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THE EFFECT OF PRAZOSIN ON THE GUINEA-PIG ILEUM

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1 The α-adrenoceptor blocking activity of prazosin was compared with that of phentolamine, yohimbine and phenoxybenzamine in the guinea-pig isolated ileum.

2 Phentolamine (2.56×10^{-8} to 2.56×10^{-6} M) and yohimbine (5.12×10^{-8} to 5.12×10^{-6} M) antagonized the sympathetic inhibition of twitches induced by transmural stimulation, whereas prazosin (5.28×10^{-8} to 5.28×10^{-6} M) and phenoxybenzamine (4.2×10^{-9} to 4.2×10^{-7} M) had no effect.

3 Phentolamine, yohimbine, prazosin and phenoxybenzamine antagonized the relaxant response of the ileum to periarterial nerve stimulation and to exogenous noradrenaline in the absence of transmural stimulation.

4 The pA_2 value for phentolamine against noradrenaline in the transmurally-stimulated gut (presynaptic α-adrenoceptor site; 8.17 ± 0.04) was significantly different from that in the non-stimulated gut (postsynaptic α-adrenoceptor site; 6.88 ± 0.12).

5 Phentolamine and prazosin probably block noradrenaline responses at the same α-adrenoceptor site on the postsynaptic membrane.

Introduction

The antihypertensive drug, prazosin, brings about a blockade of α-adrenoceptors which is thought to be different from that caused by conventional α-adrenoceptor blocking agents (Constantine, 1974). Similarly, unlike conventional α-adrenoceptor blocking agents, prazosin does not cause tachycardia or renin release in dogs (Constantine, McShane, Scriabine & Hess, 1973; Massingham & Hayden, 1975).

In the light of the knowledge that α-adrenoceptors are located on the cholinergic nerve terminals in the guinea-pig ileum and that activation of these α-adrenoceptors reduces acetylcholine released from the cholinergic nerve terminals (Vizi, 1968; Paton & Vizi, 1969; Knoll & Vizi, 1971; Kosterlitz & Lees, 1972), we decided to compare the effects of prazosin with those of phentolamine, yohimbine and phenoxybenzamine on the pre- and postsynaptic α-adrenoceptors in the guinea-pig ileum.

Methods

Guinea-pigs of either sex weighing 400 to 600 g and bred locally in the departmental animal house were used. They were killed by a blow to the head followed by exsanguination and 3 cm lengths of the proximal ileum were removed 6 to 20 cm from the duodenojejunal junction.

Each segment was mounted vertically in a 70 ml organ bath under a tension of 1 g and changes in tension were recorded with a Devices strain gauge transducer connected to a Devices F- 132 physiopolygraph. The bath fluid was aerated Tyrode solution maintained at 37°C and having the following composition (mM): NaCl 138, KCl 5.7, $CaCl_2$ 1.8, $MgCl_2$ 1.1, $NaHCO_3$ 1.5, NaH_2PO_4 0.36 and glucose 5.0. Added to the Tyrode solution were cocaine (3×10^{-5} M), corticosterone (1×10^{-5} M) and propranolol (4×10^{-6} M). Agonist drugs were diluted in saline (0.9% w/v NaCl solution) and added to the bath fluid in volumes of 0.1 or 0.2 ml. In experiments involving antagonists, the antagonist drugs were added to the bath fluid reservoir to obtain the desired concentrations. There was a contact time of 30 min for antagonists before starting experimental tests and the antagonist remained in contact with the tissue during the test periods.

Simultaneous transmural and periarterial stimulation

Twitches of the guinea-pig ileum were obtained by transmural stimulation as described by Paton (1955) using supramaximal square pulses of 30 V, 0.125 Hz and 1 ms duration. After the amplitude of the twitches had become steady, the effect on them of simultaneous stimulation of the periarterial sympathetic

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nerves (10 V, 0.3 ms) was determined at intervals. Three frequencies of sympathetic stimulation were used (10, 30 and 50 Hz) and a total of 750 pulses was delivered at each frequency. In a series of experiments, the sympathetic stimulation was performed before and after the addition of various concentrations of phentolamine, yohimbine, prazosin and phenoxybenzamine.

Interaction of noradrenaline with α-adrenoceptor antagonists in the transmurally stimulated ileum

Transmurally evoked contractions of the guinea-pig ileum were inhibited by adding cumulative doses of noradrenaline to the bath. Each dose was allowed to act until a steady level of inhibition was established, before the addition of the next dose. Maximum response was assumed to be reached when three successive doses failed to produce further inhibition. This procedure was repeated in the presence of various concentrations of prazosin, phentolamine, yohimbine and phenoxybenzamine.

Perarterial stimulation without transmural stimulation

The periarterial nerves of pieces of ileum suspended in Tyrode solution were stimulated with square pulses (10 V, 0.3 ms) at 5, 10, 20, 30 and 50 Hz for 150, 75, 37.5, 25 and 15 s respectively. After obtaining the frequency-response curve, the experiment was repeated in the presence of various concentrations of prazosin, phentolamine, yohimbine and phenoxybenzamine.

Interaction of noradrenaline with phentolamine, yohimbine, prazosin and phenoxybenzamine in the non-stimulated ileum

Cumulative doses of noradrenaline were added to the bath fluid containing proximal ileum until maximum relaxation was attained. This procedure was repeated in the presence of various concentrations of phentolamine, prazosin, yohimbine, phenoxybenzamine and a combination of phentolamine and prazosin. In all experiments, the agonist was added for a period sufficient to ensure that the response to the administered concentration of the drug reached its maximum. A contact time of 1 min was found to be adequate for noradrenaline. In experiments in which the combined effect of phentolamine and prazosin was studied, the two antagonists were added to the bath fluid reservoir to obtain the required individual concentrations.

Dose-ratio determinations

Dose-ratios were obtained by estimating the concentrations of agonist producing 50% maximum relaxant responses in the absence and presence of the antagonists; 100% response was the maximum response attained by the tissue in the absence of antagonist. The pA_2 and pA_{10} of the antagonist were estimated from the regression line drawn for each experiment.

Statistical analysis of results

Results are given in the text and Tables as means ± s.e. means. The significance of differences between sets of data was assessed by Student's t test and probability levels less than 0.05 were taken to indicate significant differences between group means.

Drugs

Drugs used were: (−)-noradrenaline bitartrate (Sigma), phentolamine mesylate (CIBA), cocaine hydrochloride (B.P.), corticosterone (Sigma), phenoxybenzamine hydrochloride (SK&F), yohimbine hydrochloride (Sigma), (±)-propranolol (ICI) and prazosin hydrochloride (Pfizer).

Results

Twitches of the guinea-pig ileum induced by transmural stimulation were inhibited by simultaneous stimulation of the periarterial sympathetic nerves. This inhibition by periarterial nerve stimulation was frequency-dependent (Figure 1). In the presence of phentolamine (2.56×10^{-8} to 2.56×10^{-6} M) and yohimbine (5.12×10^{-8} to 5.12×10^{-6} M), the height of the transmurally evoked twitches was unchanged but the inhibition of the twitches by sympathetic stimulation was antagonized (Figure 1, a and b). Phenoxybenzamine (4.2×10^{-9} to 4.2×10^{-8} M) and prazosin (5.28×10^{-8} to 5.28×10^{-6} M) similarly had no effect on the transmurally evoked twitches, but at these concentrations these drugs also failed to antagonize the sympathetically induced inhibition of the twitches (Figure 1, c and d). Phenoxybenzamine, 4.2×10^{-7} M, depressed the transmurally induced twitches of the ileum by 10 to 15% but failed to antagonize the sympathetically-induced inhibition of the twitches.

Like sympathetic stimulation, noradrenaline also inhibited the twitches of the guinea-pig ileum induced by transmural stimulation. The effect of noradrenaline was dose-dependent and was antagonized by phentolamine (2.56×10^{-8} to 2.56×10^{-7} M) and yohimbine (5.12×10^{-8} to 5.12×10^{-6} M) but not by prazosin (5.28×10^{-8} to 5.28×10^{-6} M) and phenoxybenzamine (4.2×10^{-9} to 4.2×10^{-7} M) (Figure 2). Analysis of the antagonism of noradrenaline by phentolamine and yohimbine by the method of Arunlakshana & Schild (1959) gave the pA_2 values and slopes

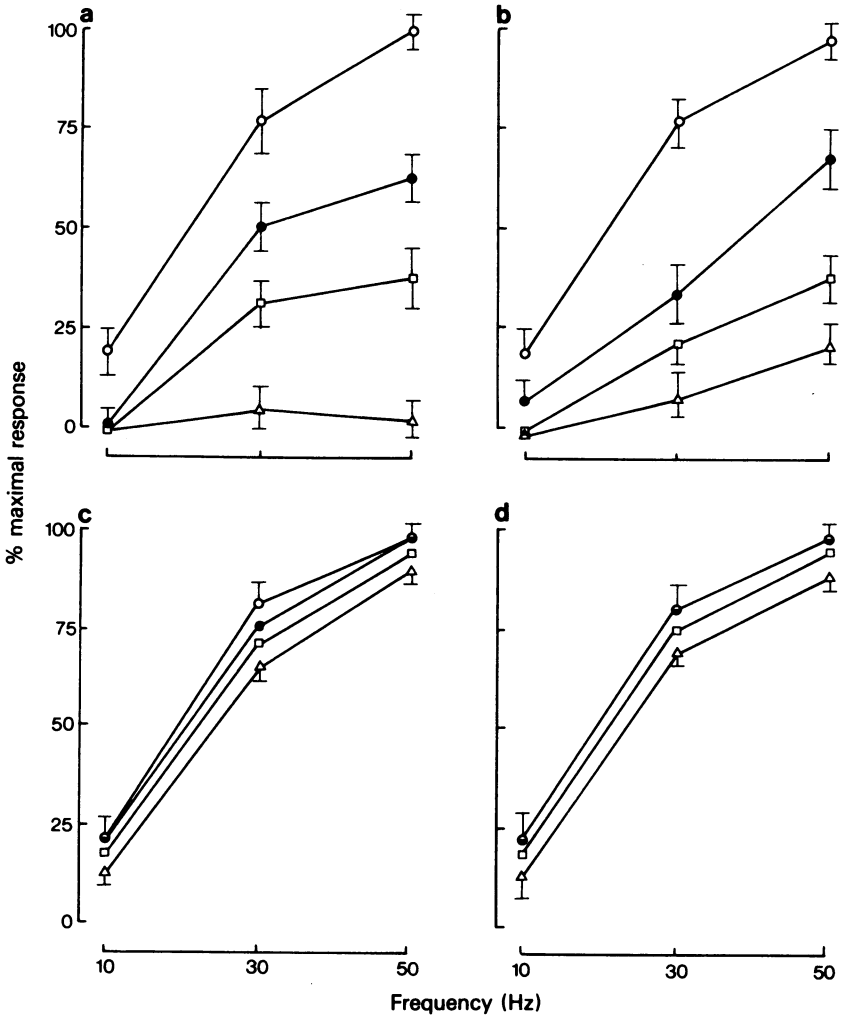

Figure 1 Inhibition of transmurally evoked twitches of the guinea-pig ileum by periarterial sympathetic stimulation at 10, 30 and 50 Hz in the presence and absence of (a) phentolamine, (b) yohimbine, (c) phenoxybenzamine and (d) prazosin. (○) No antagonist; (●) phentolamine (2.56×10^{-8} M) or yohimbine (5.12×10^{-8} M) or phenoxybenzamine (4.2×10^{-9} M) or prazosin (5.28×10^{-8} M); (□) phentolamine (2.56×10^{-7} M) or yohimbine (5.12×10^{-7} M) or phenoxybenzamine (4.2×10^{-8} M) or prazosin (5.28×10^{-7} M); (△) phentolamine (2.56×10^{-6} M) or yohimbine (5.12×10^{-6} M) or phenoxybenzamine (4.2×10^{-7} M) or prazosin (5.28×10^{-6} M). Values are mean of 6 experiments. Vertical bars show s.e. mean.

Table 1 The pA_2 and slope of phentolamine and yohimbine on noradrenaline-induced inhibition of neurally evoked contractions of the guinea-pig ileum

Antagonist	*Phentolamine*	*Yohimbine*
pA_2	8.17 ± 0.04	8.15 ± 0.05
Slope	0.96 ± 0.04	0.95 ± 0.05

Values are mean ± s.e. mean; $n = 6$.

shown in Table 1, suggestive of a competitive antagonism.

Stimulation of the periarterial nerve without simultaneous transmural stimulation produced a frequency-dependent relaxation of the ileum. The relaxation was preceded by contraction in the case of stimulation at 5 and 10 Hz. This sympathetically-induced relaxation of the ileum was partially inhibited by prior treatment with phentolamine (7.16×10^{-8} to 7.16×10^{-6} M), yohimbine (5.12×10^{-8} to

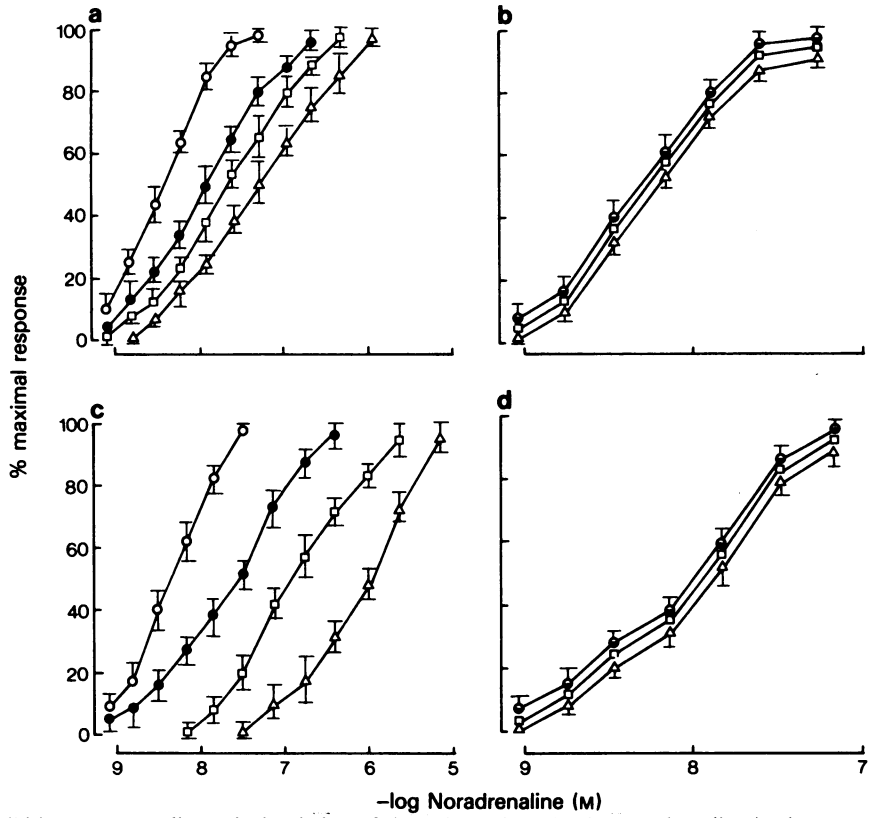

Figure 2 Inhibition transmurally evoked twitches of the guinea-pig ileum by noradrenaline in the presence and absence of (a) phentolamine, (b) prazosin, (c) yohimbine and (d) phenoxybenzamine. (○) No antagonist; (●) phentolamine (2.56×10^{-8} M) or prazosin (5.28×10^{-8} M) or yohimbine (5.12×10^{-8} M) or phenoxybenzamine (4.2×10^{-9} M); (□) phentolamine (5.12×10^{-8} M) or prazosin (5.28×10^{-7} M) or yohimbine (5.12×10^{-7} M) or phenoxybenzamine (4.2×10^{-8} M); (△) phentolamine (2.56×10^{-7} M) or prazosin (5.28×10^{-6} M) or yohimbine (5.12×10^{-6} M) or phenoxybenzamine (4.2×10^{-7} M). Values are mean of 6 experiments. Vertical bars show s.e. mean.

5.12×10^{-6} M), prazosin (5.28×10^{-8} to 5.28×10^{-6} M) and phenoxybenzamine (5.88×10^{-9} to 5.88×10^{-7} M) (Figure 3).

Noradrenaline added to the bath fluid produced graded relaxation of the ileum which was antagonized by phentolamine (3.58×10^{-7} to 3.58×10^{-6} M), prazosin (3.77×10^{-7} to 3.77×10^{-6} M), yohimbine (2.56×10^{-7} to 2.56×10^{-6} M) and phenoxybenzamine (2.94×10^{-9} to 2.94×10^{-8} M) (Figure 4). Plots of the noradrenaline log (dose-ratio − 1) against the negative log molar concentrations of phentolamine, prazosin and yohimbine (Arunlakshana & Schild, 1959) gave regression lines with slopes and horizontal intercepts (pA_2) shown in Table 2. The pD'_2 (the negative logarithm of the antagonist concentration required to produce one-half maximum blockade, Ariens & Van Rossum, 1957; Nickerson, 1957) for phenoxybenzamine was 7.12 ± 0.42 ($n = 6$).

In order to test whether the observed $pA_2 - pA_{10}$ values were significantly different from the theoretical value of 0.95 (Arunlakshana & Schild, 1959) necessary to support a competitive antagonism, the method of Marshall (1955) was used: the theoretical value of $pA_2 - pA_{10}$ (0.95) was added to each of the pA_{10} values and then using Student's t test, it was determined whether the sums differed from the observed pA_2 values. The difference between the pA_2 values for phentolamine, yohimbine and prazosin and the sums were not statistically significant ($P > 0.05$, Table 2).

From the observed similarity between the pA_2 values for phentolamine and prazosin, the question arose as to whether these two antagonists were acting at the same site on the receptor or at different sites as previously suggested by Constantine (1974). If prazosin and phentolamine were acting at the same locus to produce their effect, then the antagonism produced in

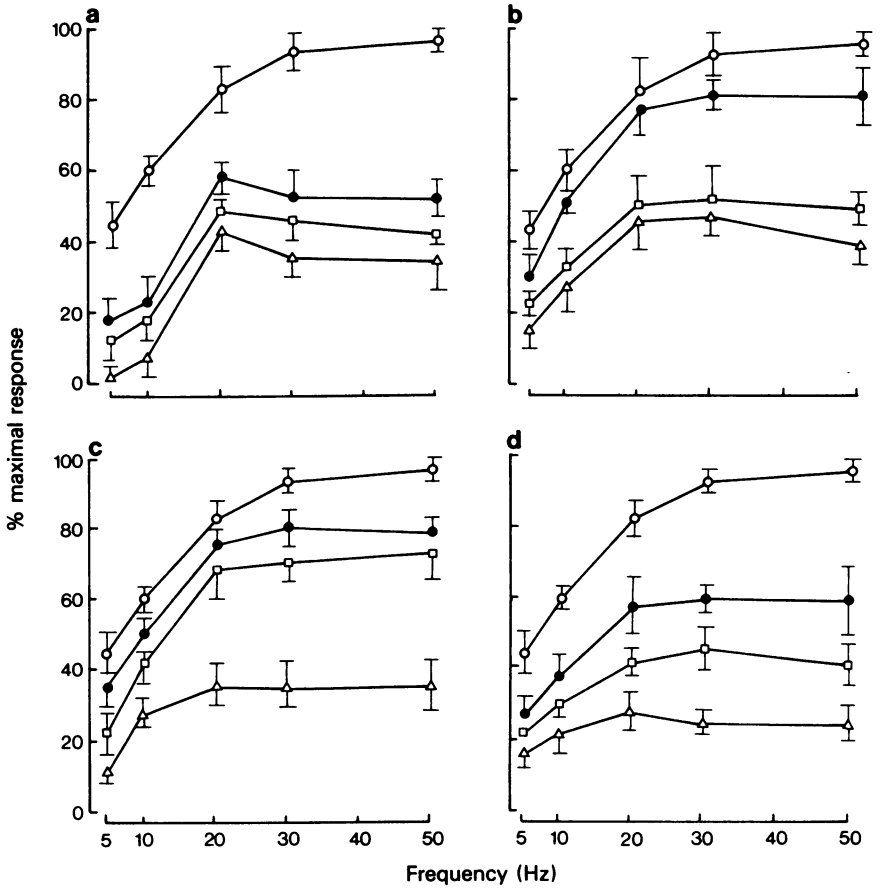

Figure 3 Relaxation of the guinea-pig ileum induced by stimulating the periarterial sympathetic nerves at 5, 10, 20, 30 and 50 Hz in the presence and absence of (a) phentolamine, (b) yohimbine, (c) prazosin and (d) phenoxybenzamine. (○) No antagonist; (●) phentolamine (7.16×10^{-8} M) or yohimbine (5.12×10^{-8} M) or prazosin (5.28×10^{-8} M) or phenoxybenzamine (5.88×10^{-9} M); (□) phentolamine (7.16×10^{-7} M) or yohimbine (5.12×10^{-7} M) or prazosin (5.28×10^{-7} M) or phenoxybenzamine (5.88×10^{-8} M); (△) phentolamine (7.16×10^{-6} M) or yohimbine (5.12×10^{-6} M) or prazosin (5.28×10^{-6} M) or phenoxybenzamine (5.88×10^{-7} M). Values are mean of 6 experiments. Vertical bars show s.e. mean.

the presence of both antagonists should be approximately additive.

The equilibrium dose ratio, DR_{AB}, when two competitive antagonists (A and B) are used together is equal to $DR_A + DR_B - 1$ where DR_A and DR_B are the dose-ratios obtained for antagonists A and B respectively, when the same concentrations of the antagonists are given separately (Paton & Rang, 1965). If however, one acts at either a point more distal to the receptor than the other or at a different site on the

Table 2 The pA_2 of prazosin, yohimbine and phentolamine against noradrenaline in the guinea-pig ileum

Antagonist	pA_2	*Slope*	pA_{10}	$pA_2 - pA_{10}$	$pA_{10} + 0.95$
Prazosin	6.26 ± 0.08	1.12 ± 0.06	5.44 ± 0.14	0.82 ± 0.04	6.39 ± 0.13
Phentolamine	6.88 ± 0.12	0.96 ± 0.04	5.78 ± 0.16	1.10 ± 0.02	6.73 ± 0.15
Yohimbine	6.51 ± 0.12	0.92 ± 0.05	5.49 ± 0.12	1.02 ± 0.02	6.44 ± 0.13

Values are mean ± s.e. mean; $n = 6$.

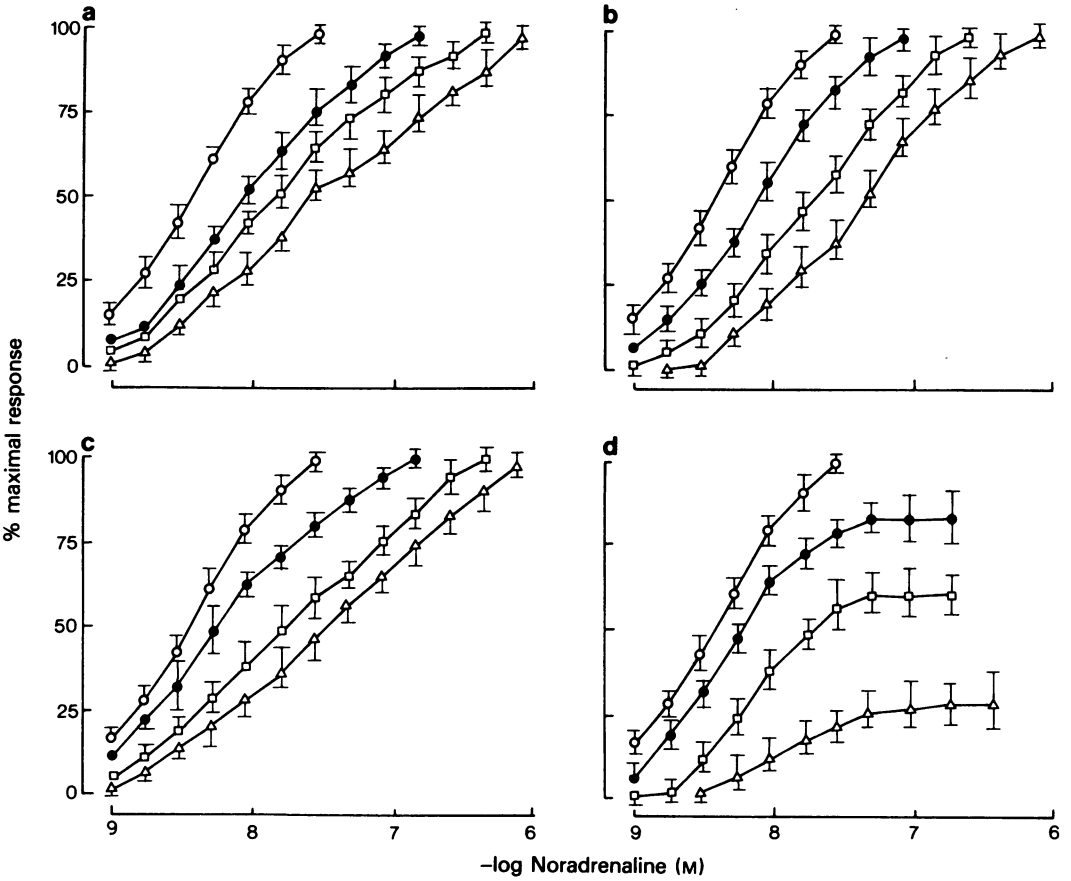

Figure 4 Guinea-pig isolated ileum. Response to exogenously administered noradrenaline in the presence and absence of (a) phentolamine, (b) yohimbine, (c) prazosin and (d) phenoxybenzamine. (○) No antagonist; (●) phentolamine (3.58×10^{-7} M) or yohimbine (2.56×10^{-7} M) or prazosin (3.77×10^{-7} M) or phenoxybenzamine (2.94×10^{-9} M); (□) phentolamine (7.1×10^{-7} M) or yohimbine (1.28×10^{-6} M) or prazosin (1.81×10^{-6} M) or phenoxybenzamine (5.88×10^{-9} M); (△) phentolamine (3.58×10^{-6} M) or yohimbine (2.56×10^{-6} M) or prazosin (3.77×10^{-6} M) or phenoxybenzamine (2.94×10^{-8} M). Values are mean of 6 experiments. Vertical bars show s.e. mean.

receptor, then the antagonism produced by the two antagonists combined should be equal to the product of the dose-ratios of the same concentrations tested separately, that is $DR_{AB} = DR_A \times DR_B$ (Paton & Rang, 1965). Figure 5 shows the effect of a combination of phentolamine and prazosin on the noradrenaline dose-response curve. The experimentally obtained dose-ratios for the two antagonists acting together approximated closely to the theoretical value, $DR_A + DR_B - 1$, and differed substantially from the theoretical value, $DR_A \times DR_B$ (Table 3).

Discussion

The guinea-pig ileum contains both α- and β-adrenoceptors (Furchgott, 1960) situated on the smooth muscle. Stimulation of either type of receptors produces a relaxant response. In the transmurally stimulated gut, stimulation of the periarterial nerves causes release of noradrenaline which acts on the presynaptic α-adrenoceptors situated on the cholinergic nerve terminals to inhibit the release of acetylcholine and thus reduce the amplitude of the transmural twitches (Vizi, 1968; Paton & Vizi, 1969).

Blockade of these α-adrenoceptors by α-adrenoceptor blocking drugs prevents the inhibition of the transmural twitches by both periarterial nerve stimulation and exogenous noradrenaline. The inability of prazosin, in contrast to yohimbine and phentolamine, to antagonize the inhibitory response to periarterial nerve stimulation and exogenous noradrenaline in the transmurally stimulated ileum suggests that prazosin

Table 3 The dose-ratios of phentolamine and prazosin (singly and in combination) against noradrenaline in the guinea-pig ileum

	Experimental dose-ratios			*Predicted dose-ratios*	
Antagonist concentrations	*Prazosin* (A)	*Phentolamine* (B)	*Prazosin + Phentolamine* (A + B)	*Prazosin + Phentolamine − 1* (A + B − 1)	*Prazosin × Phentolamine* (A × B)
*A^1, B^1	1.52 ± 0.67	2.73 ± 0.73	2.93 ± 0.65	3.25	4.15
A^2, B^2	7.47 ± 0.93	4.92 ± 1.27	11.99 ± 1.23	11.39	36.75
A^3, B^3	12.99 ± 1.24	10.92 ± 1.27	20.45 ± 1.04	22.91	141.85

*A^1, A^2, A^3 = 3.77×10^{-7}, 1.81 ± 10^{-6}, 3.77 ± 10^{-6} M Prazosin concentrations respectively.
B^1, B^2, B^3 = 3.58×10^{-7}, 7.1 ± 10^{-7}, 3.58×10^{-6} M Phentolamine concentrations respectively.

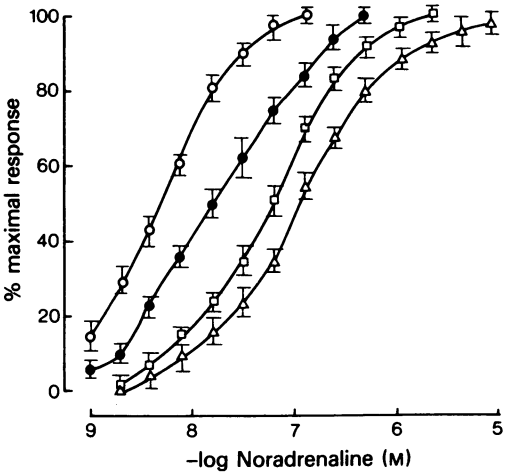

Figure 5 Guinea-pig isolated ileum. Response to exogenously administered noradrenaline in the presence and absence of phentolamine and prazosin. (○) No antagonist; (●) phentolamine (3.58×10^{-7} M) plus prazosin (3.77×10^{-7} M); (□) phentolamine (7.1×10^{-7} M) plus prazosin (1.81×10^{-6} M); (△) phentolamine (3.58×10^{-6} M) plus prazosin (3.77×10^{-6} M). Values are mean of 6 experiments. Vertical bars show s.e. mean.

has no effect on presynaptic α-adrenoceptors on the cholinergic nerves of this tissue.

Studies by Dubocovich & Langer (1974), Starke, Borowski & Endo (1975) and Drew (1976) have indicated that the postsynaptic α-adrenoceptors that mediate the responses of the effector organ may not be identical with the presynaptic α-adrenoceptors that regulate the release of the trasmitter, noradrenaline, during nerve stimulation. This conclusion is based in part on the different sensitivities of the two receptors to a variety of α-adrenoceptor agonists and antagonists. In the present study, prazosin and phenoxybenzamine, in concentrations that have no effect on presynaptic α-adrenoceptors located on cholinergic nerves, antagonize the effect of noradrenaline postsynaptically. This finding suggests that the α-adrenoceptors located on the membrane of the cholinergic nerve endings in the guinea-pig ileum similarly differ from those located on the postsynaptic membrane. Unlike prazosin and phenoxybenzamine, phentolamine and yohimbine block both the α-adrenoceptors located presynaptically on the cholinergic nerve endings and those on the postsynaptic cell membrane at all the concentrations tested. However, the pA_2 values for phentolamine and yohimbine at the postsynaptic site are significantly less than the values at the presynaptic site, suggesting that these drugs are more active presynaptically than postsynaptically. Starke *et al.* (1975) and Borowski, Ehrl & Starke (1976) similarly found phentolamine to be more potent at the presynaptic α-adrenoceptors located on the sympathetic nerve endings than at the postsynaptic α-adrenoceptors.

Finally, the result obtained with a combination of phentolamine and prazosin at the postsynaptic α-adrenoceptor indicates that the two antagonists act at the same site on the receptor and not at different sites as previously suggested by Constantine (1974).

References

ARIENS, E.J. & VAN ROSSUM, J.M. (1957). pDx, pAx, pD'x values in the analysis of pharmacodynamics. *Archs int. Pharmacodyn.*, **110**, 275–299.

ARUNLAKSHANA, O. & SCHILD, H.O. (1959). Some quantitative uses of drug antagonists. *Br. J. Pharmac. Chemother.*, **14**, 48–58.

BOROWSKI, E., EHRL, H. & STARKE, K. (1976). Relative pre- and postsynaptic potencies of α-adrenolytic drugs. *Naunyn-Schmiedebergs Arch. Pharmac.* Suppl. **293,** R. No. 8.

CONSTANTINE, J.W. (1974). Analysis of the hypotensive action of prazosin. In *Prazosin-Evaluation of a New Antihypertensive Agent.* ed. Cotton, D.W.K. pp. 16–36. Amsterdam: Excerpta Medica.

CONSTANTINE, J.W., MCSHANE, W.K., SCRIABINE, A. & HESS, H.J. (1973). Analysis of the hypotensive action of prazosin. In *Hypertension: Mechanisms and Management.* ed. Onesti, G., Kim, K.E. & Moyer, J.H., pp. 429–444. New York: Grune and Stratton Inc.

DREW, G.M. (1976). Effects of α-adrenoceptor agonists and antagonists on pre- and postsynaptically located α-adrenoceptors. *Eur. J. Pharmac.*, **36,** 313–320.

DUBOCOVICH, M.L. & LANGER, S.Z. (1974). Negative feedback regulation of noradrenaline release by nerve stimulation in the perfused cat's spleen: differences in potency of phenoxybenzamine in blocking pre- and postsynaptic adrenergic receptors. *J. Physiol.*, **273,** 505–519.

FURCHGOTT, R.F. (1960). Receptors for sympathomimetic amines. In *Adrenergic Mechanisms* (CIBA Foundation Symposium). ed. Vane, J.R., Wolstenholm, G.E.W. & O'Connor, M. pp. 246–252. London: J. and A. Churchill. chill.

KNOLL, J. & VIZI, E.S. (1971). Effect of frequency of stimulation on the inhibition by noradrenaline of the acetylcholine output from parasympathetic nerve terminals. *Br. J. Pharmac.*, **42,** 263–272.

KOSTERLITZ, H.W. & LEES, G.M. (1972). Interrelationships between adrenergic mechanisms. In *Catecholamines, Handb. exp. Pharmac.* N.S., Vol. 33. ed. Blaschko, H. & Muscholl, E., pp. 762–812. Berlin and Heidelberg: Springer-Verlag.

MARSHALL, P.B. (1955). Some chemical and physical properties associated with histamine antagonism. *Br. J. Pharmac. Chemother.*, **10,** 270–278.

MASSINGHAM, R. & HAYDEN, M.L. (1975). A comparison of the effects of prazosin and hydrallazine on blood pressure, heart rate and plasma renin activity in conscious renal hypertensive dogs. *Eur. J. Pharmac.*, **30,** 121–124.

NICKERSON, M. (1957). Nonequilibrium drug antagonism. *Pharmac. Rev.*, **9,** 246–259.

PATON, W.D.M. (1955). The response of the guinea-pig ileum to electrical stimulation by coaxial electrodes. *J. Physiol.*, **127,** 40–41p.

PATON, W.D.M. & RANG, H.P. (1965). The uptake of atropine and related drugs by intestinal smooth muscle of the guinea-pig in relation to acetylcholine receptors. *Proc. R. Soc. B.*, **163,** 1–44.

PATON, W.D.M. & VIZI, E.S. (1969). The inhibitory action of noradrenaline and adrenaline on acetylcholine output by guinea-pig ileum longitudinal strip. *Br. J. Pharmac.*, **35,** 10–28.

STARKE, K., BOROWSKI, E. & ENDO, T. (1975). Preferential blockade of presynaptic α-adrenoceptors by yohimbine. *Eur. J. Pharmac.*, **34,** 385–388.

VIZI, E.S. (1968). The inhibitory action of noradrenaline and adrenaline on release of acetylcholine from guinea-pig ileum longitudinal strips. *Naunyn-Schmiedebergs Arch. exp. Path. Pharmak.*, **259,** 199–200.

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