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Effect of chlorpromazine on sympathetic neuroeffector transmission in the rabbit isolated pulmonary artery and aorta

[1] O.A. Nedergaard & J. Abrahamsen

Department of Pharmacology, School of Medicine, Odense University, J.B. Winsløws Vej 19, DK-5000 Odense C, Denmark

1 The effects of chlorpromazine on sympathetic neuroeffector transmission have been studied in the rabbit isolated pulmonary artery and aorta.

2 Chlorpromazine (10^{-8}–10^{-5} M), prazosin (10^{-9}–10^{-7} M) and phentolamine (3×10^{-8}–3×10^{-5} M) decreased the contractions of pulmonary artery evoked by electrical field stimulation (150 pulses; 3 Hz). The rank order of inhibitory potency (ID_{50}) was prazosin > chlorpromazine > phentolamine.

3 Rauwolscine (3×10^{-9} M–4×10^{-6} M) enhanced the neurogenic response by up to 201%. However, higher concentrations (6×10^{-6}–3×10^{-5} M) reduced the contractions evoked by transmural stimulation.

4 The inhibitory effect of prazosin (10^{-6} M) was reversible, while that of chlorpromazine (10^{-8} M) was not.

5 Chlorpromazine (10^{-8}–10^{-4} M), desmethylimipramine (3×10^{-9}–10^{-5} M), cocaine (10^{-7}–3×10^{-4} M) and phentolamine (10^{-5}–3×10^{-4} M) reduced the accumulation of [^{3}H]-noradrenaline ([^{3}H]-NA, 10^{-8} M) by aorta. The rank order of inhibitory potency (ID_{50}) was: desmethylimipramine > chlorpromazine > cocaine > phentolamine. Prazosin (10^{-7}–10^{-5} M) and rauwolscine (10^{-8}–10^{-4} M) did not reduce [^{3}H]-NA accumulation.

6 Chlorpromazine (10^{-8}–10^{-6} M) and prazosin (3×10^{-9}–10^{-7} M) antagonized the contractions of aorta evoked by exogenous noradrenaline (10^{-9}–3×10^{-4} M) and phenylephrine (10^{-9}–3×10^{-3} M). The pA_2 values for chlorpromazine on the α_1-adrenoceptors were 8.24 (noradrenaline) and 8.27 (phenylephrine). The corresponding values for prazosin were 8.64 and 8.57, respectively.

7 It is concluded that chlorpromazine and prazosin are potent inhibitors of postsynaptic α_1-adrenoceptors. Chlorpromazine and phentolamine, unlike prazosin and rauwolscine, are also inhibitors of $Uptake_1$.

Introduction

Phenothiazines have significant haemodynamic effects which may be of clinical importance (Elkyam & Frishman, 1980). Thus, chlorpromazine has been used to reduce cardiac afterload in cases of myocardial infarction with congestive heart failure (Elkyam *et al.*, 1977), in the early postoperative management of cardiac surgical patients (Stinson *et al.*, 1975), in the treatment of shock (Coppolino & Wallace, 1960; Dietzman & Lillehei, 1968; Gulotta, 1970), in the management of acute hypertensive crises (Baldini & Lincoln, 1964; Danish Multicenter Study, 1980), and in the treatment of postpartum hypertension (Cassady *et al.*, 1960). Furthermore, chlorpromazine has beneficial effects on kidneys stressed to warm ischaemia (Bilde & Dahlager, 1977) and in skin flap preservation (Jurell *et al.*, 1983; Bibi *et al.*, 1986).

Some of the effects of chlorpromazine on the cardiovascular system are due to actions on the peripheral nervous system. These include blockade of postsynaptic α-adrenoceptors (Gokhale *et al.*, 1964; Thoenen *et al.*, 1965; Morgan & Van Maanen, 1980; Asano *et al.*, 1982) and inhibition of neuronal reuptake of released transmitter (Hertting *et al.*, 1961; Axelrod *et al.*, 1962; Rosell & Axelrod, 1963; Iversen, 1965; Maxwell *et al.*, 1969). Chlorpromazine also has a direct vasodilator effect on vascular smooth muscle (Asano *et al.*, 1982). In the present work, we have studied in detail the effects of chlorpromazine on sympathetic neuroeffector transmission in isolated blood vessels and compared its effects with those of

[1]Author for correspondence.

well-known α-adrenoceptor antagonists. Rabbit isolated pulmonary artery and aorta were used.

Methods

Contractions of rabbit isolated pulmonary artery evoked by electrical-field stimulation

The method described by Husted & Nedergaard (1981) was used. The main pulmonary artery was removed rapidly from an unconscious exsanguinated rabbit (1.8–2.6 kg). The artery was divided into two rings which were suitably mounted in isolated tissue baths and maintained at 10 mN resting tension. The preparations were subjected to electrical-field stimulation (225 mA; 3 Hz; 0.5 ms; 15 min intervals) by means of a stimulator (model S48; Grass Medical Instruments, Quincy, MA, U.S.A.) in connection with a constant current unit. The isometric contractions were recorded in a standard manner by means of a force transducer (type SG 4-180; Swema, Stockholm, Sweden) connected to a pen recorder (Omnigraphic, model 3000, Houston Instrument, Houston, TX, U.S.A.). Effects of drugs added cumulatively on stimulation-evoked contractions were studied in the manner previously described (Nedergaard & Schrold, 1977).

Accumulation of [^{3}H]-noradrenaline by rabbit isolated aorta

The method described previously (Nedergaard, 1980) was used. Aortic rings (8–10) were placed in isolated tissue baths filled with 20 ml physiological salt solution (PSS). Monoamine oxidase (MAO) and catechol-*O*-methyltransferase (COMT) were blocked by pargyline (5×10^{-4} M) and U-0521 (10^{-4} M), respectively. The rings were incubated with [^{3}H]-NA (10^{-8} M) for 60 min. For experiments designed to examine the ability of a drug to alter the uptake of [^{3}H]-NA, the drug was added to the bath 30 min before [^{3}H]-NA and remained in the bath throughout the experiment. After incubation, the wet weights of the rings were determined. Each ring was treated with Protosol (0.5 ml; New England Nuclear Corp.) for 16 h at room temperature in closed scintillation vials. After addition of fluor solution to the vials, radioactivity was measured by liquid scintillation spectrometry. Aliquots (0.10 ml) of the bath fluid were also counted. The accumulation of [^{3}H]-NA is expressed as ml of fluid cleared per g of tissue (ml g^{-1}).

Determination of pA_2

Five rings of aorta (width: 4 mm) were dissected free and each was suitably mounted in an isolated tissue bath filled with 20 ml PSS at a resting tension of 20 mN. The rings were washed twice with PSS during a 1 h equilibration period. The tissues were then primed twice with noradrenaline (10^{-6} M) until a steady contractile tension response had been attained. The preparations were washed 3–4 times after each exposure to NA. At the last wash, the drug-free PSS was replaced with PSS containing cocaine plus corticosterone plus propranolol. After another equilibrium period (45 min) doses of agonists (noradrenaline or phenylephrine) were added cumulatively to the bath in steps in such a way, that 4–6 contractions were elicited in the region of 15 to 85% of the maximum obtained with a high concentration of these agonists. Additions were made whenever a steady contractile response was obtained to the preceding administration. Only one concentration-response curve was determined per preparation. Experiments designed to measure the effect of potential antagonists on the contractile response elicited by agonists were carried out in the following manner: the antagonists (chlorpromazine or prazosin) were added to the bath 30 min before the addition of the lowest concentration of agonist and maintained in the bath for the remainder of the experiment. At least 4 concentrations of each antagonist were used. The antagonists by themselves had no effect on the resting tension. Control experiments with agonists alone were carried out in the same manner. The contractile response elicited by agonists was expressed as a percentage of the maximum tension developed (mN). For each group of samples, i.e. agonist alone or agonist plus antagonist, the responses for the individual experiments in the group ranging from 15 to 85% of maximum were pooled.

The pA_2 values of chlorpromazine and prazosin against the contractions evoked by either NA or phenylephrine were determined by the method of Arunlakshana & Schild (1959).

Potassium

Rings of rabbit aorta were primed once with potassium chloride (27 mM). Then potassium chloride (55 mM) was added to evoke a maximum contraction. After repeated washes of the preparations with normal PSS, followed by an equilibration period (1 h), potassium chloride (16–55 mM) was added cumulatively. Each addition of potassium chloride to the bath usually caused an initial phasic contraction, followed by a slightly lower steady tonic response. The latter was used and expressed as a percentage of the maximum response obtained with the first addition of potassium chloride (55 mM). The antagonists (chlorpromazine or prazosin) were added as described above.

Drugs

The following drugs were used: chlorpromazine hydrochloride (Dumex Ltd., Copenhagen, Denmark); (−)-cocaine hydrochloride (Pharm. Eur.); corticosterone (Sigma Chemical Co., Saint Louis, MO, U.S.A.); desmethylimipramine hydrochloride (Dr Karl Thomae GmbH, F.R.G.); 3′,4′-dihydroxy-2-methylpropiophenone (U-0521; The Upjohn Company, Kalamazoo, MI, U.S.A.); (−)-[7-^{3}H]-noradrenaline ([^{3}H]-NA; specific activity 2.7–3.2 Ci mmol^{-1}; New England Nuclear Chemicals, Dreieichenhahn, F.R.G.); (−)-noradrenaline hydrochloride (Sigma Chemical Co.), pargyline hydrochloride (Abbott Laboratories, North Chicago, IL, U.S.A.); phentolamine hydrochloride (Ciba-Geigy AG, Basel, Switzerland); (−)-phenylephrine hydrochloride (Sigma Chemical Co.); prazosin hydrochloride (Pfizer Ltd., Sandwich, England); (−)-propranolol hydrochloride (Imperial Chemical Industries Ltd., Macclesfield, England); and rauwolscine hydrochloride (Carl Roth, Karlsruhe, F.R.G.).

Stock solutions of drugs were prepared in twice distilled water and were stored at 4°C. Concentrations are expressed as mol l^{-1}.

Salt solution

The composition of the PSS was as follows (mM); Na^+ 144.2, K^+ 4.9, Ca^{2+} 1.3, Mg^{2+} 1.2, Cl^- 126.7, HCO_3^- 25.0, SO_4^{2-} 1.2, $H_2PO_4^{2-}$ 1.2 and D-(+)-glucose 11.1. The solution also contained calcium disodium ethylenediaminetetraacetate ($CaNa_2EDTA$; 3×10^{-5} M) and L-(+)-ascorbic acid (10^{-4} M). The solution was maintained at 37.0°C, equilibrated before and during the experiments with O_2 containing 5% (v/v) CO_2 in the tissue bath, and had a pH of 7.4.

Statistical analysis

The standard t test (unpaired samples) was used to compare differences between means.

Results

Effect of chlorpromazine and α-adrenoceptor antagonists on stimulation evoked contractions

In the presence of cocaine (3×10^{-5} M) plus corticosterone (4×10^{-5} M) plus propranolol (10^{-7} M), prazosin (10^{-9}–10^{-7} M), chlorpromazine (10^{-8}–10^{-5} M), phentolamine (3×10^{-8}–3×10^{-5} M) and rauwolscine (6×10^{-6}–3×10^{-5} M) reduced the contractions of pulmonary artery evoked by electrical-field stimulation (Figure 1). The rank order of inhibitory potency (ID_{50}) was prazosin>chlorpromazine > phentolamine > rauwolscine. Rauwolscine at lower concentrations (10^{-8}–3×10^{-6} M) enhanced the neurogenic contractions (Figure 1). Prazosin (10^{-9} M), but not chlorpromazine (10^{-8} M), reduced the stimulation-evoked contractions in a reversible manner (Figure 2).

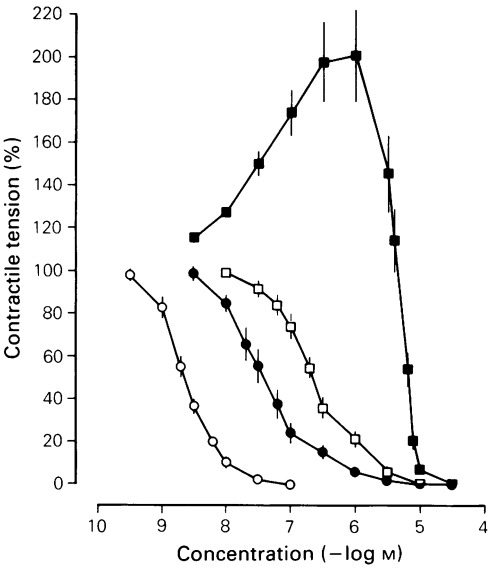

Figure 1 Inhibitory effect of chlorpromazine (●), prazosin (○), phentolamine (□) and rauwolscine (■) on stimulation-evoked contractions of rabbit isolated pulmonary artery. The contractile tension is expressed as % of the initial 'control' response. The PSS contained cocaine (3×10^{-5} M) + corticosterone (4×10^{-5} M) + propranolol (10^{-7} M). Vertical lines represent s.e.mean; $n = 6$.

Effect of chlorpromazine and various drugs on [^{3}H]-noradrenaline accumulation

Chlorpromazine (10^{-8}–10^{-4} M), desmethylimipramine (3×10^{-9}–10^{-5} M), cocaine (10^{-7}–10^{-5} M), and phentolamine (10^{-6}–3×10^{-4} M) reduced the accumulation of [^{3}H]-NA (10^{-8} M) by rabbit isolated aorta (Figure 3). The aorta was treated with pargyline (5×10^{-4} M) and U-0521 (10^{-4} M) in order to inhibit MAO and COMT, respectively. The order of inhibitory potency (ID_{50}) was desmethylimipramine > chlorpromazine = cocaine > phentolamine. Prazosin (10^{-7}–10^{-5} M) and rauwolscine (10^{-8}–10^{-4} M) did not reduce the [^{3}H]-NA accumulation.

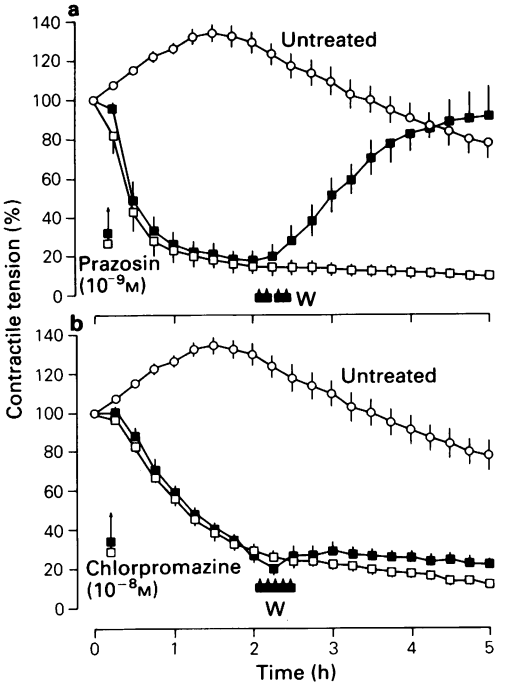

Figure 2 Reversibility of the inhibitory effect of prazosin (a) and chlorpromazine (b) on stimulation-evoked contractions of rabbit isolated pulmonary artery. The contractile tension is expressed as % of the initial 'control' response. Untreated time controls (○) are shown. Chlorpromazine and prazosin were added as indicated by the arrows and maintained in the bath for the remainder of the experiment (□) or until the artery was washed (W) several times with drug-free PSS as indicated by the arrows (■). Vertical lines represent s.e.mean; $n = 5-13$.

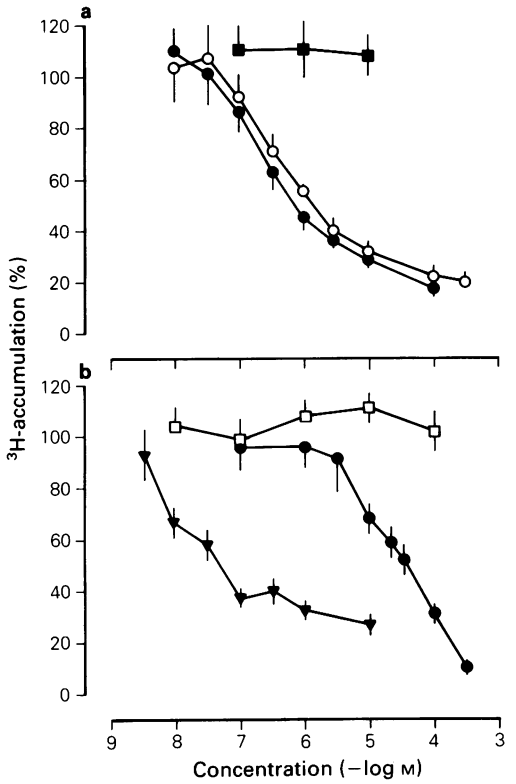

Figure 3 Effect of chlorpromazine and various drugs on the accumulation of tritium by rabbit isolated aorta incubated with [^{3}H]-noradrenaline ([^{3}H]-NA). The drugs were added to the bath 30 min before incubation with [^{3}H]-NA (10^{-8} M) for 1 h. The aorta was treated with pargyline and U-0521 (see Methods). (a) ^{3}H-accumulation in the presence of prazosin (■; $n = 6$), cocaine (○; $n = 6-12$), and chlorpromazine (●; $n = 7$). (b) ^{3}H-accumulation in the presence of rauwolscine (□; $n = 6$), phentolamine (●; $n = 8$), and desmethylimipramine (▼; $n = 8-15$). Vertical lines represent s.e.mean.

Antagonism to noradrenaline, phenylephrine and potassium

The ability of chlorpromazine and prazosin to inhibit contractions of rabbit aorta evoked by NA, phenylephrine and potassium was examined. From the concentration-response curves for NA ($10^{-9}-3 \times 10^{-4}$ M) and phenylephrine ($10^{-9}-3 \times 10^{-4}$ M) the pD_2 values were determined (Table 1). Chlorpromazine ($3 \times 10^{-8}-10^{-6}$ M) and prazosin ($3 \times 10^{-9}-10^{-7}$ M) shifted the concentration-response curves for the two agonists to the right in an apparent parallel manner (Figure 4). Plots according to Arunlakshana & Schild (1959) yielded straight lines with slopes not significantly different from −1 (Table 1). The pA_2 values demonstrated that chlorpromazine was only slightly less potent as an antagonist than prazosin (Table 1). Chlorpromazine ($3 \times 10^{-7}-10^{-5}$ M) decreased the maximal contractions evoked by potassium (16–55 mM) (Figure 5). Prazosin ($10^{-7}-10^{-5}$ M) had no effect (Figure 5).

Discussion

The present work demonstrates that chlorpromazine, prazosin and phentolamine inhibited the contractions of pulmonary artery evoked by electrical field stimulation. This confirms the effect for prazosin (Davey, 1980) and phentolamine (Borowski *et al.*, 1977; Davey, 1980).

Table 1 Antagonism between chlorpromazine or prazosin and either noradrenaline or phenylephrine in rabbit isolated pulmonary artery[a]

Agonist	pD_2[b]	*Antagonist*	pA_2	*Slope*	*Regression coefficient*	*Antagonist concentrations (M)*	n
Noradrenaline	7.35 ± 0.02	Chlorpromazine	8.24	−0.87[c]	−1.00	$3 \times 10^{-8}, 10^{-7}, 3 \times 10^{-7}, 10^{-6}$	6
	7.29 ± 0.03	Prazosin	8.64	−0.92[c]	−1.00	$3 \times 10^{-9}, 10^{-8}, 3 \times 10^{-8}, 10^{-7}$	6
Phenylephrine	6.36 ± 0.03	Chlorpromazine	8.27	−0.78[c]	−0.98	$3 \times 10^{-8}, 10^{-7}, 3 \times 10^{-7}, 10^{-6}$	8–9
	6.23 ± 0.03	Prazosin	8.54	−0.83[c]	−1.00	$3 \times 10^{-9}, 10^{-8}, 3 \times 10^{-8}, 10^{-7}$	6

[a] The PSS contained cocaine (3×10^{-5} M) + corticosterone (4×10^{-5} M) + propranolol (10^{-7} M).
[b] Mean values ± s.e.mean in the absence of antagonists.
[c] Not significantly ($P > 0.05$) different from −1 as determined by Student's *t* test.

The chlorpromazine-induced inhibition of the neurogenic contractions is probably due mainly to a blockade of postsynaptic α_1-adrenoceptors. Chlorpromazine is a potent α_1-adrenoceptor antagonist (see below) and the excitatory adrenoceptors in smooth muscle of the pulmonary artery are α_1-adrenoceptors (Docherty & Starke, 1981). At chlorpromazine concentrations of 3×10^{-7} M and higher, a direct action on smooth muscle also may have contributed to the block, since chlorpromazine at these concentrations antagonized the potassium-evoked contractions of rabbit isolated aorta (Figure 5).

Rauwolscine is a stereoisomer of yohimbine which is a local anaesthetic with about the same potency as cocaine (Bowman & Rand, 1980). It is unlikely that the rauwolscine-induced inhibition of the stimulation-evoked contractions (Figure 1) was due to a presynaptic local anaesthetic action whereby the transmitter release would be decreased. This view is supported by the observation that rauwolscine in a concentration which caused complete blockade of the neurogenic contractions, enhanced the ^{3}H-overflow from the pulmonary artery preloaded with [^{3}H]-NA (unpublished data).

Rauwolscine is considered to be an α-adrenoceptor antagonist on postsynaptic receptors (Nickerson, 1949; Kohli *et al.*, 1957). Weitzell *et al.* (1979) assumed that rauwolscine reduced the stimulation-evoked contractions of rabbit pulmonary artery by blockade of postsynaptic α-adrenoceptors. Evidence has been obtained to suggest that some blood vessels contain two subtypes of postsynaptic α-adrenoceptors, namely α_1 and α_2 (Docherty *et al.*, 1979; Timmermans *et al.*, 1979; Starke 1981; McGrath, 1982; Langer & Shepperson, 1982; De Jonge *et al.*, 1986). It has been established that the postjunctional α-adrenoceptor of rabbit pulmonary artery is purely of the α_1-subtype (Docherty & Starke, 1981). Although rauwolscine is considered to be a rather selective α_2-adrenoceptor antagonist (Starke, 1981; McGrath, 1982), it is most likely that the inhibition of the stimulation-evoked contractions of the pulmonary artery seen with high concentrations of rauwolscine (Figure 1) is due to inhibition of postsynaptic α_1-adrenoceptors. This is supported by the fact that rauwolscine has a postjunctional α_1-adrenoceptor pA_2 value of approximately 6 in rabbit pulmonary artery (Weitzell *et al.*, 1979) and other tissues (McGrath, 1984).

Rauwolscine in low concentrations enhanced the contractions of the pulmonary artery evoked by sympathetic nerve stimulation, which confirms the finding obtained with the same tissue (Weitzell *et al.*, 1979). The enhancement is no doubt due to an inhibition of presynaptic α_2-adrenoceptors causing a facilitation of stimulation-evoked release of transmitter which was quite marked, probably as a result of the fact that neuronal and extraneuronal uptake of trans-

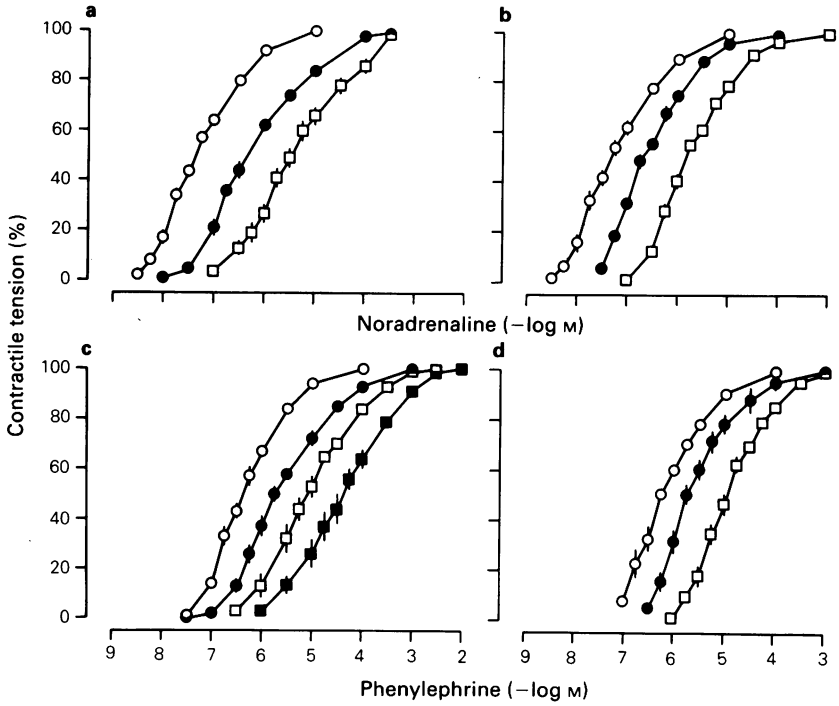

Figure 4 Inhibitory effect of chlorpromazine and prazosin on contractions of rabbit aorta evoked by noradrenaline and phenylephrine. The contractile tension is expressed as a percentage of the maximal tension developed by using a high concentration of the agonist. The PSS contained cocaine (3×10^{-5} M) + corticosterone (4×10^{-5} M) + propranolol (10^{-7} M). Data from these curves were used in the pA_2 determinations (Table 1). Only representative curves are shown. Responses to noradrenaline or phenylephrine alone (control) (○). (a) Effect of chlorpromazine: 10^{-7} M (●), 10^{-6} M (□). (b) Effect of prazosin: 10^{-8} M (●), 10^{-7} M (□). (c) Effect of chlorpromazine: 3×10^{-8} M (●), 3×10^{-7} M (□), 10^{-6} M (■). (d) Effect of prazosin: 10^{-8} M (●), 10^{-7} M (□). Vertical lines represent s.e.mean; $n = 6-9$.

mitter had been inhibited by cocaine and corticosterone, respectively. This is supported by the observation that rauwolscine in the same concentration range enhanced the stimulation-evoked release of [^{3}H]-NA release in the rabbit pulmonary artery (Weitzell *et al.*, 1979; Nedergaard, 1986).

Chlorpromazine reduced the accumulation of ^{3}H by aorta preloaded with [^{3}H]-NA. This is consistent with previous reports that chlorpromazine reduces the uptake of [^{3}H]-NA *in vivo*: cat heart, spleen and adrenal glands (Hertting *et al.*, 1961; Axelrod *et al.*, 1962), and rat heart (Rosell & Axelrod, 1963) as well *in vitro*: rat heart (Iversen, 1965), rabbit aorta (Maxwell *et al.*, 1969), rat brain synaptosomes (Richelson & Pfenning, 1984), and squid brain synaptosomes (Pollard *et al.*, 1975).

The chlorpromazine-induced reduction in accumulation of [^{3}H]-NA is probably primarily due to an inhibition of the $Uptake_1$ transport mechanism. This is supported by the findings that chlorpromazine reduced the formation of [^{3}H]-DOPEG in the stimulation-evoked ^{3}H-overflow from rabbit aorta preloaded with [^{3}H]-NA (Nedergaard & Abrahamsen, 1987). Evidence has accumulated to support the view (Langer, 1974) that [^{3}H]-DOPEG in stimulation-evoked ^{3}H-overflow is formed intraneuronally after re-uptake of released [^{3}H]-NA. Thus, the well-known $Uptake_1$ inhibitor, cocaine, decreased [^{3}H]-DOPEG overflow (Langer & Enero, 1974; Borowski *et al.*, 1977; Endo *et al.*, 1977; Schrold & Nedergaard, 1979).

Chlorpromazine inhibited the uptake of catecholamines in isolated storage granules from bovine adrenal medulla (Carlsson *et al.*, 1963). It is possible that inhibition of the granule membrane pump to a small degree also may have contributed to the reduction in accumulation of [^{3}H]-NA seen in the present study.

Chlorpromazine was equipotent with cocaine in

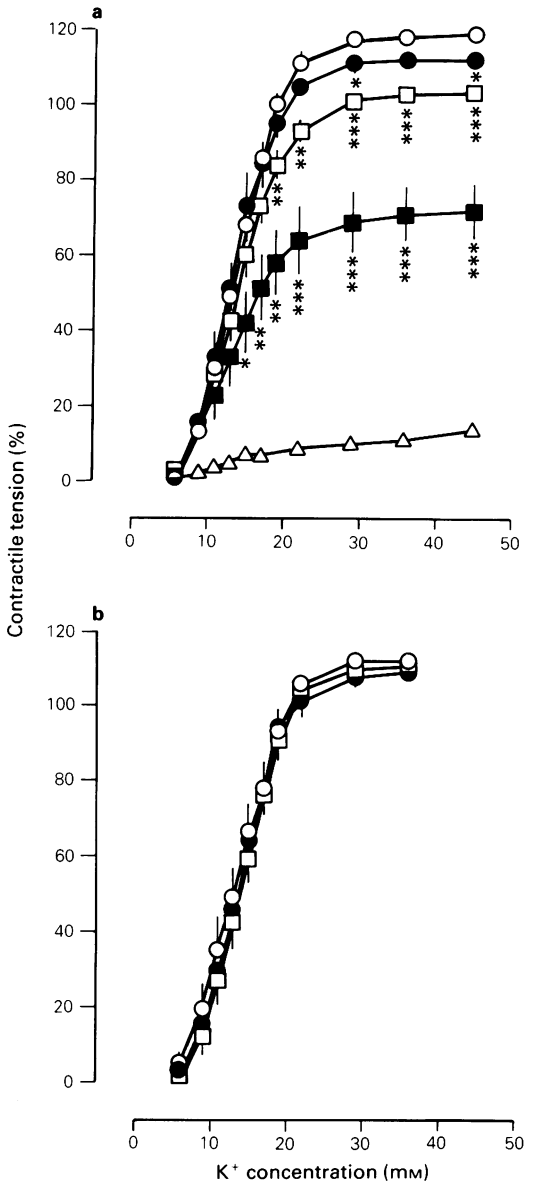

Figure 5 Effects of chlorpromazine and prazosin on contractions of rabbit isolated aorta evoked by potassium. The ordinate scales represent contractile tension expressed as a percentage of an initial maximum response to potassium chloride (55 mM) before construction of the cumulative curves. Responses to potassium alone (control) (○). (a) Responses to potassium in the presence of chlorpromazine: 3×10^{-7} M (●), 10^{-6} M (□), 3×10^{-6} M (■), 10^{-5} M (△). (b) Responses to potassium in the presence of prazosin: 10^{-6} M (●), 10^{-5} M (□). For the sake of clarity, the results for 10^{-7} M prazosin are not shown. Vertical lines represent s.e.mean; $n = 6-7$.

reducing the accumulation of [^{3}H]-NA by aorta. The inhibitory effect of cocaine is considered to be due to a selective action on the Uptake$_1$ transport mechanism in the plasmalemma. Only at high concentrations of cocaine may the local anaesthetic property of this amine possibly contribute to the inhibition. This is most likely also the case with chlorpromazine although it is a much more potent local anaesthetic than cocaine (Seeman, 1972). Thus, the nerve-blocking concentration in frog sciatic nerve is 10^{-5} M for chlorpromazine (Seeman, 1972) and 2.6×10^{-3} M for cocaine (Skou, 1954). However, at a concentration (10^{-5} M) where chlorpromazine caused a 75% reduction in [^{3}H]-NA accumulation (present work), it enhanced the stimulation-evoked ^{3}H-overflow from rabbit pulmonary artery preloaded with [^{3}H]-NA (unpublished data).

Phentolamine is an inhibitor of Uptake$_1$ (Starke *et al.*, 1971), but not of Uptake$_2$ (Cole & O'Donnell, 1982) and in rather high concentrations this drug reduces the accumulation of [^{3}H]-NA by rat brain slices (Schlicker *et al.*, 1983). On the other hand, phentolamine did not change amine uptake by the nictitating membrane of the cat (Langer & Trendelenburg, 1969). The inhibition of ^{3}H accumulation by aorta preloaded with [^{3}H]-NA (Figure 3) is most likely due to a blockade of the Uptake$_1$ transport mechanism.

Neither prazosin nor rauwolscine reduced the accumulation of [^{3}H]-NA by aorta (Figure 3). This indicates that these α-adrenoceptor antagonists do not interfere with the Uptake$_1$ mechanism.

Chlorpromazine and prazosin antagonized the contractions of aorta evoked by noradrenaline and phenylephrine in a competitive manner. Similar results were obtained with chlorpromazine in dog femoral artery (Morgan & Van Maanen, 1980) and rabbit aorta (Gokhale *et al.*, 1964; Asano *et al.*, 1982), and with prazosin in dog mesenteric artery, femoral artery and vein (Davey, 1980), rat blood vessels (Cohen *et al.*, 1979), rat mesenteric artery (McPherson *et al.*, 1984), rabbit pulmonary artery (Cambridge *et al.*, 1980), rabbit ear artery and saphenous vein (Purdy *et al.*, 1980) and human arteries (Jauernig *et al.*, 1978), human omental arteries and veins (Steen *et al.*, 1984; Skärby & Andersson, 1984) and human temporal artery (Skärby & Andersson, 1984). The antagonism indicates that chlorpromazine is a highly selective inhibitor of postsynaptic α_1-adrenoceptors. This is supported by the following: (1) Rabbit aorta contains only α_1-adrenoceptors (Docherty *et al.*, 1981); (2) phenylephrine is a selective α_1-adrenoceptor agonist (Drew & Whiting, 1979); and (3) the pA_2 values obtained with chlorpromazine were very similar to those seen with the highly selective α_1-adrenoceptor antagonist prazosin (Doxey *et al.*, 1977) (cf. Table 3).

The pA_2 values for chlorpromazine obtained in the

Table 2 pA_2 values for chlorpromazine against noradrenaline (NA), adrenaline (Ad) and phenylephrine (PE) in isolated tissues

Species	*Tissue*	*Agonist*	*pA_2*	*Reference*
Dog	Femoral artery	NA	9.04	Morgan & Van Maanen, 1980
		PE	8.83	
Rabbit	Fundus	PE	8.96	Ruffolo & Patil, 1978
Rabbit	Aorta	NA	14.12	Gokhale *et al.*, 1964
		Ad	14.0	
Rabbit	Aorta	NA	8.24	Present work
		PE	8.27	

Table 3 pA_2 values for prazosin against noradrenaline (NA) and phenylephrine (PE) in isolated blood vessels

Species	*Tissue*	*Agonist*	*pA_2*	*Reference*
Rat	Aorta	NA	10.99	Decker *et al.*, 1984
	Aorta	PE	10.20	*Ibid.*, 1984
	Aorta	PE	9.60	Digges & Summers, 1983
	Portal vein	PE	8.17	*Ibid.*, 1983
	Mesenteric artery	PE	9.88	Agrawal *et al.*, 1984
	Mesenteric artery	NA	9.89	Cohen *et al.*, 1980
	Mesenteric artery	NA	8.52	McPherson *et al.*, 1984
Guinea-pig	Aorta	PE	9.0	Ennis & Cox, 1980
	Aorta	NA	9.09	Grundström *et al.*, 1981
Rabbit	Aorta	PE	8.64	Awad *et al.*, 1983
	Aorta	NA	8.59	Cavero *et al.*, 1978
	Aorta	PE	8.4	Docherty & Starke, 1981
	Aorta	PE	8.4	Docherty *et al.*, 1982
	Aorta	NA	8.64	Present work
		PE	8.57	
	Portal vein	PE	8.2	Docherty & Starke, 1981
	Pulmonary artery	NA	8.38	Cambridge *et al.*, 1980
	Pulmonary artery	PE	8.6	Docherty & Starke, 1981
	Renal artery	NE	7.22	Dalrymple *et al.*, 1981
	Renal artery	PE	7.6	*Ibid.*, 1981
Cat	Lingual artery	NA	8.76	Skärby *et al.*, 1983
	Mesenteric artery	NA	8.70	*Ibid.*, 1983
Dog	Coronary artery	PE	8.6	Rimele *et al.*, 1983
	Femoral artery	NA	8.48	Davey, 1980
	Femoral artery	NA	7.9	De Mey & Vanhoutte, 1981
	Femoral vein	NA	8.50	Davey, 1980
	Mesenteric artery	NA	8.60	*Ibid.*, 1980
	Mesenteric artery	NA	8.4	Muramatsu *et al.*, 1983
	Mesenteric artery	NA	8.65	Toda, 1983
	Saphenous artery	NA	8.3	Müller-Schweinitzer, 1983
	Saphenous vein	NA	7.94	*Ibid.*, 1983
	Saphenous vein	NA	8.48	Sullivan & Drew, 1980
	Saphenous vein	PE	8.15	*Ibid.*, 1980
	Saphenous vein	NA	8.00	Shoji *et al.*, 1983
	Portal vein	NA	8.54	Shoji *et al.*, 1983
	Splenic artery	NA	7.9	De Mey & Vanhoutte, 1981
Monkey	Mesenteric artery	NA	9.08	Toda, 1983
Homo sapiens	Femoral artery	NA	7.96	Glusa & Markwardt, 1983
	Temporal artery	NA	9.21	Skärby & Andersson, 1984
	Omental artery	NA	9.45	*Ibid.*, 1984
	Omental artery	NA	9.48	Steen *et al.*, 1984
	Omental vein	NA	9.72	*Ibid.*, 1984
	Epigastric artery	NA	9.17	Sjöberg *et al.*, 1987

present work are slightly less than those obtained with the dog femoral artery (Morgan & Van Maanen, 1980) and rabbit fundus (Ruffolo & Patil, 1978) and considerably lower than those obtained by Gokhale *et al.* (1964) using rabbit aorta (Table 2). In contrast to our work, none of the other authors used inhibitors to decrease removal of agonists by neuronal- and extraneuronal uptake. This may in part explain the slight difference between our results and those obtained with dog femoral artery and rabbit fundus. The extremely high pA_2 value reported for rabbit aorta by Gokhale *et al.* (1964) is very surprising and no ready explanation is at hand for this considerable difference.

Chlorpromazine is reportedly a selective calmodulin antagonist (Levin & Weiss, 1979). At chlorpromazine concentrations of 3×10^{-7} M and 10^{-6} M, the purported inhibition of calmodulin may conceivably have played a minor role in the chlorpromazine-induced shift of the NA and phenylephrine concentration-response curves to the right. This view gains support from the finding that chlorpromazine (3×10^{-7} M and higher) decreased the potassium-evoked contractions of rabbit aorta (Figure 5). On the other hand, Asano *et al.* (1982) concluded that the inhibitory effect of 10^{-6} M chlorpromazine on NA-induced contractions of rabbit aorta was due to a specific action against α-adrenoceptors. At a higher concentration, 10^{-4} M, the observed inhibitory effect of chlorpromazine may in their view reflect the interaction with intracellular calmodulin. The highest concentration of chlorpromazine used in the present antagonism study was 10^{-6} M (Table 1).

The present pA_2 values for prazosin are in good accord with those determined in rabbit aorta and in several blood vessels in the rabbit, cat, dog and man (Table 3). However, both higher and lower values have been determined in several blood vessels (Table 3). It has recently been suggested on the basis of affinity studies that there appear to be two subtypes of α_1-adrenoceptor in vascular smooth muscle of blood vessels (Flavahan & Vanhoutte, 1986; 1987). On the other hand, Docherty (1987) states that the evidence in favour of a subclassification is equivocal and that the proposal by Flavahan & Vanhoutte (1986) is premature. This controversy needs to be resolved before a clear-cut interpretation can be made with regard to the differences between the present pA_2 values for rabbit aorta and the high values reported for some blood vessels (cf. Table 3). In order to make a proper comparison of pA_2 values for different tissues, it seems important that the experiments are carefully controlled and carried out under the optimal conditions as described by Furchgott (1972) for this type of receptor analysis.

Our results are in agreement with the view that prazosin is a highly selective α_1-adrenoceptor antagonist (Stokes, 1984). According to Constantine *et al.* (1973), prazosin has a direct relaxant action on smooth muscle. The failure of prazosin to alter the potassium-evoked contractions (Figure 5) indicates that this is not the case for rabbit aorta. A similar conclusion was reached for the rabbit ear artery (Purdy *et al.*, 1980).

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