Br. J. Pharmac. (1982), **76**, 569–578

DISTRIBUTION AND TYPES OF ADRENOCEPTORS IN THE GUINEA-PIG ILEUM: THE ACTION OF α- AND β-ADRENOCEPTOR BLOCKING AGENTS

V. BAUER

Institute of Experimental Pharmacology, Centre of Physiological Sciences of the Slovak Academy of Sciences, Bratislava, Czechoslovakia

1 Transmurally stimulated segments of the guinea-pig ileum have been used to analyse the different adrenoceptors in the terminal (0 to 3 cm) and the proximal (> 50 cm from the ileocaecal valve) ileum.

2 The prejunctional adrenoceptors (located on the final, cholinergic, motor nerve terminals) and postjunctional adrenoceptors (located on the smooth muscle membrane) have been characterized according to their sensitivity to α- and β-agonists and antagonists.

3 Phentolamine, phenoxybenzamine and yohimbine, in concentrations of 0.1 μM, transiently enhanced (up to 10%) the twitch response. At higher concentrations all the α- and β-antagonists studied depressed the neurogenic twitches and relaxed the smooth muscle.

4 The twitch-inhibitory effects of adrenoceptor agonists (noradrenaline, adrenaline and ephedrine) were not antagonized by phenoxybenzamine (0.1, 0.5 and 1 μM), carbidine (0.5, 1 and 5 μM) and propranolol (0.5, 1 and 5 μM); however, they were depressed by phentolamine (0.1, 0.5, 1.25 and 5 μM) and yohimbine (0.25, 0.5 and 5 μM).

5 The smooth muscle contractions induced by noradrenaline and adrenaline in the terminal ileum and by phenylephrine in both the terminal and proximal ileum were antagonized by phenoxybenzamine, carbidine and phentolamine but were not influenced by yohimbine and propranolol.

6 The smooth muscle relaxations of the proximal ileum induced by noradrenaline, adrenaline and ephedrine were inhibited by yohimbine, phentolamine, carbidine and phenoxybenzamine, and the isoprenaline-induced relaxation was antagonized by propranolol.

7 All the agonists studied, except phenylephrine, elicited relaxations of the acetylcholine-induced sustained contraction of both proximal and terminal ileum. The relaxation induced by isoprenaline was antagonized by propranolol, and the effects of noradrenaline and ephedrine by yohimbine.

8 It is concluded that in the guinea-pig ileum there are postsynaptic β-adrenoceptors and at least two types of α-adrenoceptors: α_1-excitatory postjunctional adrenoceptors activated by phenylephrine, noradrenaline and adrenaline and antagonized by phenoxybenzamine, carbidine and phentolamine; α_2-inhibitory prejunctional adrenoceptors activated by ephedrine, noradrenaline and adrenaline and inhibited by yohimbine and phentolamine. The inhibitory postjunctional α-adrenoceptors are more close to the α_2-adrenoceptors, since they were stimulated predominantly by ephedrine and noradrenaline and inhibited by yohimbine.

9 It has been shown that all α-adrenoceptor subtypes are to be found at every distance (0 to 70 cm) from the ileocaecal valve and that they can be activated in the resting or in the acetylcholine-contracted states.

Introduction

It has been shown that the same prejunctional inhibitory action of adrenoceptor agonists occurs at all distances (up to 70 cm) from the ileocaecal valve of the guinea-pig ileum (Bauer, 1981). There is considerable evidence that cholinergic nerve terminals have α-adrenoceptors, which play an inhibitory role in acetylcholine release from the prejunctional nerve terminals of the intramural myenteric plexus (Kosterlitz, Lydon & Watt, 1970; Paton, Vizi & Zar, 1971; Drew, 1977b). The prejunctional adrenoceptors (α_2) located in intramural postganglionic nerve fibres of the guinea-pig ileum show pharmacological characteristics different from the postjunctional adrenoceptors (α_1) (Wikberg, 1977; 1978) and can be

0007-1188/82/080569-10 $01.00

selectively stimulated by ephedrine and phenylephrine, respectively (Bauer, 1981). The postjunctional excitatory α_1- and inhibitory β-adrenoceptors could be detected not only in the terminal but also in the proximal parts of the ileum (Bauer, 1981), in agreement with the findings of Anderson & Lees (1976) and Wikberg (1978). It has been suggested that a pharmacological difference exists between inhibitory prejunctional and excitatory postjunctional adrenoceptors, as in other smooth muscle preparations (Langer, 1974; Starke, Endo & Taube, 1975; Drew, 1977a) and that an inhibitory postjunctional α-adrenoceptor, which is as yet uncharacterized, is also present (Bauer, 1981).

The aim of the present study was to characterize the pre- and postjunctional α-adrenoceptors and to analyse whether the pharmacological differences found between agonists could be detected also among adrenoceptor antagonists in different ileal segments of the terminal and the proximal ileum.

Preliminary reports of some of the results have been given at the International Symposium on the Physiology and Pharmacology of Smooth Muscle (Bauer, 1979a) and to the Czechoslovak Pharmacological Society (Bauer, 1979b).

Methods

Experiments were performed on the guinea-pig isolated ileum (segments 0 to 70 cm from the oleocaecal junction). Segments of whole ileum, 3–4 cm long were stimulated transmurally (Paton, 1955) and longitudinal muscle-myenteric plexus preparations (Paton & Vizi, 1969) were excited by electrical field stimulation in a modified Krebs solution of the following composition (mM): NaCl 120, KCl 5.9, $CaCl_2$ 2.5, $NaHCO_3$ 15.4, $MgCl_2$ 1.2, NaH_2PO_4 1.2 and glucose 11.5 at 37°C under an initial tension of 1.5 g. The solution was aerated with a mixture of 95% O_2 and 5% CO_2. For further details see Bauer (1981).

The following drugs were used: acetylcholine hydrochloride (VEB Berline Chemie), adrenaline hydrochloride (Spofa), carbidine hydrochloride (Pharmacol. Inst., Medical Academy of Sciences, Moscow), ephedrine hydrochloride (Spofa, Merck), isoprenaline hydrochloride (Spofa), noradrenaline hydrogentartrate (Spofa), phenoxybenzamine (SK & F), phentolamine mesylate (Ciba-Geigy), phenylephrine hydrochloride (Koch Light, Boehringer Ingelheim), propranolol hydrochloride (ICI) and yohimbine hydrochloride (Spofa).

Fresh stock solutions were prepared in distilled water. The agonists were in contact with the preparation for 45–120 s except when drugs were given cumulatively, in which case the interval between successive concentrations was adjusted to allow the effect of each concentration to develop fully. A concentration-response curve to agonists was first established. Exposure to agonists was then discontinued; when twitch responses had recovered, the antagonist was added to the bathing fluid. The concentration-response curves to agonists were repeated after the antagonists had been present in the bathing fluid for 15 min.

The results are expressed as arithmetic means ± s.e.means. Differences were tested by Student's t test for paired observations. Agonist dose-ratios were determined from the concentrations causing 50% of the maximum effect in the absence and presence of each concentration of the antagonists. The pA_2 values were determined by Schild plot analysis (Arunlakshana & Schild, 1959). The slopes and x-intercept of the Schild plot (mean and 95% confidence limits) were determined by least-squares regression analysis (Tallarida, Cowan & Adler, 1979).

Results

The effect of adrenoceptor antagonists on the twitch response

The time-course of the effects of adrenoceptor antagonists on the twitch response of the supramaximally stimulated guinea-pig ileum are given in Table 1. Phentolamine, phenoxybenzamine, and yohimbine (all at 0.1 μM) transiently enhanced the twitch responses. At higher concentrations all the α- and β-antagonists studied, namely phentolamine (0.5 to 5 μM), phenoxybenzamine (0.5 to 5 μM), yohimbine (0.25 to 50 μM), carbidine (0.5 to 50 μM) and propranolol (0.5 to 5 μM) depressed the neurogenic twitches in a concentration-dependent manner in the terminal (0 to 3 cm) and the proximal (> 50 cm from the ileocaecal valve) part of ileum. Phenoxybenzamine was the most active and phentolamine the least active agent. The maximal twitch inhibition developed over 1 to 4 min. The twitch inhibition caused by carbidine gradually disappeared in spite of its continued presence in the bathing solution. In contrast, the inhibition induced by phenoxybenzamine (1–5 μM) remained unchanged during its contact with the preparation. The time-courses of twitch inhibition produced by yohimbine, propranolol and phentolamine were intermediate between those of phenoxybenzamine and carbidine.

The concentrations of adrenoceptor antagonists employed have been widely used for the characterization of α-adrenoceptors (Doxey, Smith & Walker, 1977; Drew, 1978; Wikberg, 1978). The twitch inhibition, in agreement with findings of Drew (1978),

Table 1 Time courses of the effects of adrenoceptor antagonists on the size of twitch responses of the transmurally stimulated guinea-pig proximal and terminal ileum

Antagonist (μM)		*% change in twitch size* (mean ± s.e.mean) *Duration of contact (min)*					n
		1	2	5	10	15	
Yo	0.1	+3.9±1.8	+9.0±2.5*	+6.3±4.2	−1.8±2.7	−4.0±1.9	5
	0.25	−3.6±3.1	−8.8±2.1*	−12.2±2.9*	−8.4±3.0*	−4.4±1.9*	10
	0.5	−8.0±4.2	−14.5±2.5*	−16.9±1.8*	−12.4±2.1*	−9.3±2.3*	12
		−11.3±5.4	−19.2±4.3*	−21.2±3.5*	−15.8±2.9*	−13.2±3.0*	9
	5	−16.2±6.1*	−25.0±4.9*	−27.9±4.0*	−21.9±3.6*	−20.2±3.5*	17
	50	−38.1±9.3*	−59.8±7.5*	−63.5±4.3*	−50.7±5.9*	−44.5±5.1*	4
Ph	0.1	+2.4±1.6	+4.0±2.1	+3.2±2.4	+2.0±2.6	+0.4±2.0	5
	0.5	+0.8±0.9	+1.8±1.7	−0.7±2.3	−2.1±2.2	−3.5±1.6	11
	1.25	−3.9±2.7	−8.9±3.5*	−9.8±3.4*	−8.0±2.6*	−6.3±2.4*	16
	5	−10.3±5.2	−19.8±4.1*	−20.4±4.7*	−14.9±3.7*	−13.6±2.1*	14
Pbz	0.1	−0.15±0.9	+0.33±1.2	+6.0±2.5*	+10.1±2.8*	+8.7±3.3*	12
	0.5	−0.9±1.3	−2.05±1.7	−1.4±1.6	+1.7±1.6	+0.6±0.9	11
	1	−7.2±3.1	−14.9±5.2*	−15.3±5.1*	−10.8±4.5*	−9.7±3.8*	14
	5	−21.9±7.8*	−45.2±6.4*	−45.2±5.6*	−43.5±5.0*	−41.0±5.7*	6
Crb	0.5	−8.3±4.1	−14.7±3.9*	−11.7±2.3*	−8.0±2.5*	−5.8±4.4	13
	1	−13.7±5.2*	−20.1±3.9*	−18.1±3.5*	−6.8±3.2	−4.0±2.8	13
	5	−22.3±7.3*	−37.7±5.6*	−30.7±5.8*	−12.4±4.1*	−1.6±3.1	11
	50	−26.7±8.0*	−45.8±5.7*	−45.2±5.4*	−35.2±4.0*	−34.8±4.2*	6

In control preparations the twitch size varied during the 30 min period by 2.35 ± 1.7%.

* Significantly different from the control twitch amplitude at $P < 0.05$.

Yo = yohimbine, Ph = phentolamine, Pbz = phenoxybenzamine, Crb = carbidine, n = number of trials.

is probably due to their local anaesthetic and post-junctional anti-acetylcholine actions, since these antagonists when used in higher concentrations not only depressed the responses to transmural stimulation and exogenous acetylcholine (0.1 μM), but also depressed the basal tension of the ileal smooth muscle by 5 to 25% of the initial value.

Interactions between agonists and antagonists on the twitch response

The concentration-dependent twitch inhibition induced by noradrenaline (0.01 to 100 μM), ephedrine (0.5 to 1000 μM), adrenaline (0.1 to 100 μM), isoprenaline (0.01 to 100 μM) and phenylephrine (0.1 to 1000 μM) applied cumulatively showed no significant differences in both the terminal and proximal regions of the whole ileum and the longitudinal muscle-myenteric plexus preparation (see also Bauer, 1981). Therefore the results were considered together, when the interactions between agonists and antagonists were studied.

Yohimbine (0.25, 0.5 and 5 μM) and phentolamine (0.1, 0.5, 1.25 and 5 μM) produced parallel,

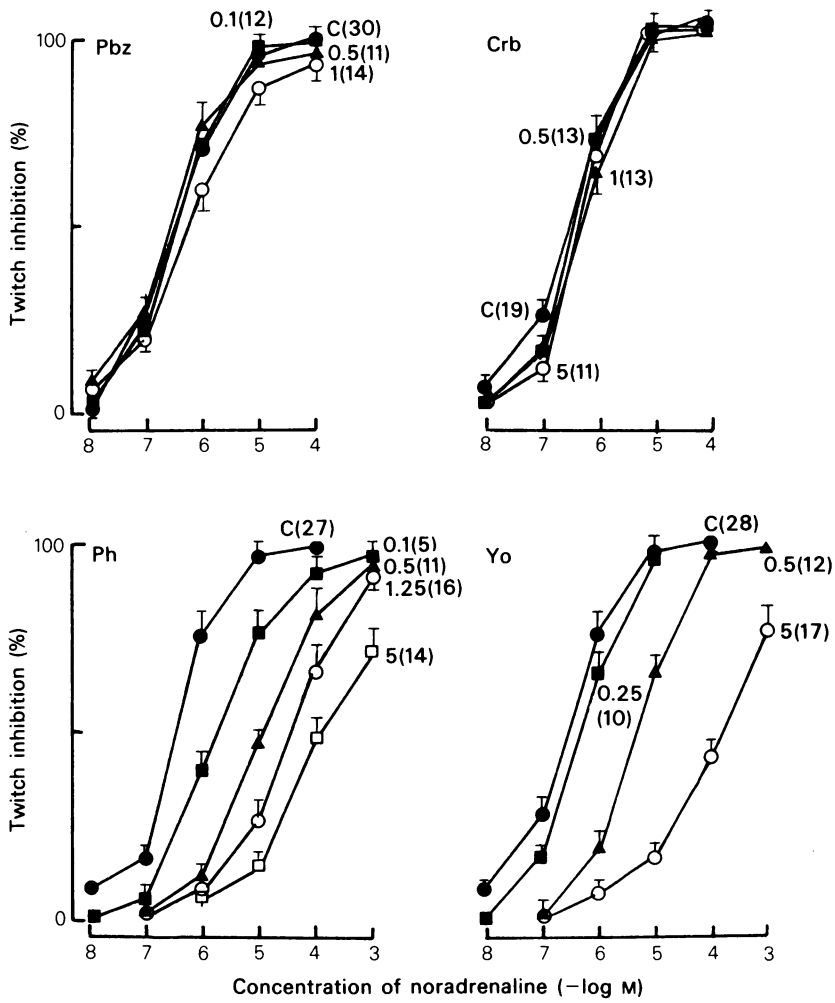

Figure 1 Guinea-pig proximal and terminal ileum. The effect of α-adrenoceptor antagonists upon the twitch inhibitory effects of noradrenaline. C (●) is the twitch inhibition induced by noradrenaline, alone. The numbers indicate the concentrations of antagonists in μM: ascending order of concentrations used represented by (■), (▲), (○), (□). Note the pronounced action of yohimbine (Yo) and phentolamine (Ph) and the ineffectiveness of phenoxybenzamine (Pbz) and carbidine (Crb). Each point represents the mean; vertical lines show s.e.mean; number of trials is given in parentheses.

concentration-dependent shifts to the right of the noradrenaline-, adrenaline- and ephedrine-induced concentration-response curves, whereas phenoxybenzamine (0.1, 0.5 and 1 μM) and carbidine (0.5, 1 and 5 μM) did not change significantly the neurogenic twitch inhibition by noradrenaline. The interaction between noradrenaline and α-adrenoceptor antagonists is illustrated in Figure 1.

The mean pA_2 values (with 95% confidence limits) for phentolamine and yohimbine at the prejunctional α-adrenoceptors of the guinea-pig ileum activated by noradrenaline were 7.56 (7.22–7.9) and 7.09 (6.57–7.61), respectively. Schild plots gave linear regressions; the slopes of the regressions were not significantly different from unity and were 1.27 (0.96–1.58) and 1.09 (0.85–1.32), respectively. The

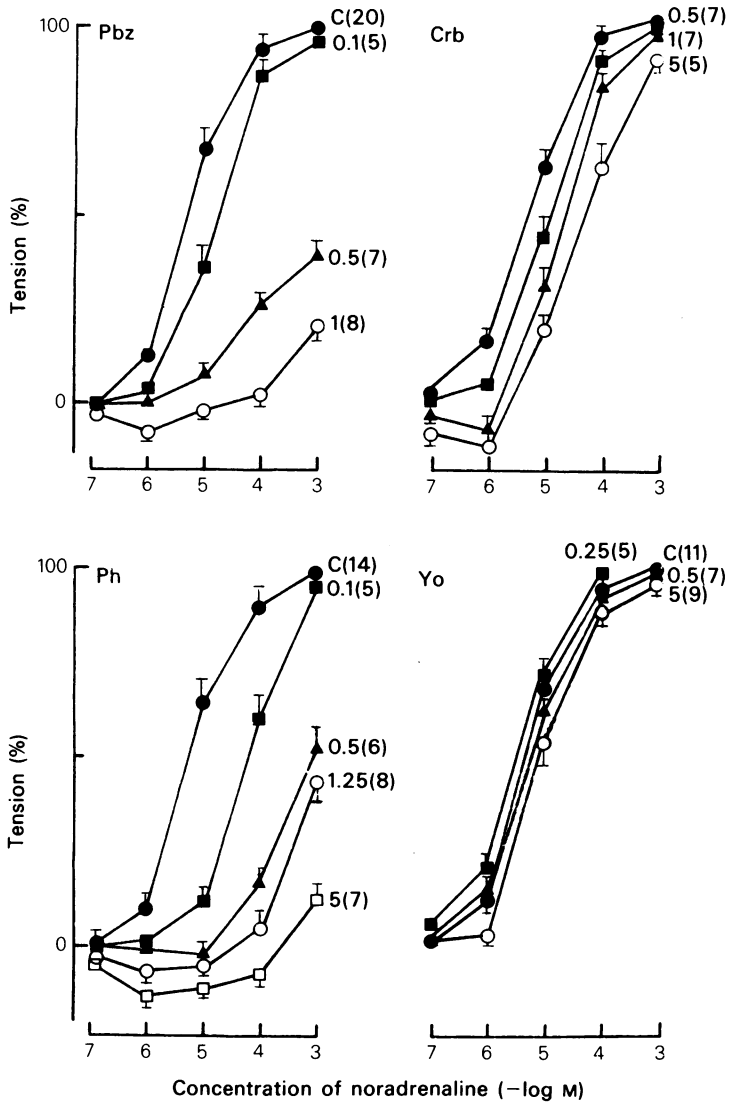

Figure 2 Guinea-pig terminal ileum. The effect of α-adrenoceptor antagonists upon the smooth muscle contraction induced by noradrenaline. C (●) is the control concentration-response contraction. The numbers indicate the concentrations of antagonists in μM; ascending order of concentrations used represented by (■), (▲), (○), (□). Note the pronounced action of phenoxybenzamine (Pbz), phentolamine (Ph) and carbidine (Crb) and ineffectiveness of yohimbine (Yo). Each point represents the mean; vertical lines show s.e.mean; number of trials is given in parentheses.

twitch-inhibition induced by higher concentrations of isoprenaline and phenylephrine reached 25–45% and was antagonized by phentolamine (0.5 to 5 μM) and yohimbine (0.5 to 5 μM) but not significantly influenced by propranolol (0.5 to 5 μM), phenoxybenzamine (0.1 to 1 μM) or carbidine (1 to 5 μM).

Interactions between agonists and antagonists on changes in basal tone

Increases in tone The concentration-response curves for noradrenaline-induced contractions of the terminal ileum were displaced to the right by phenoxybenzamine (0.1, 0.5 and 1 μM), phentolamine (0.1, 0.5, 1.25 and 5 μM) and carbidine (0.5, 1 and 5 μM). The contractions induced by noradrenaline (0.1–100 μM) were not only diminished by these antagonists, but in several cases were also changed to a relaxation; in contrast, yohimbine (0.25, 0.5 and 5 μM) did not change them significantly. The interaction between noradrenaline and α-adrenoceptor antagonists is shown in Figure 2.

The mean pA_2 values (with 95% confidence limits) for phentolamine and carbidine when noradrenaline was the agonist at the postjunctional α-adrenoceptors of the guinea-pig ileum were 7.76 (7.53–7.99) and

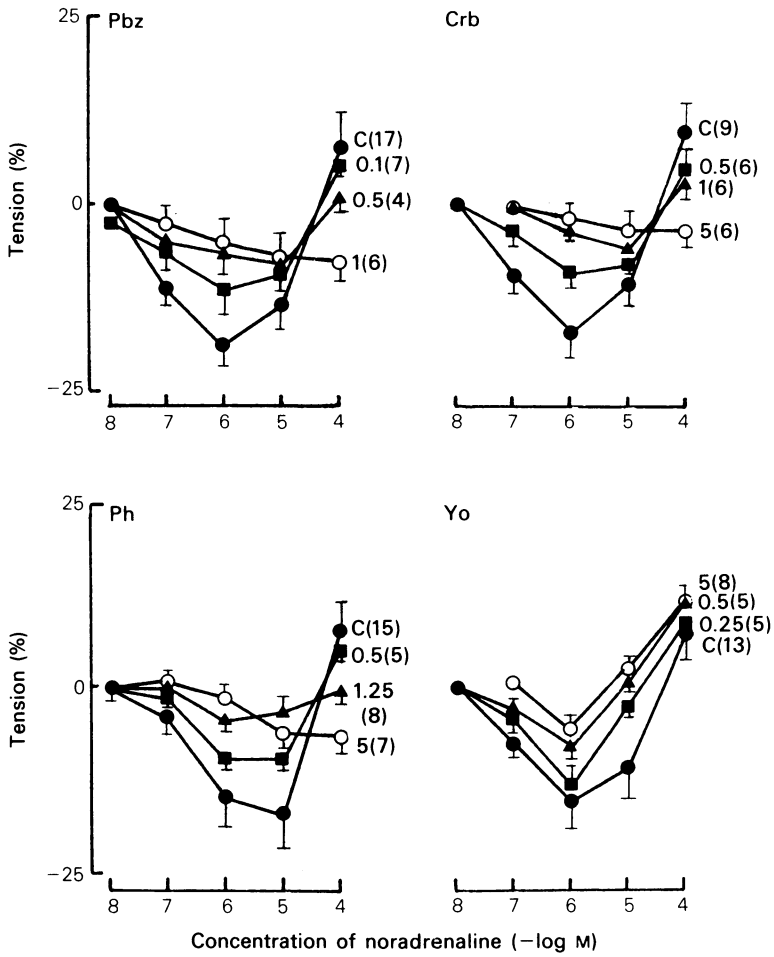

Figure 3 Guinea-pig proximal ileum. The effect of α-adrenoceptor antagonists (Pbz = phenoxybenzamine; Crb = carbidine; Ph = phentolamine; Yo = yohimbine) upon the smooth muscle relaxation and contraction induced by noradrenaline. C (●) is the control concentration-response curve. The numbers indicate the concentrations of antagonists in μM; ascending order of concentrations used represented by (■), (▲), (○). Note the inhibitory effect of all antagonists on relaxant action of noradrenaline and the ineffectiveness of yohimbine in antagonizing the smooth muscle contraction induced by a high noradrenaline concentration. Each point represents the mean; vertical lines show s.e.mean; number of trials is given in parentheses.

6.95 (6.54–7.36), respectively. Schild plots gave linear regressions with slopes not significantly different from unity (1.27 ± 0.34 and 0.76 ± 0.28, respectively). The concentration-response curves for adrenaline-induced contractions of the terminal ileum were displaced to the right and changed to concentration-dependent biphasic (relaxation then contraction) responses by phentolamine (1 and 5 μM) and carbidine (1 and 5 μM). Phenoxybenzamine (0.5 and 1 μM), phentolamine (1 and 5 μM) and carbidine (1 μM) displaced to the right the phenylephrine concentration-dependent contractions at both the terminal and proximal parts of ileum, while there was no significant depression of the action of phenylephrine by yohimbine in concentrations up to 5 μM.

Decreases in tone Isoprenaline (0.01 to 100 μM) decreased the basal tension of the smooth muscle of the ileum at all points along the guinea-pig ileum. Phentolamine (0.5 μM) had no significant effect on this isoprenaline concentration-response curve, while the highest phentolamine concentration tested (5 μM) slightly depressed the smooth muscle relaxation induced by isoprenaline (10–100 μM), probably indicating the additional activation of α-adrenoceptors by higher isoprenaline concentrations.

Noradrenaline- (0.01–10 μM) and ephedrine- (1–1000 μM) induced concentration-dependent relaxations of the proximal ileum but at 100 μM, noradrenaline significantly increased the basal tension of the proximal ileum. Phenoxybenzamine (0.1, 0.5 and 1 μM), carbidine (0.5, 1 and 5 μM), phentolamine (0.5, 1.25 and 5 μM) and yohimbine (0.25, 0.5 and 5 μM) were approximately equally effective in inhibiting noradrenaline- and ephedrine-induced relaxations of the proximal ileum. As in the terminal ileum, the contraction induced by the highest concentration of noradrenaline was insensitive to the action of yohimbine. The effect of α-adrenoceptor antagonists on the relaxation of the proximal ileum induced by noradrenaline is illustrated in Figure 3.

The relaxations of the proximal ileum induced by noradrenaline and adrenaline remaining after pretreatment with phentolamine, phenoxybenzamine, yohimbine or carbidine were markedly depressed by propranolol (0.5 and 1 μM) indicating the additional activation of β-adrenoceptors by noradrenaline and adrenaline.

Interaction between agonists and antagonists on changes in acetylcholine-induced increase in basal tension

In both the terminal and the proximal ileum, propranolol (5 μM) markedly reduced or blocked the relaxation elicited by isoprenaline (10 μM) and inhibited the relaxation induced by noradrenaline (10 μM) during the increased tension evoked by acetylcholine (5 μM). In contrast, the contraction induced by phenylephrine (0.1 mM) was not influenced and the relaxation induced by ephedrine (0.5 mM) was enhanced with propranolol pretreatment of the proximal and terminal ileal segments.

Phenoxybenzamine (1 μM), which has little effect on the action of isoprenaline, enhanced the effect of ephedrine and did not influence significantly the action of noradrenaline in either the proximal or the terminal ileum. The contraction induced by phenylephrine during the acetylcholine-evoked sustained increase in tension was fully counteracted by phenoxybenzamine pretreatment.

Yohimbine (5 μM) did not influence significantly the effects of isoprenaline or phenylephrine, but markedly depressed the smooth muscle relaxation induced by noradrenaline and ephedrine in both the terminal and the proximal ileal portions (Figure 4).

It was found in a separate series of experiments (Bauer & Matušák, unpublished results) that the α-adrenoceptor antagonists at the concentrations used in this study, had no significant influence on acetylcholine-induced contractions.

Discussion

Inhibitory and excitatory effects of sympathomimetic amines on the guinea-pig ileum have been described by many workers but the mechanisms involved are still not fully understood. This is in part due to complexities of the innervation of the smooth muscle, the multiplicity of adrenoceptor types and the complex pharmacological properties of the adrenoceptor agonists and antagonists used to characterize the receptor-mediated events. In this study, essentially five different aspects have been examined, namely the potentiation effects of adrenoceptor antagonists and the inhibitory effects of both adrenoceptor agonists and antagonists on the twitch responses of the ileum to electrical stimulation, the contractor responses of the muscle to adrenoceptor agonists and the relaxant responses of the muscle to adrenoceptor agonists applied to the resting muscle or to the ileum contracted by acetylcholine.

Potentiation of the twitch by adrenoceptor antagonists

Phentolamine, phenoxybenzamine and yohimbine, all at a concentration of 0.1 μM, potentiated the twitch responses induced by electrical stimulation at 0.07 Hz. These results thus confirm previous reports that some α-adrenoceptor antagonists enhance the twitch responses of guinea-pig ileum (Drew, 1978). Since, in concentrations that potentiated the twitch responses, phenoxybenzamine did not block the ac-

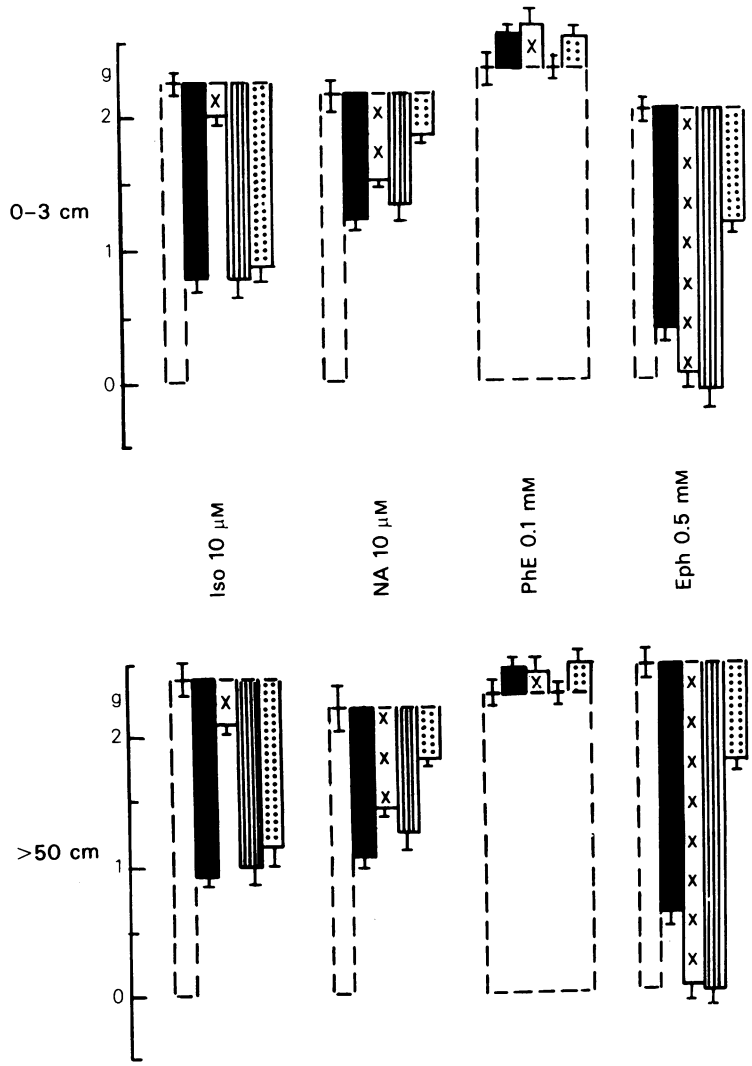

Figure 4 Action of isoprenaline (Iso; 10 μM), noradrenaline (NA; 10 μM), phenylephrine (PhE; 0.1 mM) and ephedrine (Eph; 0.5 mM) during acetylcholine-induced contractions (open columns), before (solid columns) and after 5 min pretreatment of the terminal (0–3 cm) and the proximal (> 50 cm) ileum with propranolol (crosses; 5 μM), phenoxybenzamine (stripes; 1 μM) and yohimbine (stippled columns; 5 μM. Each column represents the mean; vertical lines show s.e.mean of at least five trials.

tion of exogenously applied noradrenaline on cholinergic responses and yohimbine had a significant inhibitory effect only in concentrations higher than those which potentiate the twitch responses, the involvement of prejunctional α-adrenoceptors mediating inhibition of acetylcholine release is unlikely.

A similar phenomenon has also been seen in the vas deferens (Boyd, Chang & Rand, 1960; Bülbring, 1968; Ambache & Zar, 1971; Drew, 1977a). Bülbring (1968) demonstrated that phenoxybenzamine potentiates responses to both direct and indirect (neuronal) stimulation of the vas deferens and Drew (1977a) suggested that its postsynaptic potentiating action is unrelated to an action on α-adrenoceptors. The explanation in the guinea-pig ileum remains obscure since, in contrast to the action of noradrenaline, the action of acetylcholine was not signific-

antly changed by low concentrations of the antagonists, thus making a postjunctional mechanism also unlikely.

Inhibition of the twitch by antagonists

In agreement with findings of Boyd, Burnstock, Campbell, Jowett, O'Shea & Wood (1963) and Drew (1978), the twitch inhibition induced by the adrenoceptor antagonists, in concentrations widely used for the characterization of α-adrenoceptors (Doxey *et al.*, 1977; Drew, 1978; Wikberg, 1978), is probably due to their local anaesthetic and anti-acetylcholine actions since these agents depressed the responses to transmural stimulation and to exogenously administered acetylcholine, in addition to depressing the basal tension of the muscle; moreover, the kinetics of the twitch-inhibition were the same as those due to local anaesthetic agents (Hirnerová & Bauer, 1978).

Inhibition of the twitch by adrenoceptor agonists

It was found that the inhibitory actions of noradrenaline, adrenaline, isoprenaline, ephedrine and phenylephrine were not dependent on the region of the ileum nor on the presence of the circular muscle. The twitch-inhibition induced by noradrenaline, adrenaline and ephedrine is probably due to a reduction in acetylcholine release, as shown previously for the catecholamines (Paton *et al.*, 1971; Vizi, 1974). The very low potency of isoprenaline and phenylephrine inhibiting the twitches is consistent with their ineffectiveness in reducing acetylcholine release (Paton *et al.*, 1971).

Contractions evoked by adrenoceptor agonists

As shown previously (Bauer, 1981), noradrenaline and adrenaline contracted the ileal smooth muscle in the terminal portion and phenylephrine at every distance from the ileocaecal junction. Phentolamine was slightly more potent in blocking these postjunctional excitatory adrenoceptors than in blocking the prejunctional inhibitory α-adrenoceptors on the final motor (cholinergic) neurones, whereas yohimbine had no antagonistic effects on the postjunctional stimulatory α-adrenoceptors. In inhibiting the latter type of receptor, carbidine was acting selectively (Bauer, Štolc & Dugátová, 1980).

Relaxation mediated by adrenoceptors

Although Kosterlitz *et al.* (1970) and Wikberg (1976) were of the opinion that only inhibitory β-adrenoceptors were present in the longitudinal muscle of the guinea-pig ileum, Anderson & Lees (1976) adduced evidence for α-adrenoceptors on ileal muscle. The results described in the present paper indicate that in the proximal part of the ileum under resting conditions, α-adrenoceptors, as well as β-adrenoceptors, mediate inhibitions of resting tension induced by noradrenaline, ephedrine and isoprenaline. The postjunctional inhibitory effect of isoprenaline was predominantly the result of β-adrenoceptor activation; participation of α-adrenoceptors is also seen but only if higher concentrations are used. These results are in good agreement with the conclusions of Anderson & Lees (1976) for the guinea-pig ileum and of Bowman & Hall (1970) for the rabbit jejunum.

Reductions in tension during exposure to acetylcholine had a complex mechanism. The isoprenaline-induced relaxations were mediated solely by β-adrenoceptors since they were affected only by propranolol pretreatment. In contrast, the relaxations caused by noradrenaline and ephedrine were reduced by yohimbine but not by phenoxybenzamine and propranolol. It is concluded that a subtype of postjunctional adrenoceptor may be involved that is different from the postjunctional excitatory α- or inhibitory β-adrenoceptors.

Subclasses of α-adrenoceptor are designated according to their sensitivity to agonists and antagonists. Langer (1974) suggested that the prejunctional α-adrenoceptors of noradrenergic nerve terminals should be referred to as α_2-adrenoceptors. The same subtype of adrenoceptor on the final motor (cholinergic) nerve terminal in the guinea-pig ileum has been repeatedly confirmed (Drew, 1977a,b; Wikberg, 1978; Bauer, 1981). In noradrenergically innervated tissues, postjunctional α-adrenoceptors were designated α_1-adrenoceptors (Langer, 1974) but can be of mixed type (e.g. see Drew & Whiting, 1979). A further complication is that the stimulatory action of adrenoceptor agonists on the proximal part of the ileum may be mediated through receptors for 5-hydroxytryptamine (Innes & Kholi, 1969). However, in the present and other experiments the results indicate that the adrenoceptor agonists were stimulating the muscle via α-adrenoceptors and not 5-hydroxytryptamine receptors. While the excitatory postjunctional receptors present in the ileal smooth muscle are of the α_1-adrenoceptor type (Bauer, 1981), the inhibitory postjunctional ones seem closer to the α_2-adrenoceptor subtype, being predominantly stimulated by ephedrine and noradrenaline and inhibited by yohimbine.

References

AMBACHE, N. & ZAR, M.A. (1971). Evidence against adrenergic motor transmission in the guinea-pig vas deferens. *J. Physiol.*, **216**, 359–389.

ANDERSON, A.A. & LEES, G.M. (1976). Investigation of occurrence of tolerance to bronchodilator drugs in chronically pretreated guinea-pigs. *Br. J. Pharmac.*, **56**, 331–338.

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

BAUER, V. (1979a). Adrenoceptors and their distribution in the guinea-pig ileum. *2nd Int. Symp. Physiol. Pharmac. Smooth Muscle.*, Abstr. p. 34, Varna.

BAUER, V. (1979b). The effect of catecholamines in pre- and postjunctional adrenoceptors of nerve-muscle preparation of the guinea-pig ileum (in Slovak. *Čs. Fysiol.*, **28**, 247–248.

BAUER, V. (1981). Distribution and types of adrenoceptors in the guinea-pig ileum: the action of α- and β-adrenoceptor agonists. *Br. J. Pharmac.*, **72**, 201–210.

BAUER, V., ŠTOLC, S. & DUGÁTOVÁ, M. (1980). Effects of carbidine on smooth muscle and peripheral nerve (in Slovak). *Ann. Inst. exp. Pharmac., Slovak Academy of Sciences*, **2**, 297–320.

BOWMAN, W.C. & HALL, M.T. (1970). Inhibition of rabbit intestine mediated by α- and β-adrenoceptors. *Br. J. Pharmac.*, **38**, 399–415.

BOYD, H., BURNSTOCK, G., CAMPBELL, G., JOWETT, A., O'SHEA, J. & WOOD, M. (1963). The cholinergic blocking action of adrenergic blocking agents in pharmacological analysis of autonomic innervation. *Br. J. Pharmac. Chemother.*, **20**, 418–435.

BOYD, H., CHANG, V. & RAND, M.J. (1960). The anticholinesterase activity of some antiadrenaline agents. *Br. J. Pharmac. Chemother.*, **15**, 525–531.

BÜLBRING, E. (1968). In *Adrenergic neurotransmission.* Ciba Foundation Study Group No. 33, ed. Wolstenholme, G.E.W. & O'Connor, M., p. 60. London: Churchill Press.

DOXEY, J.C., SMITH, C.F.C. & WALKER, J.M. (1977). Sensitivity of blocking agents for pre- and postsynaptic α-adrenoceptors. *Br. J. Pharmac.*, **60**, 91–96.

DREW, G.M. (1977a). Pharmacological characterization of the presynaptic α-adrenoceptors in the rat vas deferens. *Eur. J. Pharmac.*, **42**, 123–130.

DREW, G.M. (1977b). Pharmacological characterization of the presynaptic α-adrenoceptors which regulate cholinergic activity in the guinea-pig ileum. *Br. J. Pharmac.*, **59**, 513P.

DREW, G.M. (1978). Pharmacological characterization of the presynaptic α-adrenoceptors regulating cholinergic activity in the guinea-pig ileum. *Br. J. Pharmac.*, **64**, 293–300.

DREW, G.M. & WHITING, S.B. (1979). Evidence for two distinct types of postsynaptic α-adrenoceptor in vascular smooth muscle *in vivo*. *Br. J. Pharmac.*, **67**, 207–215.

HIRNEROVÁ, D. & BAUER, V. (1978). The action of carbanilate local anaesthetics (K-1902, K-XIX and BK-52) on the terminal and proximal ileum of the guinea-pig (in Slovak). *Čs. Fysiol.*, **27**, 25–26.

INNES, I.R. & KHOLI, J.D. (1969). Excitatory action of sympathomimetic amines on 5-hydoxytryptamine receptors of the gut. *Br. J. Pharmac.*, **35**, 383–393.

KOSTERLITZ, H.W., LYDON, R.J. & WATT, A.J. (1970). The effect of adrenaline, noradrenaline and isoprenaline on inhibitory α- and β-adrenoceptors in the longitudinal muscle of the guinea-pig ileum. *Br. J. Pharmac.*, **39**, 398–413.

LANGER, S.Z. (1974). Presynaptic regulation of catecholamine release. *Biochem. Pharmac.*, **23**, 1793–1800.

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

PATON, W.D.M., VIZI, E.S. & ZAR, M.A. (1971). The mechanism of acetylcholine release from parasympathetic nerves. *J. Physiol.*, **215**, 819–848.

STARKE, K., ENDO, T. & TAUBE, H. (1975). Pre- and postsynaptic components in effect of drugs with α-adrenoceptor affinity. *Nature*, **254**, 440–441.

TALLARIDA, R.J., COWAN, A. & ADLER, M.W. (1979). pA_2 and receptor differentiation: A statistical analysis of competitive antagonism. *Life Sci.*, **25**, 637–654.

VIZI, E.S. (1974). Possible connection between the release of acetylcholine and the activity of Na^+-K^+-activated ATPase. *Ergeb. exp. Med.*, **17**, 96–116.

WIKBERG, J. (1976). Difference between α-receptors in Cholinergic neurons and smooth muscle cells. *6th Int. Congr. Pharmac.*, Abstr. p. 621, Helsinki.

WIKBERG, J. (1977). Localization of adrenergic receptors in guinea-pig ileum and rabbit jejunum to cholinergic neurons and to smooth muscle cells. *Acta physiol. scand.*, **99**, 190–207.

WIKBERG, J. (1978). Differentiation between pre- and postjunctional α-receptors in guinea-pig ileum and rabbit aorta. *Acta physiol. scand.*, **103**, 225–239.

(Received May 30, 1979. Revised February 6, 1982.)