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EFFECTS OF α-ADRENOCEPTOR AGONISTS AND ANTAGONISTS ON PRE- AND POSTSYNAPTICALLY LOCATED α-ADRENOCEPTORS

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The effects of α-adrenoceptor agonists and antagonists have been examined at pre- and post-synaptically located α-adrenoceptors in the pithed rat. The presynaptic receptors were those located at the cardiac sympathetic nerve terminals and the postsynaptic receptors were those present in vascular smooth muscle. Clonidine was approximately equipotent at pre- and post-synaptic α-adrenoceptors, whilst LSD and BAY-1470 were more active at the pre- than at post-synaptic sites. Oxymetazoline, naphazoline, methoxamine and phenylephrine were all much more active at the postsynaptic α-adrenoceptors. Phentolamine was the most potent antagonist at both pre- and post-synaptic α-adrenoceptors. Piperoxan, yohimbine and tolazoline were about 3—7× less potent than phentolamine at both sites. Thymoxamine was about 10× less potent than phentolamine at postsynaptic α-adrenoceptors but about 1000× less active at the presynaptic receptors. The differential actions of both agonists and antagonists at pre- and post-synaptic α-adrenoceptors suggest that the receptors may be of different types.

Postsynaptic α-adrenoceptors α-Adrenoceptor antagonists α-Adrenoceptor agonists
Presynaptic α-adrenoceptors

1. Introduction

It is currently believed that the release of the neurotransmitter from sympathetic nerves is modulated by α-adrenoceptors located at the nerve terminals. α-Adrenoceptor agonists depress whilst antagonists enhance transmitter release (Langer, 1974). It is unclear, however, whether presynaptic α-adrenoceptors are of the same type as those located postsynaptically at, for example, vascular smooth muscle. Accordingly, a number of α-adrenoceptor agonists and antagonists have been investigated for their effects at pre- and post-synaptically located α-adrenoceptors to determine whether there are differences between the receptors.

Changes in heart rate were used to measure the effects of compounds at presynaptic α-adrenoceptors. In this way the end-organ responses which were mediated via β-adrenoceptors were not directly affected by the test compounds.

Increases in diastolic blood pressure reflected activity at postsynaptic α-adrenoceptors.

At about the same time as the experimental work was completed, Starke et al. (1975) reported their findings with a number of α-adrenoceptor agonists at the pre- and postsynaptic α-adrenoceptors in the rabbit pulmonary artery. The present results are in general agreement with the work of these authors.

2. Materials and methods

2.1. General

Rats of either sex (200—400 g) were anaesthetized with a mixture of halothane (3.5% in oxygen) and nitrous oxide (ratio 1 : 3). After

cannulation of the trachea and the placement of an indifferent electrode s.c. in the dorsum the animals were pithed and immediately respired with room air (1 ml/100 g at a rate of 50 strokes/min) using an SRI ventilation pump. The pithing rod had been previously coated with a high resistance varnish except for a 1 cm length about 5—6 cm from the tip of the rod.

The left femoral vein was cannulated for drug injection and blood pressure was recorded from the left common carotid artery using a Bell and Howell pressure transducer (type 4-422-0001 or type 4-327-L221). The arterial pulse was also used to trigger a heart ratemeter. Blood pressure and heart rate were recorded on a Devices M4 chart recorder. Animals were kept warm by a lamp positioned about 30 cm about the chest.

Before experimentation all preparations received atropine and (+)-tubocurarine (1 mg/kg i.v. of each) and the vagus nerves were sectioned in the neck. The preganglionic nerves to the heart were stimulated continuously (1 Hz; 1 msec; supramaximal voltage) between the pithing rod and the indifferent electrode using a Devices isolated stimulator (type 2533) coupled to a Devices gated pulse generator (type 2521) (Gillespie and Muir, 1967). The position of the pithing rod was adjusted so that heart rate was increased but blood pressure showed little or no change. A similar technique has been described by Armstrong and Boura (1973).

In control experiments it was shown that stimulation in this way increased heart rate by about 100 beats/min. This increased heart rate was maintained throughout the period of stimulation and little or no decline occurred over the period of observation (at least 1 hr).

2.2. Actions of agonists at pre- and post-synaptic α-adrenoceptors

In each preparation in which heart rate was elevated by continuous stimulation of the cardiac sympathetic nerves, the doses of agonists which both reduced the heart rate by 50 beats/min and elevated the diastolic blood pressure by 50 mm Hg were determined as follows.

The agonists were injected intravenously in increasing doses. An interval of 10—20 min between doses allowed the blood pressure to return to pre-injection levels. The bradycardia induced by each dose of naphazoline, methoxamine and often by oxymetazoline, also recovered to pre-injection levels before the injection of subsequent doses. Therefore dose—response curves were plotted on an individual dose basis. However, the bradycardia produced by LSD, BAY-1470, clonidine and sometimes by oxymetazoline did not fully recover but plateaued. In these cases the fall in heart rate was plotted against the cumulative dose of the agonist. The ratio of the doses causing these responses in each experiment was calculated (blood pressure : heart rate). Thus, a compound with a ratio >1 is more active presynaptically than postsynaptically and vice versa.

After the last dose of agonist, phentolamine (1 mg/kg i.v.) was injected to confirm that the reduction in heart rate produced by the agonist was indeed mediated via α-adrenoceptors.

2.3. Actions of antagonists at presynaptic α-adrenoceptors

In these experiments the cardiac sympathetic nerves were stimulated continuously as previously described. When the tachycardia was constant a single dose of clonidine (100 μg/kg) was injected i.v. This produced a large pressor response and a bradycardia of about 80 beats/min which, in control preparations, lasted for at least 30—60 min with little or no change. When the bradycardia was fully developed, antagonists were injected i.v. in a cumulative dose schedule. Successive doses were administered at intervals of 5—10 min so that the full effect of each dose could become established. For each antagonist the dose which antagonised by 50% the bradycardia produced by clonidine was determined.

2.4. Actions of antagonists at postsynaptic α-adrenoceptors

Cardiac nerve stimulation was not carried out in these experiments. Instead, a control dose—response curve to clonidine on diastolic blood pressure was obtained. A single dose (3 mg/kg) of α-adrenoceptor antagonist was then injected and after 15 min the dose—response curve was repeated.

The antagonist potency of an antagonist was assessed from the rightwards shift of the curve measured at the level of 50 mm Hg rise in blood pressure, that is from the clonidine dose ratio.

In control experiments where a blocking agent was not administered the sensitivity to 3 successive dose—response curves to clonidine varied by less than 2-fold (n = 3).

2.5. Drugs used

The following drugs were used in this study. Atropine sulphate, 2-(2,6-dimethylphenylamino)-4-H-5,6-dihydro-1,3-thiazin (Bay-1470 · HCl, Bayer A.G.), bulbocapnine · HCl (K & K Laboratories Inc.), chlorpromazine · HCl (May & Baker), clonidine · HCl (Catapress, Boehringer Ingelheim), cyproheptadine · HCl (M.S.D.), lysergic acid diethylamide tartrate (Sandoz), methiothepin maleate (Roche), metoclopramide · HCl (Primperan, Berk), naphazoline nitrate (Ciba), oxymetazoline · HCl (Merck), phenoxybenzamine · HCl (S.K.F.), phentolamine mesylate (Ciba), L-phenylephrine · HCl (Koch—Light), piperoxan · HCl, thymoxamine · HCl (Opilon, Warner), tolazoline · HCl (Ciba), tubocurarine · HCl (Burroughs Wellcome), yohimbine · HCl (Sigma). Drugs were dissolved in saline immediately before use and doses mentioned in the text are in terms of the base.

3. Results

3.1. Actions of agonists at pre- and post-synaptic α-adrenoceptors

The α-agonists produced dose-related increases in blood pressure. Table 1 shows the mean dose of each drug required to increase diastolic pressure by 50 mm Hg. Also shown are the doses of the drugs which reduced heart rate by 50 beats/min. It can be seen that clonidine was approximately equipotent in re-

TABLE 1

Relative potencies of agonists at pre- and post-synaptic α-adrenoceptors in the pithed rat.

Agonist	n	Dose of agonist (μg/kg) producing		Ratio of doses (BP/HR) (geometric mean + 95% c.i.)
		Fall in heart rate of 50 beats/min (geom. mean + 95% c.i.)	Incr. in diastolic blood press. of 50 mm Hg (geom. mean + 95% c.i.)	
LSD	5	25.5 (12.4—52.6)	>100	>4 †
BAY-1470	6	153.9 (53.8—440.4)	553.2 (302.7—1011.3)	3.64 † (1.61—8.21)
Clonidine	7	7.5 (4.4—12.8)	5.5 (3.6—8.4)	0.73 (0.48—1.09)
Oxymetazoline	6	5.4 (2.6—11.5)	0.7 (0.4—1.2)	0.13 * (0.07—0.24)
Naphazoline	6	94.9 (15.6—576.1)	3.3 (1.3—7.1)	0.03 * (0.03—1.0)
Methoxamine	7	1061.7 (490.8—2296.3)	46.0 (33.5—63.2)	0.05 * (0.02—0.10)
Phenylephrine	4	>100	4.8 (1.5—15.2)	<0.1 *

n = number of experiments.
† Significantly greater than clonidine ($p < 0.05$).
* Significanlty less than clonidine ($p < 0.05$).

ducing heart rate and elevating blood pressure, but LSD and BAY 1470 were more effective in reducing heart rate than in increasing blood pressure. Oxymetazoline, naphazoline and methoxamine produced pressor responses at doses much lower than were required to reduce heart rate, and phenylephrine failed to reduce heart rate even at high dose levels.

In addition to these differences in selectivity, qualitative differences in the bradycardias produced by the compounds were seen. Clonidine, BAY 1470 and LSD produced falls in heart rate which developed over 3—5 min and which only partially recovered, eventually forming a plateau long after the pressor response had ended. An example illustrating the effects of BAY-1470 is shown in fig. 1.

In contrast, the bradycardia produced by naphazoline, methoxamine and usually by oxymetazoline recovered fully with a time course similar to that of the pressor response.

The bradycardia produced by the α-adrenoceptor agonists was completely abolished 1—2 min after the injection of phentolamine (1 mg/kg, fig. 1) confirming that the effects of the agonists were mediated via α-adrenoceptors.

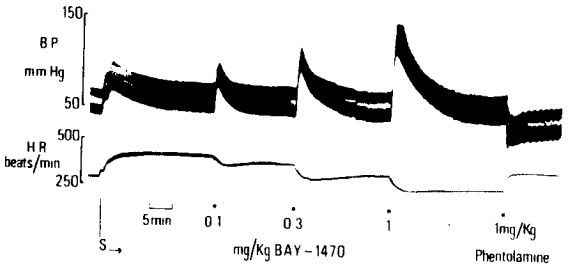

Fig. 1. The effect of BAY-1470 and phentolamine on blood pressure (BP) and heart rate (HR) in the pithed rat during stimulation of preganglionic cardiac sympathetic nerves. Stimulation at 1 Hz; 1 msec and supramaximal voltage was commenced at S and continued throughout the course of the experiment. Note the failure of the heart rate to recover to pre-injection levels after doses of BAY-1470, despite the restoration of the blood pressure. Phentolamine abolishes the bradycardia produced by BAY-1470.

The doses of agonists which reduced heart rate in the stimulated preparations had no significant effect on resting heart rate in control (unstimulated) preparations, showing that the inhibitory effects were exerted specifically against nerve stimulation.

3.2. Actions of antagonists at presynaptic α-adrenoceptors

The injection of cumulative doses of antagonists reversed, in a dose-related fashion, the bradycardia produced by clonidine in preparations where the cardiac sympathetic nerves were stimulated (fig. 2). The mean doses of the blocking agents restoring the heart rate by 50% are shown in table 2.

Phentolamine was the most potent antagonist. Piperoxan, yohimbine and tolazoline were 3—7× less potent than phentolamine. Chlorpromazine and phenoxybenzamine were only weakly active, and thymoxamine was about 1000× less potent than phentolamine.

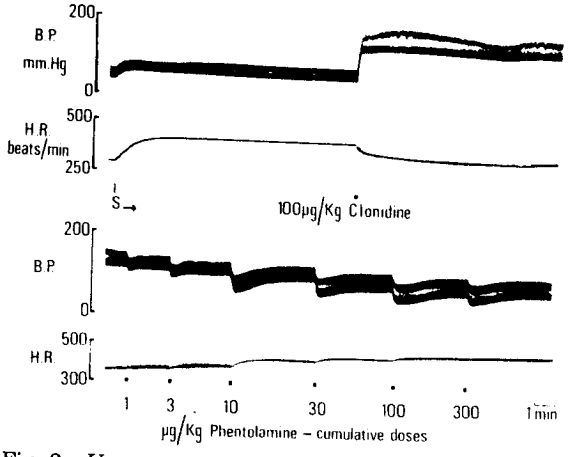

Fig. 2. *Upper panel.* The effect of clonidine (100 μg/kg) on the blood pressure (B.P.) and heart rate (H.R.) of the pithed rat during continuous stimulation (S) of the preganglionic cardiac sympathetic nerves (1 Hz, 1 msec, supramaximal voltage). *Lower panel.* Continuous with the upper panel: the dose related reversal by phentolamine of the bradycardia induced by clonidine. Stimulation was continued throughout.

TABLE 2

Relative potencies of antagonists at pre- and post-synaptic α-adrenoceptors in the pithed rat.

Antagonist	*n*	*Presynaptic α-adrenoceptor* Dose of antagonist (μg/kg) reversing clonidine-induced bradycardia by 50% (geometric mean + 95% c.i.)	*n*	*Postsynaptic α-adrenoceptor* Clonidine dose ratio 15 min after antagonist (3 mg/kg i.v.) (geometric mean + 95% c.i.)
α-Adrenoceptor antagonist				
Phentolamine	5	10.0 (3.4—29.1)	6	36.1 (17.5—74.5)
Yohimbine	6	46.6 (22.7—95.7)	4	13.8 (7.5—25.6)
Piperoxan	4	27.1 (11.8—62.0)	4	6.6 (4.8—9.1)
Tolazoline	4	67.3 (20.0—226.3)	4	5.8 (3.7—8.9)
Chlorpromazine	4	160.6 (72.7—354.8)	4	2.7 (1.4—5.0)
Thymoxamine	6	13604 (12894—14352)	5	4.4 (3.4—5.8)
Phenoxybenzamine	4	1445 (1386—1510)	—	—
Dopamine antagonist				
Bulbocapnine	2	>30000		
Metoclopramide	2	>10000		
5HT antagonist				
Cyproheptidine	2	>3000		
Methiothepin	4	510 (230—1100)	4	4.7 (2.6—8.3)
H_2-antagonist				
Metiamide	2	>10000		

In contrast, the clonidine-induced bradycardia was unaffected by the dopamine antagonists, bulbocapnine (30 mg/kg) and metoclopramide (10 mg/kg), the H_2-receptor antagonist metiamide (10 mg/kg) and the 5HT antagonist cyproheptidine (3 mg/kg). However, methiothepin, a new 5HT antagonist (Monachon et al., 1972), was weakly active in this test.

Some experiments were carried out with phentolamine to confirm that the bradycardia produced by LSD was mediated through α-receptors. In these experiments the bradycardia to LSD (30—100 μg/kg) was reversed by 50% after a mean dose of 28 μg/kg of phentolamine (95% c.i. = 14—56; n = 6), which is not significantly different from the dose which reversed by 50% the bradycardia produced by clonidine. In contrast, cyproheptidine (0.3—3 mg/kg) did not reverse the bradycardia to LSD.

In unstimulated preparations the α-adrenoceptor antagonists had no significant effect on the resting heart rate when given at dose levels which antagonised the effects of clonidine in stimulated preparations.

3.3. Actions of antagonists at postsynaptic α-adrenoceptors

All of the α-adrenoceptor antagnoists except phenoxybenzamine produced parallel shifts to the right of the clonidine vasopressor dose—response curve. Phentolamine was the most potent. Piperoxan, yohimbine and tolazoline were similar in potency, being 3—7× less active than phentolamine. In contrast to its weak action at presynaptic α-adrenoceptors, thymoxamine was only about 10× less potent than phentolamine in antagonising the pressor responses to clonidine. Results are shown in table 2.

After phenoxybenzamine, clonidine failed to raise diastolic blood pressure by 50 mm Hg and so a dose ratio could not be calculated.

4. Discussion

The effects of α-adrenoceptor agonists and antagnosits have been examined at pre- and post-synaptic α-adrenoceptors in the pithed rat. Agonist potency at postsynaptic α-adrenoceptors was assessed from vasopressor dose—response curves and at presynaptic α-adrenoceptors from the reduction in the tachycardia produced by preganglionic cardiac sympathetic nerve stimulation.

It has previously been shown that clonidine reduces the chronotropic responses to cardiac sympathetic nerve stimulation in the rat (Armstrong and Boura, 1973) and in the dog (Robson and Antonaccio, 1974; Scriabine et al., 1970). This effect of clonidine probably results from a reduction in transmitter release during nerve stimulation (Starke et al., 1972) caused by activation of α-adrenoceptors located at the nerve terminals (Langer, 1974). This mechanism presumably accounts for the reduction in heart rate produced by the α-agonists in the present experiments, since this effect was reversed by the α-adrenoceptor antagonist phentolamine. Furthermore, the presynaptic effect of clonidine was not antagonised by dopamine, H_2 or 5HT receptor antagonists. The weak effect of methiothepin in these experiments probably reflects the α-blocking properties of this compound (Keller et al., 1973).

In the experiments reported here both agonists and antagonists showed selective effects at the pre- and post-synaptic α-receptors. Thus clonidine was approximately equipotent at pre- and post-synaptic α-adrenoceptors but LSD and BAY-1470 were more active pre- than post-synaptically. Oxymetazoline, naphazoline, methoxamine and phenylephrine were more active at post- than at pre-synaptic α-adrenoceptors.

Recently, Starke et al. (1975) showed that in the rabbit pulmonary artery in vitro, phenylephrine and methoxamine were more active at post- than at pre-synaptic α-adrenoceptors. Their results differed from those reported here by the finding that clonidine and oxymetazoline were more active at pre- than at the post-synaptic sites. The differences between the present results and those of Starke et al. remain unexplained.

The present results with LSD showed the compound to be potent in reducing heart rate but weakly active in raising blood pressure. The effect on heart rate was not antagonised by cyproheptadine, suggesting that the action was not mediated via stimulation of tryptaminergic receptors (Andén, 1968). Instead, the presynaptic effect of LSD was abolished by phentolamine, indicating that the bradycardia was mediated via presynaptic α-adrenoceptors. These results are in agreement with the findings of Hughes (1973) and Ambache et al. (1975).

With regard to the antagonists examined, thymoxamine was almost equipotent with piperoxan, yohimbine and tolazoline in antagonising the vasopressor responses to clonidine, but the same compound was about 300× less potent in antagonising the clonidine-induced bradycardia in stimulated preparations. Similarly, though it is difficult to compare with the other (competitive) antagonists, phenoxybenzamine was only weakly active in antagonising the effects of clonidine on the heart rate but markedly depressed vasopressor responses. Dubocovich and Langer (1974) found phenoxybenzamine to be about 10× less potent at pre- than at post-synaptic α-adrenoceptors in the perfused cat spleen preparation.

What, then, is the explanation for the present results? It is possible that the low potency of phenylephrine and methoxamine at presynaptic α-adrenoceptors is a reflection of their inability to gain access to those sites. It might be that presynaptic α-adrenoceptors are behind some lipid barrier which cannot be penetrated by these compounds. However, in the rabbit pulmonary artery both

adrenaline and noradrenaline are about equiactive at pre- and post-synaptic α-adrenoceptors (Starke et al., 1975). Since both compounds have poor lipid solubility at physiological pH it seems unlikely that lipid solubility is important in gaining access to presynaptic α-adrenoceptors. Whether poor access to the receptors accounts for low potency of phenoxybenzamine and thymoxamine at presynaptic sites is unknown.

Alternatively, it could be suggested that phenylephrine and methoxamine exert some additional action on heart rate which masks the bradycardia which they would otherwise cause. Blockade of the neuronal recovery (uptake$_1$) of the endogenously released transmitter might be expected to produce a tachycardia which would thus offset the bradycardia resulting from presynaptic α-adrenoceptor stimulation. Indeed, both phenylephrine and methoxamine can inhibit uptake$_1$ (Iversen, 1965). However, phenylephrine still exhibits very low potency at presynaptic α-adrenoceptors even when uptake$_1$ has already been inhibited by cocaine in both the rabbit heart (Starke, 1972) and rabbit pulmonary artery (Starke et al., 1975). Thus, it seems unlikely that inhibition of uptake$_1$ by either agonist could account for their apparent low potency at presynaptic α-adrenoceptors.

A number of α-adrenoceptor antagonists also inhibit uptake$_1$ (Iversen, 1965). However, because in the present experiments the bradycardia produced by clonidine was reversed by small doses of most of the α-adrenoceptor antagonists it seems more likely that antagonism at presynaptic α-adrenoceptors, rather than uptake$_1$ inhibition, was responsible for the effects of these compounds. However, uptake$_1$ inhibition may have been responsible, at least in part, for the effects of phenoxybenzamine, since the doses reversing the clonidine-induced bradycardia are similar to those inhibiting uptake$_1$ in vivo (Iversen and Langer, 1969). Even so, Dubocovich and Langer (1974) have demonstrated an antagonistic action of phenoxybenzamine at presynaptic α-adrenoceptors at concentrations lower than were required to inhibit neuronal uptake. If, in the present experiments, inhibition of uptake$_1$ by phenoxybenzamine did contribute to the reversal of the effects of clonidine, it could only lead to an *over*-estimate of the potency of phenoxybenzamine at presynaptic α-adrenoceptors.

Therefore, taking into account the arguments presented here the most likely explanation for the differential effects of the α-adrenoceptor agonists and antagonists at pre-synaptic α-adrenoceptors is that the receptors are different and the similarity between the present results and those of Starke et al. (1975) endorse this view. Interestingly, Delbarre and Schmitt (1971, 1973) concluded that the central α-adrenoceptors mediating sedation in chicks and mice differed from peripheral postsynaptic α-adrenoceptors. Furthermore, in the rat the α-adrenoceptors in the anterior hypothalamus show a different sensitivity to α-agonists when compared with peripheral vascular receptors (Struyker-Boudier et al., 1974).

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