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CATECHOL-SUBSTITUTED PHENOXY-PROPANOLAMINES: ADRENOCEPTOR ACTIVITY IN THE ANAESTHETIZED CAT

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1 The pharmacological actions of racemic noradrenaline, adrenaline, isoprenaline and *N-t*-butylnoradrenaline have been compared with those of their corresponding derivatives containing an oxymethylene (OXY) link between the ring and ethanolamine side chain.

2 The compounds were tested in the anaesthetized cat for their ability to produce positive chronotropic effects, bronchodilator actions, changes in perfusion pressure in the perfused hind limb and decreases in soleus muscle contractions.

3 All the OXY-derivatives were potent β-adrenoceptor agonists. The inclusion of the oxymethylene link promotes selectivity for β_1- as opposed to β_2-adrenoceptor activity.

4 In comparison with the parent compounds, the OXY-derivatives of adrenaline and noradrenaline had very weak α-adrenoceptor stimulant effects.

Introduction

From a structural standpoint β-adrenoceptor antagonists fall into two main groups, ring substituted phenylethanolamines (e.g. dichloroisoprenaline, sotalol etc.) and ring substituted phenoxypropanolamines which contain an oxymethylene link between the ring and the ethanolamine side chain (e.g. propranolol, oxprenolol, pindolol etc.).

Although adrenoceptor agonists based on the phenylethanolamine nucleus have been used in numerous studies, little work has been done with phenoxypropanolamine derivatives. In 1970 Ablad, Brögard & Corrodi showed that the phenoxypropanolamine derivatives of isoprenaline and orciprenaline possessed affinity for adrenoceptor sites, since both agents produced β-adrenoceptor mediated positive chronotropic effects in anaesthetized guinea-pigs.

In the present study this work has been extended. Phenoxypropanolamine derivatives of noradrenaline, adrenaline, isoprenaline and *N-t*-butylnoradrenaline (Figure 1) have been synthesized and tested for their pharmacological actions in the anaesthetized cat. Details of the chemistry of these compounds will be reported elsewhere. For convenience these compounds will be termed OXY-derivatives of their respective parent compounds. In all experiments racemic OXY-derivatives and parent compounds have been compared in order to determine how the inclusion of the oxymethylene link affects the potency and selectivity of the agents for adrenoceptor mediated effects.

Methods

Cats of either sex weighing 1.2–5 kg were anaesthetized by the intraperitoneal injection of α-chloralose (80 mg/kg) and sodium pentobarbitone (6 mg/kg). In all experiments arterial blood pressure (1 mmHg $\approx$ 133 Pa) was monitored from a cannulated carotid artery with a Statham (P23DC) pressure transducer, and heart rate measured with a Grass tachograph (7P4) triggered by the arterial pulse.

In experiments where the cardiac chronotropic actions of the compounds were assessed, the animals were bilaterally vagotomized and artificially respired at a rate of 20 breaths/min and a stroke volume of 15 ml/kg body weight.

These respiratory parameters were also used when testing the bronchodilator actions of the compounds. In these studies intratracheal pressure was monitored with a pressure transducer connected to a side arm of the tracheal cannula as described by McCulloch, Proctor & Rand (1967). Bronchoconstriction was induced by the intravenous infusion of 5-hydroxytryptamine (8.9–58.2 $\mu g\,kg^{-1}\,min^{-1}$ in different ex-

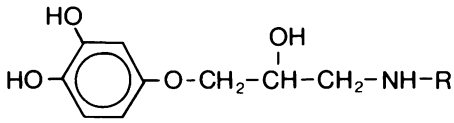

Figure 1 General formula of the racemic OXY-compounds used in the present study. Derivatives of noradrenaline (R=H), adrenaline ($R=CH_3$), isoprenaline ($R=CH(CH_3)_2$) and *N-t*-butylnoradrenaline ($R=C(CH_3)_3$) were used.

periments). When the bronchoconstriction had stabilized, the amines were injected and their bronchodilator actions monitored as reductions in intratracheal pressure. As soon as maximal bronchodilator effects had been attained the 5-hydroxytryptamine infusion was stopped and the lungs hyperinflated for three breaths in order to prevent atelectasis. If required, gallamine (3.4 μmol/kg) was injected intravenously to prevent spontaneous respiratory movements.

In experiments where hind-limb resistance was measured, blood was taken from the left femoral artery and pumped into the right femoral artery with a Watson-Marlow (Type 200) constant flow inducer. Perfusion pressure in the limb was measured with a pressure transducer (Statham P23DC) in the post-pump section of the circuit. The flow rate was initially adjusted so that perfusion pressure was approximately the same as the systemic arterial pressure. This flow rate was then maintained throughout the rest of the experiment. Drugs were injected in volumes <50 μl into the pre-pump circuit. In these experiments the cats were given bethanidine (22 μmol/kg; 6 mg/kg i.v.) to reduce sympathetic reflexes and heparin (1200 u/kg) as an anticoagulant. The perfused hind-limb was also denervated by sectioning the femoral and sciatic nerves. As a routine the animals were given 5 ml of a 10% dextran 40 solution intravenously to make up for the dead space in the external circuit.

The soleus muscle was prepared for the recording of contractions as described by Bowman & Nott (1970). The muscle was stimulated at a frequency of 8 Hz for 1 s once every 10 seconds. Sympathomimetic-induced decreases in the tension and fusion of the sub-tetanic contractions were monitored as described by Nott & Raper (1972) using a Grass FT10C force-displacement transducer.

Unless otherwise stated in the text, actions of all the amines were monitored by the use of cumulative dose-response curves. Drugs were injected intravenously into a cannulated brachial vein. In each experiment constant curves to isoprenaline were first obtained and thereafter responses to pairs of corresponding parent and OXY-compounds assessed in a randomized fashion. Control curves to isoprenaline were reassessed between each pair of drugs tested.

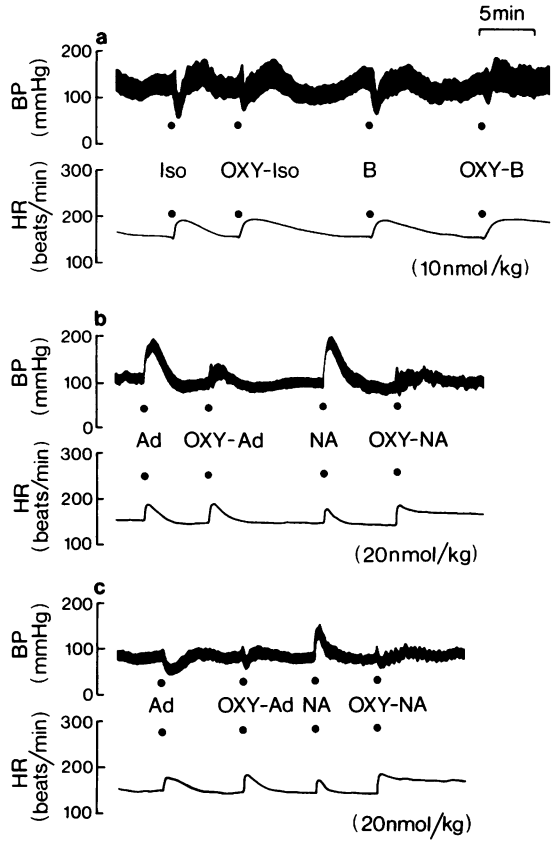

Figure 2 Recordings of arterial blood pressure (BP) and mean heart rate (HR) in anaesthetized cats. In (a) responses to isoprenaline (Iso), OXY-isoprenaline (OXY-Iso), *N-t*-butylnoradrenaline (B) and OXY-*N-t*-butylnoradrenaline (OXY-B) and in (b) and (c) responses to adrenaline (Ad), OXY-adrenaline (OXY-Ad), noradrenaline (NA) and OXY-noradrenaline (OXY-NA). Trace (b) shows responses before, and trace (c) responses after α-adrenoceptor blockade with phentolamine.

Drugs used were (±)-isoprenaline hydrochloride, (±)-noradrenaline hydrochloride, (±)-adrenaline (Sigma), (±)-*N-t*-butylnoradrenaline mesylate (Stirling Winthrop), the racemic oxymethylene derivatives of the above catecholamines (Department of Chemistry, Victorian College of Pharmacy), phentolamine mesylate (Ciba), bunitrolol hydrochloride (Kö1366, Boehringer Ingelheim), 5-hydroxytryptamine (serotonin) creatinine sulphate (Sigma), gallamine triethiodide (May & Baker) and bethanidine sulphate (Burroughs Wellcome). Solutions of the catecholamines were freshly prepared in 0.01 mol/l HCl and suitable dilutions made up in 0.9% w/vNaCl solution (saline) containing 20 μg/ml ascorbic acid.

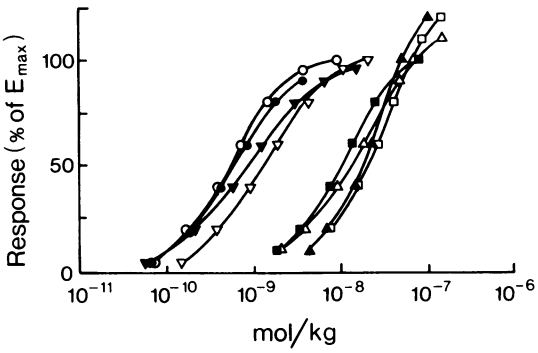

Figure 3 Mean dose-response curves showing the positive chronotropic effects of noradrenaline (□), OXY-noradrenaline (■), adrenaline (▲), OXY-adrenaline (△), isoprenaline (○), OXY-isoprenaline (●), *N-t*-butylnoradrenaline (▼), and OXY-*N-t*-butylnoradrenaline (▽) in anaesthetized cats. Responses are expressed in terms of the maximal response produced by isoprenaline (= 100% or E_{max}). For isoprenaline $n = 10$, and for the remaining compounds $n = 5$.

In all experiments traces were recorded on an ink-writing Grass Model 7C polygraph.

Results

General cardiovascular activity

In 5 pilot experiments responses to single injections of the compounds were assessed in bilaterally vagotomized and anaesthetized cats in which arterial blood pressure and heart rate were recorded. Isoprenaline, *N-t*-butylnoradrenaline and their respective OXY-derivatives produced vasodepressor responses and increases in heart rate which were completely abolished by the prior injection of the β-adrenoceptor antagonist, bunitrolol (3.5 μmol/kg; 1 mg/kg). At equivalent mol/kg doses all four agonists produced similar positive chronotropic effects, whereas the vasodepressor actions of the OXY-derivatives were smaller than those of the parent compounds (Figure 2a).

Adrenaline and noradrenaline and their respective OXY-derivatives produced increases in heart rate and vasopressor actions. Although similar cardiac responses were obtained with the same mol/kg doses of all four compounds, the vasopressor responses to OXY-adrenaline and OXY-noradrenaline were much smaller than those produced with the parent compounds (Figure 2b). After β-adrenoceptor blockade with bunitrolol (3.5 μmol/kg), the positive chronotropic actions of the compounds were abolished; pressor responses to adrenaline were slightly increased, those to noradrenaline little changed, and those to the OXY-derivatives reduced. Phentolamine (5.3 μmol/kg; 2 mg/kg), caused a slight reduction in resting blood pressure, antagonized the pressor response to noradrenaline and produced vasomotor reversal with adrenaline, OXY-adrenaline and OXY-noradrenaline (Figure 2c). These vasodepressor responses, which were unmasked after α-adrenoceptor blockade, were abolished after bunitrolol (3.5 μmol/kg) administration.

The above results suggested that the cardiovascular actions of the OXY-compounds involved effects at both α- and β-adrenoceptors, and on this basis more detailed studies were performed to assess the actions of the drugs in cardiac, vascular, bronchial and skeletal muscle.

Cardiac activity

Figure 3 shows the mean cumulative dose-response curves for the positive chronotropic effect of the parent compounds and their OXY-derivatives in vagotomized animals. Dose-response lines had a similar slope with all the compounds tested. Maximal responses to *N-t*-butylnoradrenaline and all the OXY-derivatives tested were similar to that of isoprenaline, while slightly greater values were obtained with adrenaline and noradrenaline. After maximal chronotropic effects had been obtained the times to half-return of heart rate to control levels varied within the group of compounds tested; for the parent compounds and OXY-adrenaline these times fell within the range of 3–10 min, for OXY-isoprenaline 3–17 min and for OXY-noradrenaline and OXY-*N-t*-butylnoradrenaline >30 minutes. The longer lasting responses obtained with the latter compounds can be seen in Figure 2.

In each experiment the doses of the compounds required to produce 50% of the maximal effect of isoprenaline (ED_{50} values) were interpolated. These values were used to calculate mean ED_{50} values and relative potencies with respect to isoprenaline (Table 1). When comparing the ED_{50} values of each parent compound and its OXY-derivative it was found that OXY-noradrenaline was approximately twice as potent as noradrenaline in producing positive chronotropic actions. With each of the remaining pairs of compounds there was no significant difference between the ED_{50} value of the parent drug and its corresponding OXY-derivative ($P > 0.05$).

Vascular activity

In these experiments vasoconstrictor and vasodilator responses were assessed from changes in perfusion pressure induced by single bolus injections of the compounds. Within each experiment dose-response curves were constructed, each point being the mean

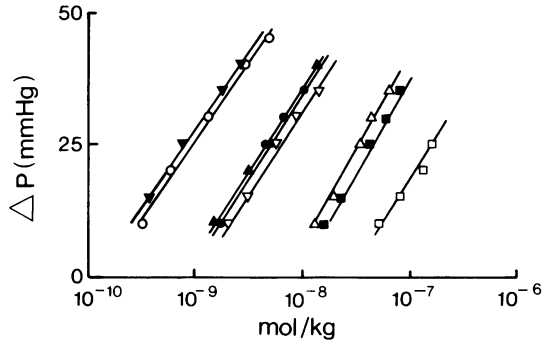

Figure 4 Mean dose-response lines showing decrease in perfusion pressure in the perfused hind-limb of anaesthetized cats in the presence of α-adrenoceptor blockade with phentolamine. Symbols for the various drugs used are indicated in Figure 3. Lines show mean results from 13 experiments with isoprenaline and 4 to 9 experiments with each of the remaining drugs except noradrenaline. The responses to the latter agent were obtained in the one experiment in which uncomplicated vasodilator responses were obtained.

obtained from 3 or 4 randomized responses to a given dose of a compound.

Vasoconstrictor actions due to α-adrenoceptor mediated effects of the compounds were monitored in preparations following β-adrenoceptor blockade with bunitrolol (3.5 μmol/kg). Under these conditions increases in perfusion pressure were only obtained with adrenaline, noradrenaline, OXY-adrenaline and OXY-noradrenaline. In comparison with the parent compounds, which produced dose-related vasoconstrictor actions, the OXY-derivatives produced only weak activity. Thus, at 20 nmol/kg adrenaline and noradrenaline produced mean increases in perfusion pressure ($\pm$s.e. mean, $n=5$) of 80 ± 10 and 76 ± 12 mmHg respectively. At this dose level the mean responses ($n=5$) to OXY-adrenaline and OXY-noradrenaline were 6.0 ± 1.7 and 4.5 ± 1.5 mmHg. In comparison with the parent compounds the dose-response curves to the OXY-derivatives were very shallow, and within individual experiments there was a poor dose-response relationship.

The ability of the drugs to produce decreases in perfusion pressure were assessed in the presence of α-adrenoceptor blockade with phentolamine. An initial dose of 5.3 μmol/kg was given and thereafter doses of 2.7 μmol/kg were administered at hourly intervals throughout the experiment. In these experiments no attempt was made to determine the maximal vasodilator actions of the compounds, since in pilot studies it was found that the reproducibility of responses was adversely affected after doses of the drugs that produced near maximal or supramaximal effects.

With the exception of noradrenaline all the compounds produced dose-related decreases in perfusion pressure (Figure 4). With the former compound weak vasodilator actions were only seen in

Table 1 Doses of the compounds and their relative potencies with respect to isoprenaline

	Heart		Vessels		Bronchi		Soleus	
	ED_{50}	*RP*	ED_{25}	*RP*	ED_{50}	*RP*	ED_{50}	*RP*
Noradrenaline	20.7	37.7	167	225	279	161	147	399
	(1.6)	(4.8)	–	–	(74)	(40.2)	(16.6)	(48.2)
OXY-noradrenaline	10.3	19.2	51.6	89.8	76.2	45.5	17.7	49.0
	(2.2)	(5.2)	(9.0)	(6.1)	(13.7)	(9.6)	(1.4)	(3.4)
Adrenaline	18.7	33.6	5.00	6.7	12.4	6.3	1.74	4.8
	(3.9)	(9.0)	(2.3)	(1.4)	(1.8)	(1.2)	(0.17)	(0.5)
OXY-adrenaline	13.2	23.1	43.1	64.0	108	49.2	23.1	62.8
	(2.1)	(3.2)	(13.6)	(9.6)	(20.4)	(7.4)	(1.5)	(8.6)
Isoprenaline	0.51	1.0	0.83	1.0	1.89	1.0	0.31	1.0
	(0.10)	–	(0.23)	–	(0.16)	–	(0.04)	–
OXY-isoprenaline	0.58	1.1	4.52	5.4	8.15	5.2	0.85	4.1
	(0.18)	(0.17)	(1.13)	(1.2)	(2.21)	(1.5)	(0.11)	(1.4)
N-t-butyl-noradrenaline	0.84	1.8	0.80	0.82	1.39	0.83	0.16	0.73
	(0.39)	(0.33)	(0.37)	(0.11)	(0.27)	(0.09)	(0.01)	(0.18)
OXY-*N-t*-butyl-noradrenaline	1.33	3.6	6.2	7.1	3.88	3.4	0.61	3.0
	(0.43)	(2.1)	(1.6)	(1.6)	(0.72)	(0.5)	(0.07)	(1.0)

Mean doses of the compounds (μmol/kg) required to produce 50% of the maximal effect (ED_{50}) in the heart, bronchi and soleus muscle and a 25 mmHg reduction in the perfusion pressure in the hind-limb (ED_{25}). Mean relative potencies (RP) with respect to isoprenaline are also shown. Standard errors of the mean are shown in parentheses. Values obtained from 4–9 experiments with each drug except noradrenaline in the perfused hind-limb, where values were obtained in the one experiment in which uncomplicated vasodilator effects were monitored.

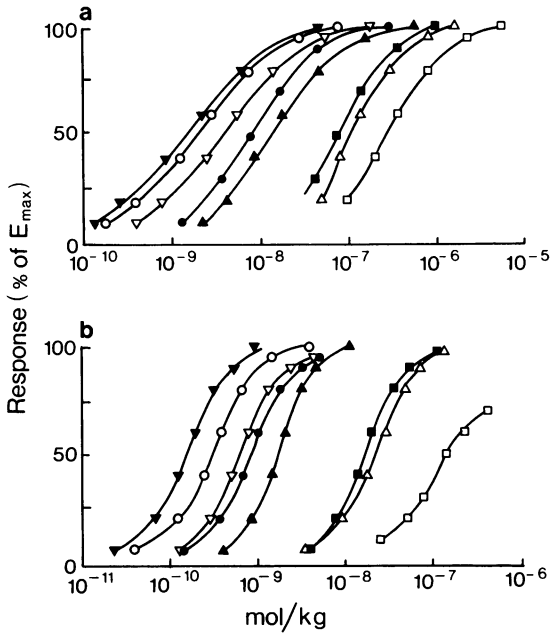

Figure 5 Mean dose-response curves for (a) bronchodilator effects and (b) reduction in the tension of sub-tetanic contractions of the soleus muscle in anaesthetized cats. Symbols for the various drugs used are shown in Figure 3. Responses are expressed in terms of the maximal effects produced with isoprenaline (=100%). For isoprenaline $n=12$ in (a) and 8 in (b). With the remaining drugs $n=4$–8.

one of five experiments. The results from this single experiment with noradrenaline are shown in Figure 4. In the remaining studies vasoconstrictor actions dominated the vascular effects produced. Increasing the dose of phentolamine reduced these vasoconstrictor effects but failed to unmask vasodilator activity. The dose of phentolamine that could be used was limited by its own vascular effects; these reduced the resting perfusion pressure to such an extent that little or no vasodilatation was apparent even when drugs such as isoprenaline were used.

Since maximal vasodilator effects were not monitored, relative potencies in each experiment were calculated from doses producing a 25 mmHg reduction of perfusion pressure (Table 1). OXY-adrenaline, OXY-isoprenaline and OXY-*N*-*t*-butylnoradrenaline were all significantly less potent ($P<0.05$) than their respective parent compounds in producing decreases in perfusion pressure. OXY-noradrenaline was more potent than noradrenaline as a vasodilator ($P<0.05$). As in the experiments where cardiac chronotropic actions were measured, OXY-noradrenaline and OXY-*N*-*t*-butylnoradrenaline produced longer lasting vasodilator actions than those found with the other compounds tested.

Bronchodilator activity

As found by previous authors (Rodger, 1974; Malta & Raper, 1976) the bronchoconstriction produced by a given infusion rate of 5-hydroxytryptamine was remarkably constant within each experiment. In the present studies reproducible bronchoconstrictor responses to 5-hydroxytryptamine and bronchodilator responses to all the compounds except OXY-noradrenaline and OXY-*N*-*t*-butylnoradrenaline could be obtained at 45 min intervals. Responses to 5-hydroxytryptamine were reduced 45 min after dose-response curves to the latter compounds had been established. This probably reflects their long duration of action, since after a further 45 min responses to 5-hydroxytryptamine returned to control levels.

All the compounds tested produced dose-related bronchodilator effects; similar maximal responses were produced and dose-response lines were closed to parallel for all compounds (Figure 5a).

In one of the initial experiments in which noradrenaline was tested, the amine produced a dose-related increase in intratracheal pressure, and in another the lower cumulative doses produced a bronchodilator action, while higher doses reversed this effect and induced a weak bronchoconstrictor effect. In both cases the bronchoconstrictor effects were abolished by the prior administration of phentolamine (5.3 μmol/kg). In the remaining 8 experiments noradrenaline produced only bronchodilator activity, maximal responses and the slope of the dose-response lines being similar to those produced by isoprenaline. In 4 of these experiments responses to noradrenaline alone were first monitored and thereafter responses were assessed in the presence of phentolamine (5.3 μmol/kg). There was no significant difference in the ED_{50} doses or the relative potencies of noradrenaline with respect to isoprenaline in the presence or absence of α-adrenoceptor blockade ($P>0.05$). A similar finding was obtained in one experiment in which the effects of adrenaline were monitored in the absence and presence of phentolamine. In these experiments phentolamine itself slightly reduced the bronchoconstrictor actions of 5-hydroxytryptamine. The infusion rate of the latter agent was therefore increased so that the bronchodilator effects of the catecholamines could be assessed against a constant degree of background constriction.

The mean ED_{50} doses of the compounds and their relative potencies with respect to isoprenaline are shown in Table 1. Since α-adrenoceptor blockade did not affect these values for noradrenaline, results obtained in the presence and absence of phentolamine have been used for calculating the means. In terms of bronchodilator activity OXY-noradrenaline was

significantly more potent than noradrenaline ($P<0.05$) and OXY-adrenaline, OXY-isoprenaline and OXY-*N*-*t*-butylnoradrenaline were significantly less potent than their respective parent compounds ($P<0.05$).

Soleus muscle contractions

The ability of β-adrenoceptor agonists to decrease the tension and fusion of sub-tetanic contractions of the cat soleus muscle has been used to assess potential tremorogenic actions of sympathomimetic bronchodilators (Bowman & Nott, 1970; Apperley, Daly & Levy, 1976). All the compounds used in the present study produced the characteristic decrease in soleus muscle contractions. With the exception of noradrenaline all compounds produced a similar maximal response to that obtained with isoprenaline and dose-response lines were close to parallel (Figure 5b). Mean ED_{50} doses are shown in Table 1. At the high doses of noradrenaline required to produce effects on soleus muscle contractions, the intense α-adrenoceptor mediated vasoconstrictor effects probably interfere with the results obtained, since in the presence of phentolamine or phenoxybenzamine there is a small shift to the left of dose-response curves to the amine and maximal responses are slightly increased (Raper, unpublished observations). However, complete abolition of pressor responses to the amine were impossible to achieve with doses of the α-adrenoceptor antagonists which did not adversely affect muscle contractility through probably non-specific actions. As in the bronchi and hind-limb the OXY-derivatives of adrenaline, isoprenaline and *N*-*t*-butyl noradrenaline were significantly less potent than their respective parent compounds ($P<0.05$) while OXY-noradrenaline was more potent than noradrenaline ($P<0.05$). As in the other tissues responses to OXY-noradrenaline and OXY-*N*-*t*-butylnoradrenaline were longer lasting than those of the other compounds.

Discussion

In the present study a series of catecholamines with and without an oxymethylene link between the ring and ethanolamine side chain have been compared for their α- and β-adrenoceptor activity in the anaesthetized cat. The results indicate that the inclusion of the oxymethylene link leads to a retention of agonistic actions at β-adrenoceptor sites and a substantial reduction in α-adrenoceptor mediated activity. In terms of potency, both the parent compounds and their OXY-derivatives have a similar activity for β_1-receptor mediated actions in the heart. With the exception of OXY-noradrenaline, the remaining derivatives are less potent than their parent compounds in producing β_2-receptor mediated effects in bronchial, vascular and skeletal muscle.

The selectivity of action of agonists at β_1- and β_2-receptor sites is best indicated by calculating selectivity ratios with respect to an internal standard such as isoprenaline (Bowman & Raper, 1976). If cardiac stimulant actions are used to represent β_1- and bronchodilator effects β_2-receptor mediated responses, the selectivity ratios [i.e. dose-ratio (heart) : dose-ratio (bronchi)] found for noradrenaline, adrenaline, isoprenaline and *N*-*t*-butylnoradrenaline are 0.23, 5.33, 1.0 and 2.17 respectively. The selectivity ratios for the corresponding OXY-derivatives are 0.42, 0.47, 0.21 and 1.05 respectively. Thus within the parent compounds noradrenaline is β_1-selective, and adrenaline and *N*-*t*-butylnoradrenaline are β_2-receptor

Table 2 Selectivities of compounds for β_1- and β_2-adrenoceptor mediated actions

	Hearts : Vessels		*Heart : Bronchi*		*Heart : Soleus*	
	RP	ED_{25}	*RP*	ED_{50}	*RP*	ED_{50}
Noradrenaline	0.16	0.12	0.23	0.07	0.09	0.14
OXY-noradrenaline	0.21	0.19	0.42	0.13	0.39	0.58
Adrenaline	5.01	3.7	5.33	1.51	7.0	10.75
OXY-adrenaline	0.36	0.30	0.47	0.12	0.36	0.57
Isoprenaline	1.0	0.61	1.0	0.27	1.0	1.64
OXY-isoprenaline	0.20	0.13	0.21	0.07	0.27	0.68
N-*t*-butyl noradrenaline	2.19	1.05	2.17	0.60	2.46	5.25
OXY-*N*-*t*-butyl-noradrenaline	0.50	0.21	1.05	0.34	1.20	2.18

$\beta_1 : \beta_2$ Receptor selectivities based on (a) the mean relative potencies (RP) of the compounds with respect to isoprenaline in the various tissues, and (b) mean ED_{50} doses in heart, bronchi and soleus, and doses to produce a 25 mmHg decrease in perfusion pressure in the hind-limb. Values greater than unity indicate β_2-receptor selectivity and values less than unity β_1-selective actions.

selective in their effects. The inclusion of the oxymethylene link appears to promote β_1-receptor selective actions, since the selectivity ratios for OXY-noradrenaline, OXY-adrenaline and OXY-isoprenaline are less than unity. This effect is also apparent with OXY-*N*-*t*-butylnoradrenaline which displays non-selective actions as opposed to the β_2-selectivity of the parent compound. The trend towards β_1-selective actions is also apparent in the OXY-derivatives if selectivity ratios are calculated using dose-ratios for β_2-receptor mediated actions in the hind-limb or soleus muscle, or if selectivity is assessed using the actual doses of the compounds (ED_{50} values) required to produce effects in the various tissues (Table 2).

In addition to changes in selectivity, the inclusion of the OXY-methylene link also affects the duration of action of the compounds. This is especially noticeable with OXY-noradrenaline and OXY-*N*-*t*-butylnoradrenaline which have a much longer duration of action than their respective parent compounds. Whether or not the longer lasting actions are due to a lower affinity of the OXY-derivatives for uptake processes or metabolizing enzymes requires further elucidation.

Although a great deal of information is available regarding the structural requirements for agents displaying β_2-adrenoceptor selective actions (Brittain, Jack & Ritchie, 1970) little comparable work has been done for β_1-selective activity. The finding that catecholamines of the phenoxypropanolamine type display selectivity for β_1- as opposed to β_2-adrenoceptor mediated effects and are virtually devoid of α-adrenoceptor stimulant actions is of interest in this regard.

Drugs which produce cardiac stimulation in the absence of marked vascular changes may be of potential use in treating low cardiac output states. Further work with agonists of the phenoxypropanolamine type may therefore be of interest.

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