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Effects of *N*-aralkyl substitution of β-agonists on α- and β-adrenoceptor subtypes: pharmacological studies and binding assays

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The pharmacological and binding properties of four β-adrenomimetic drugs with *N*-alkyl substitutions (isoprenaline, terbutaline, salbutamol and soterenol) were compared with those of four corresponding drugs with *N*-aralkyl substitutions (protokylol, ME 506, salmefamol and zinterol). BD-40 A, a very powerful β_2-agonist with a related chemical structure, was also included in this study. The β_1- and β_2-activities of these drugs were determined on guinea-pig atria and trachea, their α-adrenolytic activity was measured on rat aorta and their affinities (K_i) for α_1- and α_2-adrenoceptors on rat cortical membranes were assessed using [^{3}H]prazosin and [^{3}H]yohimbine. In this group of β-agonists, substitution of the *N*-alkyl by an *N*-aralkyl group had a variable effect on the β_2-selectivity whereas α-adrenolytic properties were always enhanced. An increase of the affinities (K_i) for both α_1- and α_2-adrenoceptors was found but the effect was much more pronounced for α_1-adrenoceptors. These results indicated that the α-adrenolytic activity observed with the *N*-aralkyl β-agonists was selective for α_1-adrenoceptors.

It has been shown that substitution of the nitrogen of catecholamines by an aralkyl group led to β-adrenoceptor agonists with additional α-adrenolytic properties, whereas the corresponding *N*-alkyl derivatives had weak α-adrenomimetic activities (Ariens 1967). More recently, it was found that *N*-aralkyl or bulky alkyl substitution conferred α-adrenolytic properties on β-antagonists (Brittain & Levy 1976; Drummer et al 1980). Aggerbeck et al (1979) have confirmed these observations using binding assays on liver membrane preparations. They showed that β-agonists and antagonists with an *N*-aralkyl group have a much higher affinity for α-receptors labelled with [^{3}H]dihydroergocryptine than the corresponding *N*-alkyl derivatives. For example, labetalol, an α- and β-blocking agent with an *N*-isopropyl benzyl group, has an inhibition constant (K_i) 2500 times lower than its *N*-t-butyl analogue AH 3474 (0·17 and 500 μM respectively). Since α-adrenoceptors have been subdivided into α_1- and α_2-receptor subtypes (for review see Berthelsen & Pettinger 1977) the *N*-aralkyl substitution may increase the α-adrenolytic activity by a differential action on α_1- and α_2-receptors. In fact, labetalol has been shown to have a selectivity for α_1-receptors (Blakeley & Summers 1977; Drew 1978).

The present study was focused on β_2-adrenomimetic drugs and its aim was to determine if the antagonistic effect caused by the *N*-aralkyl group is selective for the α_1- or α_2-adrenoceptors. Accordingly, we studied the effect of the replacement of an *N*-alkyl by an *N*-aralkyl group on both β-selectivity and on the affinity for α_1- and α_2-receptors. For this purpose, we selected pairs of drugs with different substitutions on the amino group but having the same phenylethanolamine moieties (Table 1). We also added to this series another *N*-aralkyl derivative: BD-40 A which is a potent β_2-adrenomimetic agent (Ida 1976). The agonistic β_1- and β_2-activities and the α-adrenolytic effects were determined in vitro on guinea-pig atria and trachea, and on rat aorta respectively. In order to assess the effect of *N*-aralkyl substitution on the affinity for α_1- and α_2-adrenoceptors, we performed direct competition binding experiments with two selective antagonists. Since there is as yet no published method to study the binding of α_2-adrenergic ligands in vessels, binding studies were carried out on brain membranes which appear to reflect the drug specificity observed in isolated organs (U'Prichard & Snyder 1979; Kapur et al 1979). α_1-Adrenoceptors were labelled by [^{3}H]prazosin as previously described by several authors (Greengrass & Bremner 1979; Hornung et al 1979; Miach et al 1980). For the α_2-adrenoceptors we chose the preferential α_2-antagonist [^{3}H]yohimbine. This ligand has already been reported to label α_2-receptors in platelets (Motulsky et al 1980; Daiguji et al 1981) and in liver (Hoffman et al 1981)

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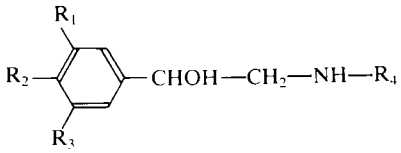
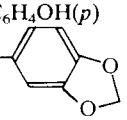
Table 1. Chemical structures of the series of β-agonists studied.



	R_1	R_2	R_3	R_4
Isoprenaline	H	OH	OH	$-CH(CH_3)_2$
ME 454	H	OH	OH	$-C(CH_3)_2-CH_2-C_6H_4OH(p)$
Protokylol	H	OH	OH	
Terbutaline	OH	H	OH	$-C(CH_3)_3$
ME 506	OH	H	OH	$-C(CH_3)_2-CH_2-C_6H_4OH(p)$
Salbutamol	H	OH	CH_2OH	$-C(CH_3)_3$
Salmefamol	H	OH	CH_2OH	$-CH(CH_3)-CH_2-C_6H_4OCH_3(p)$
Soterenol	H	OH	$NHSO_2CH_3$	$-CH(CH_3)_2$
Zinterol	H	OH	$NHSO_2CH_3$	$-C(CH_3)_2-CH_2-C_6H_5$
BD-40 A	H	OH	NHCHO	$-CH(CH_3)-CH_2-C_6H_4OCH_3(p)$

and we have demonstrated that it also possesses the binding features required for an α_2-ligand in rat brain crude membranes (submitted).

METHODS

β-*Adrenomimetic activity*

Guinea-pigs were pretreated with reserpine (5 mg kg^{-1} i.p.) 24 h before death. Tracheal chain and spontaneously beating atrial preparations were prepared as described by Levy & Wilkenfeld (1970) and by Horii et al (1974) respectively. They were set up in Krebs Henseleit solution aerated with 95% O_2 and 5% CO_2 at temperatures and resting tensions of 37 °C and 1 g for trachea, and 32 °C and 0·5 g for atria. Tracheal chains were allowed to gain tone spontaneously and relaxation responses to β-adrenoceptor agonist drugs were recorded on a polygraph by means of a force displacement transducer. Atrial rate was also recorded on a Gilson polygraph. We used the conditions of Furchgott (1972): α-adrenoceptors, extraneuronal uptake and neuronal uptake were blocked by phenoxybenzamine (50 μmol $litre^{-1}$ for 30 min followed by several washes). Dose-response curves to both isoprenaline and the test compound were obtained on each preparation except that on atrial preparations where two control curves were plotted; the results of the first one were discarded since the slope was generally lower than that of the next curve. pD_2 values were determined by the method of Ariens & van Rossum (1957) ($pD_2 = -\log ED50$). The β_2-selectivity was defined by the antilog of the difference between the tracheal and atrial pD_2.

α-*Adrenolytic activity*

Helically cut strips of Wistar rat aorta 1·5 to 2 cm long and 3 to 4 mm wide, were prepared as described by Liebau et al (1966). Preparations were suspended in a 20 ml bath containing Krebs-Henseleit solution kept at 37 °C and aerated with a mixture of 95% O_2 and 5% CO_2. They were set up at a resting tension of 2 g and allowed to stabilize for approximately 2 h before the experiment. β-Receptors were blocked with sotalol at 10^{-5} M for 20 min. Two cumulative dose-response curves, with (±)-noradrenaline as agonist, were made before and after addition of the antagonist. The pre-incubation time with the antagonist was 30 min; each preparation was tested with only one concentration of antagonist ranging from 10^{-7} to 10^{-5} M. The α-adrenergic blocking activity was expressed in terms of pA_2 values for competitive antagonists according to Arunlakshana & Schild (1959). When the antagonism was not competitive, it was expressed as pD'_2 (colog of the molar concentration of antagonist which inhibits 50% of the maximal effect of the agonist) according to Ariens & van Rossum (1957).

Binding assays

Binding assays were performed on Wistar rat cerebral cortex preparations. Shortly after decapitation of rats, the cortex was dissected and homogenized at 0 °C in 30 volumes of 50 mM Tris HCl pH 7·0, using a Polytron setting no. 6 for 30 s. The homogenate was then centrifuged at 50 000 *g* for 15 min. The supernatant was discarded and the pellet resuspended in 30 volumes of the same buffer and then centrifuged

as before. Pellets were then frozen and stored at −30 °C. For the binding assays, pellets were thawed and resuspended in 100 volumes of Tris buffer. The assays were carried out in glass test tubes containing 50 µl of the ligand, about 100 000 counts min^{-1} of [^{3}H]yohimbine (New England Nuclear, 81·4 Ci $mmol^{-1}$) or about 4000 counts min^{-1} of [^{3}H]prazosin (Amersham 28 Ci $mmol^{-1}$), 20 µl of various concentrations of the displacer (dissolved in Tris buffer, plus 0·1% ascorbic acid), and 930 µl of Tris buffer. Incubation was initiated by adding 1 ml of the tissue suspension prepared as above (0·5–0·6 mg of protein for [^{3}H]yohimbine and about 0·25 mg for [^{3}H]prazosin). The contents of the tubes were rapidly filtered under vacuum through GF/B Whatman filters and washed four times with 5 ml of ice cold Tris buffer. The radioactivity on the filters was then counted after addition of 9 ml of Beckmann GP scintillation cocktail (counting efficiency 34–36%). Specific binding was defined as the difference in binding with or without 100 µM (−)-noradrenaline or 10 µM phentolamine. In typical experiments using 1 nM of [^{3}H]yohimbine total binding was about 1500 counts min^{-1} of which non-specific binding was 600 to 650 counts min^{-1}. For [^{3}H]prazosin at 0·09 M the total binding was about 900 counts min^{-1} of which non-specific binding was 150 counts min^{-1}.

IC50 values were derived by log-probit analysis. Binding of [^{3}H]yohimbine and [^{3}H]prazosin were independently determined by Scatchard plots to have K_D values of 11·7 ± 4·4 and 0·05 ± 0·01 respectively. These values were used to convert IC50 values to K_i's according to the equation of Cheng & Prusoff (1973): $K_i = IC50/(1 + L/K_D)$. Each value is the mean of at least 3 independent determinations run in triplicate.

Drugs

Drugs were obtained from the following sources: BD40A, 3-formylamino-4-hydroxy-α-(*N*-1-methyl-2-*p*-methoxyphenethyl-aminomethyl)-benzylalcohol fumarate dihydrate (Yamanouchi Pharmaceutical Co.), isoprenaline hydrochloride (Sigma), ME 454, 3,4-dihydroxy-α-(*N*-1-methyl-2-*p*-methoxyphenethyl-aminomethyl)-benzyl alcohol base (gift from S. O'Donnell), ME 506, 3,5-dihydroxy-α-(*N*-1-methyl-2-*p*-methoxyphenethyl-aminomethyl)-benzylalcohol hydrobromide (Boehringer Ingelheim) reserpine (Serpasil, Ciba Geigy), salbutamol sulphate (Glaxo), salmefamol base (Glaxo), sotalol hydrochloride (Allard), soterenol hydrochloride (Mead-Johnson), terbutaline sulphate (Lematte et Boinot), zinterol hydrochloride (Mead-Johnson). All other chemicals were of analytical grade.

RESULTS

β_1- and β_2-Adrenomimetic effects

pD_2 values and intrinsic activities are listed in Table 2 along with the β_2/β_1 selectivity. On trachea, the pD_2 values varied from 9·3 to 6·4 while on atria the values ranged from 8·6 to 5·2. These values are generally in good agreement with those reported (Hartley et al 1968; O'Donnell 1972; Davey et al 1974; O'Donnell & Wanstall 1974; Ida 1976; Larsen & Hermansen 1977). Isoprenaline and its *N*-aralkylated derivatives had roughly the same potency on tracheal chain and

Table 2. In vitro β_2- and β_1-activities of β-agonists determined on trachea and atria of guinea-pigs.

	Trachea		Atria		
	pD_2 ± s.e.m.[a]	Intrinsic[b] activity	pD_2 ± s.e.m.[a]	Intrinsic[b] activity	β_2-Selectivity Antilog Δ pD_2
Isoprenaline	8·57 ± 0·02 (91)	1	8·62 ± 0·04 (67)	1	0·9
ME 454	8·80 ± 0·02 (6)	0·94	7·86 ± 0·10 (4)	0·95	8·7
Protokylol	8·20 ± 0·22 (8)	0·89	8·00 ± 0·18 (5)	1·15	1·6
Terbutaline	6·43 ± 0·13 (9)	0·83	5·17 ± 0·04 (5)	0·89	18
ME 506	7·36 ± 0·20 (8)	0·91	6·16 ± 0·20 (6)	1·09	16
Salbutamol	7·13 ± 0·16 (6)	0·91	5·90 ± 0·13 (4)	0·75	17
Salmefamol	8·23 ± 0·13 (10)	0·92	6·78 ± 0·20 (6)	0·82	28
Soterenol	7·59 ± 0·09 (11)	0·90	6·26 ± 0·15 (7)	0·56	21·4
Zinterol	8·53 ± 0·12 (8)	0·91	6·25 ± 0·12 (9)	0·70	190
BD-40 A	9·29 ± 0·08 (9)	0·94	6·98 ± 0·08 (8)	0·94	204

[a] pD_2 ± standard error of the mean with the number of experimental values in parentheses.
[b] The value of intrinsic activity was calculated as the ratio of the maximum response to each compound to the maximum response to isoprenaline; isoprenaline = 1.

on atria. The modification of the catechol moiety on *N*-alkylated compounds resulted in a decrease in β-activity which was more marked for β_1- than for the β_2-activity. The introduction of an *N*-aralkyl group on the non-catechol compounds increased their β_2- and β_1-activities by approximately 10-fold thus keeping their selectivities at similar levels. This was not the case for zinterol which had the same degree of effect on atria as soterenol.

The index of selectivity was 0·9 and 1·6 for the non-selective compounds isoprenaline and protokylol whereas all other compounds had a β_2-selectivity ranging from about 9 for ME 454 to 204 for BD-40 A. The values of intrinsic activity on trachea were all close to unity indicating that the compounds can be considered as full agonists. On atria, the intrinsic activities were more varied; the results indicate that salbutamol, soterenol and zinterol are only partial agonists.

α-Adrenolytic activity

None of the drugs tested exhibited α-adrenomimetic action at the concentrations used except isoprenaline which had a pD_2 value around 5, in agreement with previous results (Drummer et al 1980). From Table 3, it can be seen that *N*-aralkyl substituted compounds, but not BD-40 A, had pA_2 values higher than 7. The *N*-alkyl derivatives had lower pA_2 values than the corresponding *N*-aralkyl compounds. The slopes of Schild plots for these molecules were not significantly different from 1 except for terbutaline, soterenol and BD-40 A. Phentolamine, the classical α-antagonist, had a pA_2 value of 8 which is only slightly higher than the values obtained for the *N*-aralkyl β-agonists studied. For a direct comparison with the binding studies, the dissociation constants K_B for rat aorta α-adrenoceptors are given in Table 3.

Inhibition of [³H]prazosin and [³H]yohimbine binding by β-agonists

The values of inhibition constants obtained in direct competition experiments are listed in Table 3. The K_i values of β-agonists varied between 0·09 to 88μM for [³H]prazosin binding and were generally higher for [³H]yohimbine binding: 4·10 to 330μM. These K_i values are in agreement with those reported by Hanoune's group with [³H]DHE (Aggerbeck et al 1979). The typical α-lytic drug phentolamine had K_i values in the nanomolar range for both binding sites. The *N*-aralkyl derivatives had higher affinities for α-receptors than the corresponding *N*-alkyl analogues. Comparison of pairs of molecules revealed that introduction of an *N*-aralkyl group increased the affinity for [³H]prazosin binding sites between 87 and 733 times. This increase in affinity was not so pronounced for [³H]yohimbine binding sites; the maximal ratio of 23 was obtained for the paired drugs terbutaline and ME 506. Nevertheless, K_i variations

Table 3. α-adrenolytic activity and binding constants of the studied β-agonists.

	Rat aorta			Binding on rat cortex membranes			
				[³H]prazosin		[³H]yohimbine	
	$pA_2 \pm s$[a]	(n)	K_B (μM)	K_i (μM)[f]	Ratio[g]	K_i (μM)[f]	Ratio[g]
Isoprenaline	5·05[b]	(6)		13 ± 1·7		29·5 ± 17·4	
ME 454	7·29 ± 0·23	(6)	0·051	0·15 ± 0·02	87	—	—
Protokylol	8·11 ± 0·61	(14)	0·008	0·09 ± 0·03	144	4·10 ± 0·68	7·2
Terbutaline	6·09 ± 0·29[c]	(8)	0·813	74 ± 12		330 ± 5·2	
ME 506	7·32 ± 0·32	(10)	0·048	0·19 ± 0·04	389	14·1 ± 1·7	23
Salbutamol	5·50 ± 0·23	(6)	3·162	82 ± 9		139 ± 1·7	
Salmefamol	7·08 ± 0·21	(12)	0·083	0·15 ± 0·04	547	9·60 ± 0·49	14
Soterenol	4·94 ± 0·11[c]	(6)	11·481	88 ± 20		47·2 ± 2·4	
Zinterol	7·34 ± 0·34	(8)	0·046	0·12 ± 0·04	733	5·20 ± 0·67	9
BD-40 A	d		—	1·25 ± 0·3		6·67 ± 0·51	
Phentolamine	8·01 ± 0·27	(11)	0·010	0·009 ± 0·001		0·007 ± 0·001	

α-Adrenolytic activities were determined on rat aorta and the inhibition constants of [³H]prazosin and [³H]yohimbine binding were performed on crude rat cortex membranes.

[a] $pA_2 \pm$ standard error with the number of experimental values in parentheses.

[b] Adrenomimetic activity, pD_2.

[c] Slope different from 1.

[d] α-adrenergic antagonism cannot be quantified in term of pA_2: the dose-response curve displacement of noradrenaline was not dose-dependent for BD-40 A.

[e] pD'_2.

[f] $K_i \pm$ s.e.m. values.

[g] The ratio K_i *N*-alkyl/K_i *N*-aralkyl for each pair of compounds is given.

from compound to compound were similar for the two binding sites and also parallelled the changes observed in pA_2 values. These observations can be correlated in a quantitative fashion. Thus the pA_2 values of α-lytic activity correlate better with pK_i (prazosin) r = 0·93 than with pK_i (yohimbine) r = 0·78 (n = 7; isoprenaline, ME 454, BD-40 A and phentolamine excluded). There is also a correlation between pK_i (prazosin) and pK_i (yohimbine) values since the correlation coefficient was 0·84 (n = 10; ME 454 and phentolamine excluded).

DISCUSSION

The present study shows that the replacement of an *N*-alkyl by an *N*-aralkyl group in a series of β-agonists has no predictable effect on their β_1- and β_2-activities. Thus, the aromatic group on the amino chain generally enhanced β_1- and β_2-activities but the increase did not occur in the case of molecules with a catechol moiety. Furthermore, the *N*-aralkyl substitution can preferentially increase the potency for β_2-receptors: zinterol had a higher β_2-potency than soterenol but the same β_1-activity. On the other hand, *N*-aralkyl substitution markedly increased the α-adrenolytic action on rat aorta as well as the affinities for α_1- and α_2-receptors on rat brain membranes. However, the increase in affinity for the α_1-receptors (from 87 to 733) was more pronounced than for the α_2-receptors (from 7·2 to 23). Since phentolamine, a non-selective antagonist, has about the same K_i for α_1- and α_2-receptors, a direct comparison of the K_i values obtained with [^{3}H]prazosin and [^{3}H]yohimbine can be made. The ratio K_i (α_2)/K_i (α_1) for the *N*-aralkyl derivatives, ranging from 43 to 74, indicates an α_1-adrenergic selectivity. This result is consistent with the work of Grisar et al (1981) on a series of α- and β-blockers derived from medroxalol. These authors reported that for one of their compounds, 'studies in progress suggest that α-adrenergic antagonism is predominantly postsynaptic' (i.e. α_1). One should note that the dose-dependency of the α-adrenolytic activity of BD-40 A on rat aorta did not follow a normal competitive pattern; its K_i value for the [^{3}H]prazosin binding sites was about 10 times lower than the other *N*-aralkyl compounds. This particular behaviour can be attributed to the formamide group at the *meta*-position of the phenylethanolamine since this is the only difference from the structure of salmefamol.

The fact that for the β-agonists tested the α-adrenolytic activity (pA_2) correlates better with the affinity (pK_i) for α_1- (r = 0·93) than for the α_2-adrenoceptors (r = 0·78) also suggests that their antagonist effect on rat aorta is mainly mediated through α_1-receptors. However, there is a discrepancy when K_B and K_i value of the *N*-aralkylated β-agonists are compared with those of the classical α-antagonist phentolamine. Thus, the latter had an affinity for the [^{3}H]prazosin binding sites similar to its K_B determined on rat aorta whereas the *N*-aralkyl derivatives have K_i values 2 to 11·5 times smaller than their K_B values.

To explain this slight discrepancy, one might argue that the pA_2 values for the *N*-aralkylated β-agonists were overestimated simply because of their β-agonistic effects on aorta. However, our studies have been carried out in presence of 10^{-5} M sotalol, a β-blocker chosen for its lack of α-adrenolytic activity. Sotalol is not a very potent β-blocking agent and at the higher concentrations tested, potent β_2-agonists might have partially displaced sotalol from the β-receptors. In any case, the extent of the β_2 effect should be limited since BD-40 A, a potent β_2-agonist, had a low α-adrenolytic activity in agreement with its relatively low affinity for α-adrenoceptors. It is possible that an additional non-adrenergic mechanism could contribute to the α-adrenolytic activity of the *N*-aralkyl substituted compounds. Such a phenomenon has already been described with these types of compounds (Lish et al 1960; Dage et al 1981). However, the slopes of the Schild plot we obtained, close to unity, demonstrate that this additional effect if present is not important.

In conclusion, we have confirmed that the substitution of the amine of β-agonists by an aralkyl group enhanced their α-adrenolytic activity on rat aorta and also their affinities for the α-adrenoceptors. Furthermore, we have shown that the increase in affinity was more marked for the α_1-adrenoceptors indicating that the *N*-aralkyl β-agonists have an α_1-adrenolytic selectivity.

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