoprenaline concentration-response curve Iso_1 and subsequent washing, pindolol was added in increments of 1 log unit until the maximal effect was established. A second isoprenaline concentration-response curve Iso_2 was then constructed with the final concentration of pindolol still present in the organ bath.

with 10^{-11} M, isoprenaline was added in increments of 0.5 log units. For each concentration, the tissue response was followed until it was steady. After recording the isoprenaline concentration-response curve the preparation was washed and allowed to stabilize for 90 min before the next concentration-response curve was started. This involved administration of one of the following partial agonists: alprenolol, oxprenolol, practolol or pindolol. For these compounds, the concentration-response curve was started at 10^{-11} M and continued in increments of 1 log unit. For each concentration of the partial agonist, the tissue response was measured until it had reached equilibrium (within 10–15 min). After the maximal effect of the partial agonist had been established, a second isoprenaline concentration-response curve was constructed, with the final concentration of the partial agonist still present in the bath (10^{-6} or 10^{-5} M, Figure 1).

It has been suggested that very long incubation periods are required for a partial agonist like pindolol to obtain a steady-state tissue response (Kaumann & Blinks, 1980; Walter *et al.*, 1984). This was examined in strips of rat uterus and right atrium incubated in various pindolol concentrations for 30–45 min. In these experiments, the maximal response to each concentration was always obtained within the first 10–15 min. Differences in temperature (37°C in this study) and the thickness of the preparations used may explain the discrepancy between our findings and the earlier observations by Kaumann and coworkers.

The concentration-response curves for the agonists were determined by applying the experimental points to a hyperbolic function by the method of least squares fit, using a procedure modified from that described by Parker & Waud (1971). For each concentration-response curve, the negative log of the agonist concentration which elicited 50% of the maximal effect was determined ($-\log EC_{50} = pD_2$). The intrinsic activity of the partial agonist was expressed as percentage of the maximal response produced in the tissue by isoprenaline. The β-adrenoceptor antagonistic potency of the partial agonist was determined from the shift in the concentration-response curve to isoprenaline (Figure 1). The negative logarithm of the equilibrium dissociation constant (pK_B) for the partial agonist was calculated according to Kaumann & Blinks (1980).

In some experiments, the tissue was incubated (30 min) with the β_1-selective antagonist pafenolol (Mattsson *et al.*, 1982; Ek & Nahorski, 1986) or the β_2-selective antagonist ICI 118551 (erythro-DL-1 (7-methylindan-7-yloxy)-3-isopropylaminobutan-2-ol) Bilski *et al.*, 1983) before recording the concentration-response curve for the partial agonist. For the uterus experiments, two strips were taken from each rat. The antagonist was added to one of the strips and the concentration-response curve for the action of the partial agonist on this strip was compared to that of the parallel, control, strip. The pA_2 for ICI 118551 was calculated from the shifts in the concentration-response curves for pindolol (Arunlakshana & Schild, 1959). Since the slope was not significantly different from -1 (Figure 2), the best-fit line of slope $= -1$ was determined to obtain the $-\log$ equilibrium dissociation constant (pK_B). In the experiments with only one concentration of pafenolol or ICI 118551, the pK_B for the antagonist (B) was calculated from the equation: $pK_B = \log$ (dose-ratio -1) $-\log$ conc. B.

Relative efficacy

The efficacy, relative to isoprenaline, was calculated for alprenolol, oxprenolol, pindolol and practolol. Using the concepts and terms introduced by Stephenson (1956), the tissue response (R) was regarded as a function of the stimulus (S) given to the tissue by the agonist, $R = f(S)$. The stimulus (S) is the product of the fractional receptor occupancy (y) of an agonist and its efficacy (e), $S = e \times y$. The assumption was then made that, for a partial agonist (PA) and isoprenaline (Iso), equal responses in the same tissue corresponded to equal stimuli, $e_{PA} \times y_{PA} = e_{Iso} \times y_{Iso}$. Thus, the efficacy of the partial β-agonist relative to isoprenaline (e_{PA}/e_{ISO}) is obtained from the relative receptor

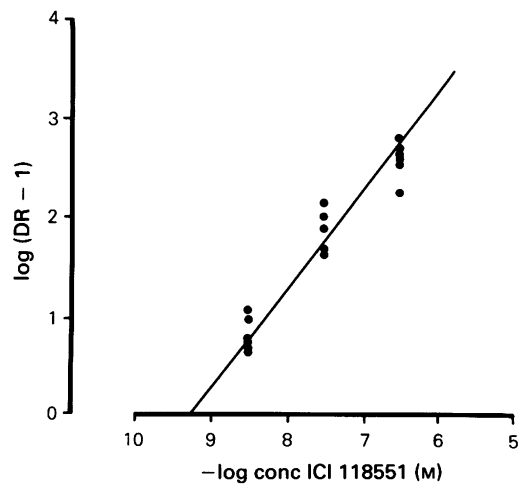

Figure 2 Schild plot for ICI 118551 on rat isolated uterus using pindolol as agonist. Ordinate scale: logarithm of (dose-ratios -1); abscissa scale: negative logarithm of molar concentrations of ICI 118551. The slope of the Schild plot was 0.91 ± 0.12 (95% confidence interval, $n = 17$). Fitting the data to a regression line with a slope $= -1$ (shown in the figure) gives an equilibrium dissociation constant (pK_B) of 9.28 ± 0.22 (mean $\pm$ s.d.)

occupancies of the two compounds (y_{Iso}/y_{PA}) required to produce an equal tissue response (Furchgott, 1966; Furchgott & Bursztyn, 1967).

In the present study, the tissue responses generated by the partial β-agonists were, in many cases, rather small. Thus, the efficacies of the compounds, relative to isoprenaline, were obtained from ratios of receptor occupancies (y_{Iso}/y_{PA}) calculated at only one set of equi-active concentrations, corresponding to 50% of the maximal response of the partial agonist. The receptor occupancy (y) was calculated from the equation; $y = A/(A + K_A)$ where A is the concentration of agonist which elicits the response and K_A is the equilibrium dissociation constant. The dissociation constant for isoprenaline on β_1- and β_2-adrenoceptors (3×10^{-7} M) was obtained from previous β-adrenoceptor binding studies (Kaumann, 1978; Hedberg & Mattsson, 1981; Brodde *et al.*, 1983). For the partial β-agonist, the equilibrium dissociation constant was obtained from the shift in the concentration-response curve for isoprenaline (see above). The mean value for the dissociation constant (Table 3) was used to calculate the receptor occupancy (y). The relative efficacy was calculated as $-\log (e_{PA}/e_{Iso})$ since a logarithmic transformation stabilizes the variance and normalizes the distribution of this variable.

Statistics

Results are expressed as mean values ± s.d. Linear regression analysis was done by the method of least squares. Statistical analyses were performed with the non-parametric Mann-Whitney U-test.

Results

Right atrium

Pindolol (Figure 1), alprenolol, oxprenolol and practolol caused a concentration-dependent increase in the frequency of the rat isolated right atrium. Pafenolol (10^{-7} M) inhibited the pindolol effect while ICI 118551 (10^{-8} M) was without effect (Table 1). A pK_B of 7.8 for pafenolol was calculated from the shift in the pindolol concentration-response curve. This is in agreement with the β_1-adrenoceptor affinity of pafenolol found previously (Ek & Nahorski, 1986). β_1-Adrenoceptor blockade with pafenolol (10^{-7} M) also shifted the concentration-response curves to the right for oxprenolol: the pD_2 (oxprenolol) decreased from 8.54 ± 0.52 ($n = 20$, controls) to 7.66 ± 0.24 ($n = 10$, with pafenolol), $P < 0.01$. A similar effect of pafenolol (10^{-7} M) was also found in experiments with alprenolol, in which the pD_2 (alprenolol) decreased from 8.42 ± 0.33 ($n = 17$, controls) to 7.39 ± 0.51 ($n = 4$, with pafenolol), $P < 0.05$.

Table 1 The effect of the β_1-selective antagonist pafenolol and the β_2-selective antagonist ICI 118551 on pindolol pD_2 and intrinsic activitity in the rat isolated right atrium

		Pindolol	
	n	pD_2	*Intrinsic activity* (%)
Control	27	8.47 ± 0.04	21 ± 2
+ Pafenolol 10^{-7} M	7	7.61 ± 0.08**	17 ± 1
+ ICI 118551 10^{-8} M	6	8.48 ± 0.15	19 ± 4

pD_2: $-\log EC_{50}$ for stimulation. Intrinsic activity is expressed as % of the maximal isoprenalin effect. Results presented are mean values ± s.d. n = number of experiments. **$P < 0.01$ versus control.

Table 2 The effects of the β_2-selective antagonist ICI 118551 on pD_2 and intrinsic activity for alprenolol and oxprenolol in the rat isolated uterus

		Alprenolol		*Oxprenolol*	
	n	pD_2	*Intrinsic activity* (%)	pD_2	*Intrinsic activity* (%)
Control	6	8.80 ± 0.09	44 ± 4	8.28 ± 0.18	28 ± 5
● ICI 118551 10^{-8} M	6	7.52 ± 0.15**	53 ± 5	7.44 ± 0.08**	41 ± 4

Two uterus strips were taken from each rat. The antagonist was added to one of the strips while the other was used as control (see Methods). pD_2: $-\log EC_{50}$ for stimulation.
Intrinsic activity is expressed as % of the maximal isoprenaline effect.
Results are presented as mean values ± s.d. n = number of experiments. **$P < 0.01$ versus control.

Table 3 pD_2 and pK_B values for partial β-agonists in the rat isolated right atrium and uterus

	Alprenolol		*Oxprenolol*		*Pindolol*		*Practolol*	
	pD_2	pK_B	pD_2	pK_B	pD_2	pK_B	pD_2	pK_B
Right atrium	8.48 ± 0.64*	8.73 ± 0.22	8.42 ± 0.52**	8.68 ± 0.18	8.47 ± 0.45***	9.21 ± 0.21	7.29 ± 0.17	7.04 ± 0.06
Uterus	8.77 ± 0.26***	8.98 ± 0.20	8.54 ± 0.38	8.77 ± 0.27	8.87 ± 0.25	8.93 ± 0.21	—	—

pD_2: − log EC_{50} for stimulation. pK_B: − log equilibrium dissociation constant, obtained from the shift in the isoprenaline concentration-response curve (see Methods). Results are presented as mean values ± s.d. of 17–27 experiments. *$P<0.05$, **$P<0.01$, ***$P<0.001$ versus pK_B.

Uterus

Pindolol (Figure 1), alprenolol and oxprenolol caused a concentration-dependent relaxation of the rat isolated uterus. The effect of pindolol was competitively inhibited by ICI 118551 (Figure 2). The pK_B (9.28) obtained from the Schild plot is in agreement with the previously reported β_2-adrenoceptor affinity of ICI 118551 (Brodde *et al.*, 1983). The effects of oxprenolol and alprenolol on the uterus were also found to be inhibited by the β_2-selective blocker ICI 118551 (Table 2).

Correlation between β-adrenoceptor activation and β-adrenoceptor occupation of the partial agonists

The concentrations needed for half-maximal response (pD_2) were significantly greater than those required for the occupation of half the receptors (pK_B) for alprenolol (right atrium and uterus), oxprenolol (right atrium) and pindolol (right atrium) (Table 3). For pindolol, this difference between pD_2 and pK_B was significantly greater ($P<0.001$) in the right atrium compared to that in the uterus.

In the right atrium, the fraction of β-adrenoceptors occupied by the partial agonists at the pD_2 concentrations were: alprenolol 62 ± 20%, oxprenolol 63 ± 20%, pindolol 81 ± 16% and practolol 44 ± 26% (mean values ± s.d.). The corresponding values in the uterus were: alprenolol 61 ± 12%, oxprenolol 61 ± 19% and pindolol 53 ± 13% (mean values ± s.d.). For pindolol, the fractional receptor occupancy was significantly higher ($P<0.001$) in the right atrium than in the uterus at the pD_2 concentration. In the right atrium, the β-adrenoceptor occupancy at the pindolol concentration causing 20% of its maximal effect was 45 ± 24% (mean value ± s.d.). In the uterus, the corresponding β-adrenoceptor occupancy of pindolol was 28 ± 13%.

Correlation between the intrinsic activity of the partial agonist and the tissue sensitivity to isoprenaline

The intrinsic activity was significantly higher in the uterus than in the right atrium for all three

Table 4 Correlation between the tissue sensitivity to isoprenaline stimulation and the intrinsic activity of a partial β-agonist

	Right atrium				*Uterus*		
	Alprenolol	*Oxprenolol*	*Pindolol*	*Practolol*	*Alprenolol*	*Oxprenolol*	*Pindolol*
Intrinsic activity (%)	15 ± 8**	16 ± 7*	21 ± 9***	22 ± 10	34 ± 14	25 ± 14	44 ± 19
Isoprenaline pD_2	9.42 ± 0.15	9.39 ± 0.19	9.47 ± 0.24	9.52 ± 0.30	9.51 ± 0.25	9.41 ± 0.36	9.49 ± 0.38
Correlation (pD_2 Iso-intrinsic activity)	$r=0.58$ ($P<0.01$)	$r=0.42$ ($P<0.05$)	$r=0.33$ (n.s.)	$r=0.64$ ($P<0.01$)	$r=0.81$ ($P<0.001$)	$r=0.86$ ($P<0.001$)	$r=0.89$ ($P<0.001$)

Iso = Isoprenaline. pD_2 = − log EC_{50} for stimulation. n.s. = not statistically significant. Intrinsic activity is expressed as % of the maximal isoprenaline effect. Results are presented as mean values ± s.d. of 17–27 experiments. *$P<0.05$, **$P<0.01$, ***$P<0.001$ versus uterus. Linear regression analysis was performed by the method of least squares.

compounds studied (Table 4). In the uterus, the intrinsic activity of pindolol varied between individual preparations from 0 to 79% (Figure 3). A similar variation was also found for oxprenolol (0 to 48%) and alprenolol (14 to 61%, Figure 4). A high correlation between the intrinsic activity of the partial agonist and the sensitivity of the tissue to β-adrenoceptor stimulation by isoprenaline was observed in the uterus (Figures 3 and 4, Table 4).

In the right atrium, a similar variation in the intrinsic activity was observed for pindolol (6 to 40%, Figure 3), alprenolol (3 to 33%, Figure 4), oxprenolol (6 to 26%) and practolol (from 4 to 36%). However, the correlation between the intrinsic activity of the compound and the sensitivity to isoprenaline stimulation was weaker in the right atrium than in the uterus (Table 4).

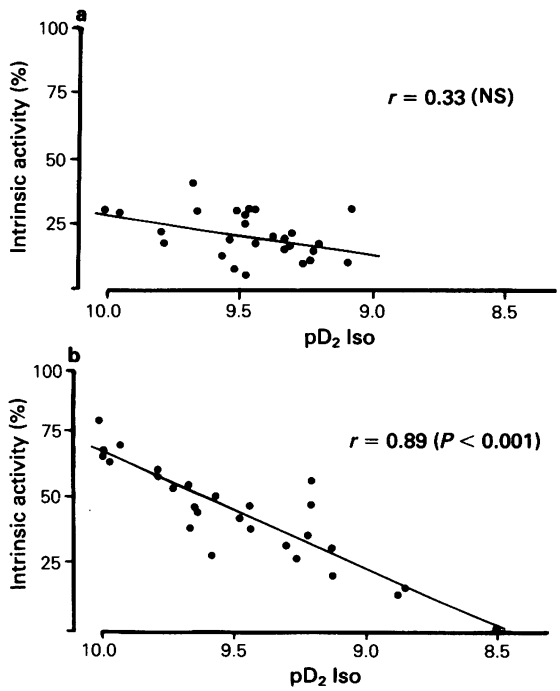

Figure 3 Correlation between the intrinsic activity of pindolol and the tissue sensitivity to β-adrenoceptor stimulation by isoprenaline in the right atrium (a) and uterus strip (b). Intrinsic activity is expressed as % of the maximal tissue response generated by isoprenaline. The isoprenaline sensitivity is expressed as pD_2 ($-\log EC_{50}$), the concentration of isoprenaline causing 50% of its maximal tissue response. Linear regression was performed by the method of least squares. Iso = Isoprenaline. NS = not statistically significant.

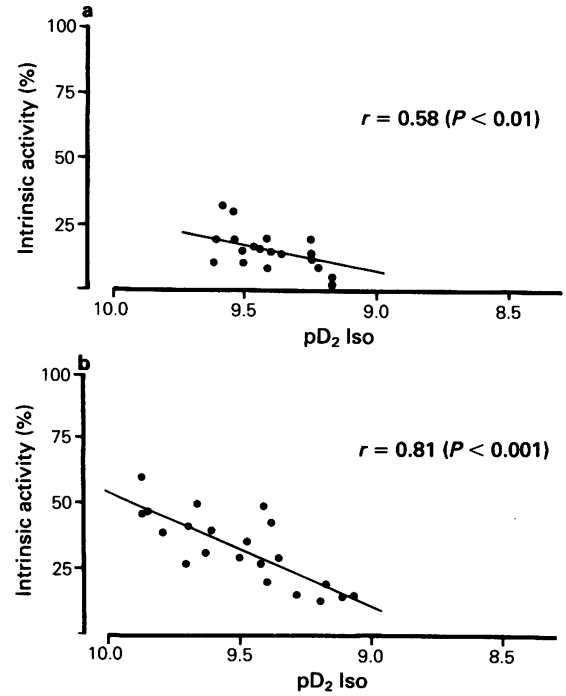

Figure 4 Correlation betweeen the intrinsic activity of alprenolol and the tissue sensitivity to β-adrenoceptor stimulation by isoprenaline (Iso) in the right atrium (a) and uterus strip (b). For other details see legend to Figure 3.

Relative efficacy of the partial β-agonists

The estimated efficacies, relative to isoprenaline, of the partial β-agonists are presented in Table 5. A significant β_2-selectivity regarding the efficacy was observed for all the three compounds examined. The β_2-selectivity was: 3.0 (pindolol), 2.0 (alprenolol) and 1.4 (oxprenolol).

Discussion

In order to examine β_1- and β_2-adrenoceptor stimulatory effects of partial agonists the tissue response studied has to be mediated by a homogeneous receptor population. The frequency increase of the rat right atrium is mediated by β_1-adrenoceptor stimula-

Table 5 Efficacies relative to isoprenaline for partial β-agonists on β_1-adrenoceptors (right atrium) and β_2-adrenoceptors (uterus)

	β_1	$-\log(e_{PA}/e_{Iso})$ β_2	*β_2-selectivity ratio* (β_2/β_1)
Alprenolol	3.82 ± 0.32	3.53 ± 0.19**	2.0
Oxprenolol	3.77 ± 0.31	3.63 ± 0.18*	1.4
Pindolol	3.79 ± 0.31	± 3.32 ± 0.18***	3.0
Practolol	3.47 ± 0.53	—	—

e = efficacy, Iso = isoprenaline, PA = partial agonist. The relative efficacy was calculated as $-\log(e_{PA}/e_{Iso})$, see Methods. Results are presented as mean values ± s.d. of 17–27 experiments.
* $P<0.05$, ** $P<0.01$, *** $P<0.001$ versus β_1-adrenoceptors (right atrium).

tion (Mattson *et al.*, 1982; O'Donnell & Wanstall, 1985) whereas the relaxation of the rat uterus is due to β_2-adrenoceptor stimulation (Nahorski, 1981; Kenakin, 1982; Mattson *et al.*, 1982). These earlier observations in the rat were confirmed in this study, using the β_1-selective blocker pafenolol (Mattsson *et al.*, 1982; Ek & Nahorski, 1986) and the β_2-selective blocker ICI 118551 (Bilski *et al.*, 1983).

A marked dissociation between β-adrenoceptor activation and β-adrenoceptor occupation was observed for pindolol in the right atrium in the present study. In contrast, there was no dissociation between activation and occupation for pindolol in the uterus. These observations thus suggest that, for pindolol, the dissociation between β-adrenoceptor activation and occupation only applies to the action of the compound on the β_1-adrenoceptors. In the right atrium, 45 and 85% of the β-adrenoceptors were occupied by pindolol at the concentrations producing 20 and 50% of its maximal stimulatory effect, respectively. Thus a receptor occupancy of pindolol below 30–40% seems insufficient to initiate a tissue response such as atrial frequency increase.

Kaumann and coworkers reported a dissociation of β-adrenoceptor occupation and β-adrenoceptor activation for both the racemic (Kaumann & Blinks, 1980) and the active S-form of pindolol (Walter *et al.*, 1984). For the S-form of pindolol, this dissociation was found both for relaxation of the guinea-pig isolated trachea and for the frequency stimulation of the guinea-pig isolated right atrium. In these studies, the concentration-response curves for both S-pindolol and racemic pindolol (cat atrial frequency response) were biphasic and spread over at least 4 log units (Walter *et al.*, 1984; Kaumann & Blinks, 1980). This is in contrast to the concentration-response curves for pindolol obtained in the rat right atrium and uterus (Figure 1). The reason for the discrepancies between the observations by Kaumann and coworkers and the present study is not clear but one important difference may be that the β-mediated frequency increase in cat (Carlsson *et al.*, 1972) and guinea-pig atria (Johansson & Persson, 1983) and relaxation of guinea-pig trachea (O'Donnell & Wanstall, 1979) are tissue responses which are all mediated by both β_1- and β_2-adrenoceptors. In the uterus of the progesterone-treated rat, and in the rat right atrium, however, pure β_1- and β_2-adrenoceptor-mediated responses are obtained.

Both *in vivo* and *in vitro* pindolol has displayed β_2-adrenoceptor agonistic selectivity (Clark, 1984), although there is some controversy (Mian & Malta, 1985). In this study, the calculation of relative efficacy of the partial β-agonists demonstrates that pindolol, as well as alprenolol and oxprenolol, do possess β_2-selectivity as partial agonists. A β_2-adrenoceptor selectivity in efficacy is also indicated from the greater intrinsic activity of these compounds obtained in the uterus when compared to that observed in the right atrium. In fact, there was a good correlation ($r = 0.98$) between the intrinsic activity of alprenolol, oxprenolol and pindolol (mean values, Table 4) and the estimated relative efficacy of these compounds on β_1- and β_2-adrenoceptors.

Rat right atrium and uterus were found to be equally sensitive to β-adrenoceptor stimulation by isoprenaline. In both organs, however, the sensitivity to isoprenaline varied between individual tissues, probably reflecting an individual variation in the efficiency of receptor coupling to the response (Mattsson *et al.*, 1983; Kenakin, 1984). In the uterus there was a high correlation between the intrinsic activity of the partial agonist and the sensitivity of the tissue to isoprenaline stimulation. This observation indicates that the level of intrinsic activity of a weak partial agonist depends on the efficiency of the receptor coupling to the final tissue response studied (Mattsson *et al.*, 1983; Kenakin & Beek, 1984). The correlation between the intrinsic activity of the partial β-agonist and the tissue sensitivity to isoprenaline stimulation in the right atrium was weaker than in the uterus. It is possible that this relation weakens at a low efficacy as is the case for alprenolol, oxprenolol and pindolol on the β_1-adrenoceptors in the rat right atrium.

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