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Effects of amosulalol on the electrical responses of guinea-pig vascular smooth muscle to adrenoceptor activation

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1 The effects of amosulalol, a newly synthesized sulphonamide-substituted phenylethylamine derivative, on electrical responses of smooth muscle cells of the guinea-pig vascular tissues to noradrenaline, isoprenaline and perivascular nerve stimulation were investigated.

2 Amosulalol (10^{-10}–10^{-5}M) did not alter the resting membrane potential of smooth muscle cells of the mesenteric artery, the mesenteric vein, the main pulmonary artery and the portal vein.

3 In the mesenteric artery, main pulmonary artery and portal vein, but not in the mesenteric vein, membrane depolarizations produced by noradrenaline were antagonized by amosulalol.

4 In the portal vein, membrane hyperpolarizations produced by isoprenaline were antagonized by amosulalol.

5 In the mesenteric artery, amosulalol (over 10^{-6}M) enhanced the amplitude of excitatory junction potentials (e.j.ps) produced by perivascular nerve stimulation.

6 Amosulalol antagonized the noradrenaline-induced decrease in the e.j.p. amplitude; this effect was much weaker than that of phentolamine. Amosulalol also antagonized the isoprenaline-induced enhancement of the e.j.p. amplitude.

7 In the mesenteric vein, the slow depolarizations produced by perivascular nerve stimulation were depressed by amosulalol (over 10^{-6}M), but the effect was much weaker than that of prazosin, yohimbine or phentolamine.

8 Actions of amosulalol on electrical properties of vascular tissues can be summarized as follows: amosulalol blocks α_1- and β-adrenoceptors. It also blocks α_2-adrenoceptors, though weakly.

Introduction

Amosulalol, a sulphonamide substituted phenylethylamine derivative, is a newly synthesized antihypertensive agent with combined α- and β-adrenoceptor blocking properties (Takenaka *et al.*, 1982), e.g. pharmacological studies have shown that amosulalol has a high selectivity for α_1-adrenoceptors (Takenaka *et al.*, 1982; Asano *et al.*, 1983) and has no selectivity for either β_1- or β_2-adrenoceptors (Tomita *et al.*, 1982; Asano *et al.*, 1983).

In these experiments, we investigated the effects of amosulalol on electrical responses to activation of α- and β-adrenoceptors in guinea-pig isolated vascular tissues, i.e., the mesenteric and main pulmonary arteries and the mesenteric and the portal veins. Smooth muscle membranes of the mesenteric artery (Kuriyama & Makita, 1983), main pulmonary artery (Suzuki, 1983) and portal vein (Takata, 1980) possess α_1-adrenoceptors, through which exogenously applied noradrenaline depolarizes the membrane. In perivascular adrenergic nerve terminals of the mesenteric artery, α_2- and β-adrenoceptors are present, and stimulation of the former decreases and of the latter increases the e.j.p. amplitude (Kuriyama & Makita, 1983). In the portal vein, stimulation of the α_1-adrenoceptor depolarizes and of the β-adrenoceptor hyperpolarizes the muscle membrane (Takata, 1980).

We found that in the guinea-pig vascular tissues, amosulalol possesses inhibitory actions on α_1-, α_2- and β-adrenoceptors, although the effect on the α_2-adrenoceptor was weak.

Methods

Albino guinea-pigs of either sex, weighing 200–300g, were stunned and bled. The mesenteric vascular beds

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distributing to the ileal region, the main pulmonary artery and the portal vein were excised and kept in Krebs solution at room temperature. The mesenteric artery and vein were about 10 mm in length and 0.1–0.12 mm in diameter. The pulmonary artery or the portal vein was cleaned by removing connective tissues and cut open longitudinally. These tissues were mounted in an organ bath made of Lucite plate, with the outer surface uppermost, and warmed (35°C) Krebs solution was superfused at a constant flow rate of about 2 ml min^{-1}.

Electrical responses of smooth muscle cells were recorded by means of glass capillarly microelectrodes filled with 3 M KCl, with the tip resistance ranging between 40 and 80 MΩ. The microelectrode was impaled from the outer surface of the tissue. Electrotonic potentials were produced by the partition stimulating method (Abe & Tomita, 1968). Perivascular nerves were stimulated with a suction electrode (Kuriyama & Suzuki, 1981) or by the point stimulation method (Suzuki, 1983). Electrical responses were displayed on a pen-writing recorder (Nihon Kohden RJG4024).

The Krebs solution has the following ionic composition (mM); Na^+ 137.4, K^+ 5.9, Mg^{2+} 1.2, Ca^{2+} 2.6, HCO_4^- 15.5, $H_2PO_4^-$ 1.2, Cl^- 134 and glucose, 11.5. The solution was bubbled with O_2 containing 3% CO_2, and the pH of the solution was kept at 7.2–7.4.

The drugs used were amosulalol (5[1-hydroxy-2-[(2-(0-methoxyphenoxy)ethyl)amino]ethyl]-2-methylbenzenesulphonamide hydrochloride, YM-09538, Yamanouchi), (−)-noradrenaline HCl (Sigma), (−)-isoprenaline HCl (Nakarai), phentolamine mesylate (Ciba Geigy), prazosin HCl (Pfizer), yohimbine HCl and guanethidine sulphate (Tokyo Kasei). The solutions were prepared fresh for each experiment.

The experimental values were expressed as means ± s.d., and the statistical significance was assessed by Student's t test ($P < 0.05$).

Results

Effects of amosulalol on membrane properties and on noradrenaline-induced responses

Smooth muscle cells of the guinea-pig mesenteric artery and vein and the main pulmonary artery were electrically quiescent, and there was no spontaneous electrical activity (spike potentials or slow waves). The resting membrane potential of the smooth muscle cells was approximately −70 mV in the mesenteric artery (Kuriyama & Suzuki, 1981), in the range of −65 to −70 mV in the mesenteric vein (Suzuki, 1981), in the range of −50 to −55 mV in the main pulmonary artery (Suzuki, 1983) and in the range of −46 to −53 mV in the portal vein (Takata, 1980). Amosulalol (10^{-8}–10^{-5} M) did not alter the resting membrane potentials of these tissues after up to 1 h. In the mesenteric artery, the effects of amosulalol on membrane conductance were observed by recording electrotonic potentials produced by alternate application of various intensities of inward and outward current pulses (1.5 s in duration). Guanethidine (5×10^{-6} M) was applied throughout the experiment to prevent possible involvement of transmitters released from perivascular adrenergic nerves. The electrotonic potentials were recorded in close proximity (at about 0.1 mm distance) from the stimulating electrode, a distance short enough in comparison with the length

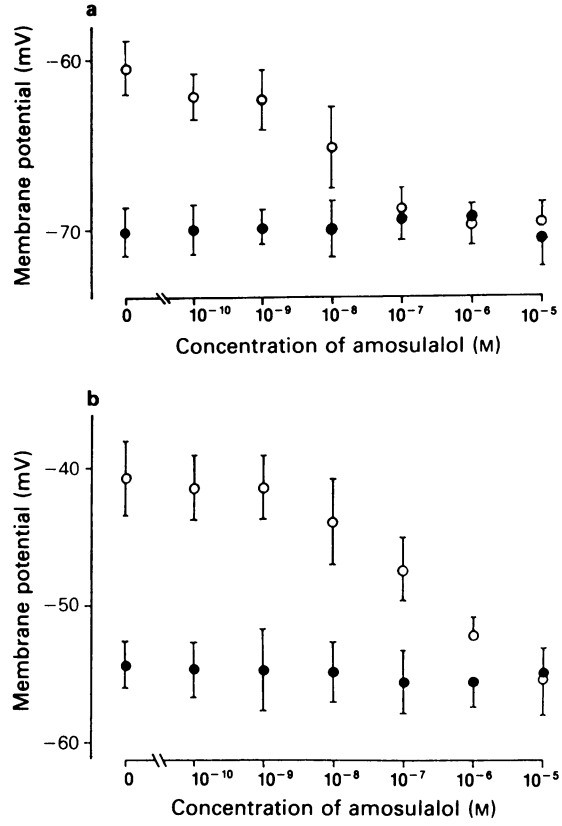

Figure 1 Effects of amosulalol on membrane depolarizations produced by (a) 10^{-5} M noradrenaline (○) in the mesenteric artery, or (b) 5×10^{-6} M noradrenaline (○) in the main pulmonary artery; (●) control in (a) and (b). The preparations were pretreated with amosulalol (10^{-10}–10^{-5} M) for 5 min, after which noradrenaline was added for a further 10–15 min. The membrane potentials were measured by successive impalements of different cells by the electrode, and the mean (n = 7–15) is shown; s.d. shown by vertical lines.

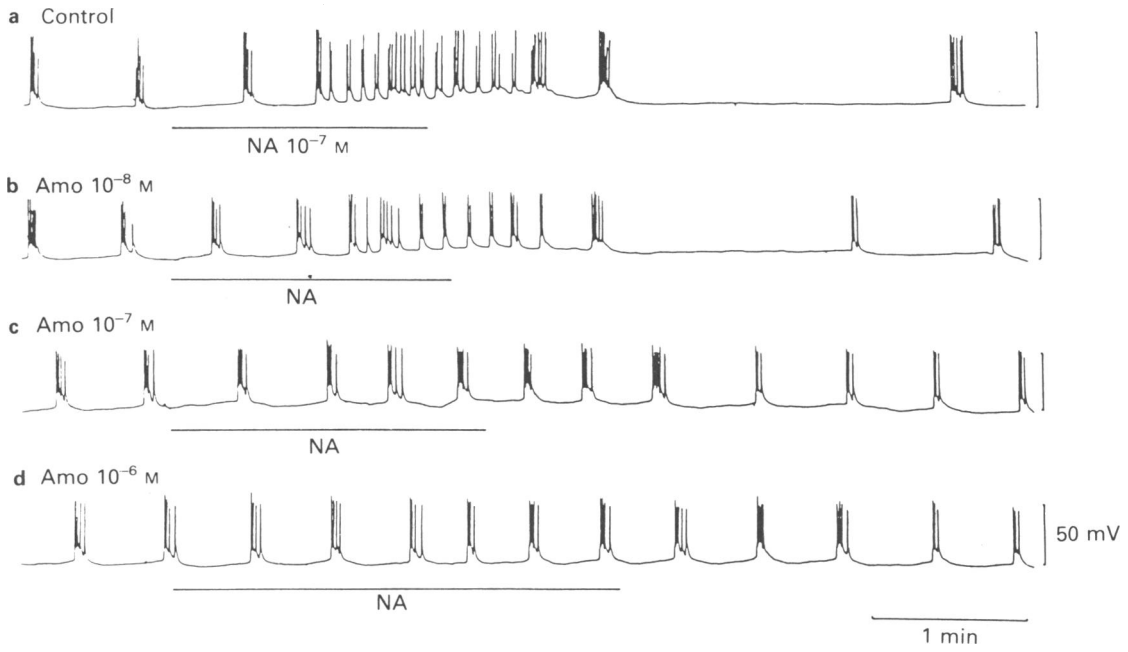

Figure 2 Effects of amosulalol (Amo) on noradrenaline (NA)-induced electrical responses in the portal vein. NA (10^{-7}M) was applied at the bar under each record, in the absence (a) or after pretreatment for 5 min with 10^{-8}M amosulalol (b), 10^{-7}M amosulalol (c) or 10^{-6}M amosulalol (d). All the records were obtained from a single cell.

constant of this artery (0.8 mm, Kuriyama & Suzuki, 1981). Amplitudes of electrotonic potentials plotted against the intensity of currents showed a linear relationship, and during treatment with amosulalol (10^{-7}–10^{-5}M), this relationship remained unchanged, i.e. amosulalol did not alter the membrane resistance of muscle cells.

Effects of amosulalol on membrane depolarization produced by exogenously applied noradrenaline were observed in the mesenteric or main pulmonary arteries. Membrane potentials were measured by impalements with the electrode of different cells while a fixed concentration (10^{-5}M or 5×10^{-6}M) of noradrenaline was applied for 10–15 min in tissues which had been pretreated with various concentrations (10^{-10}–10^{-5}M) of amosulalol for 5 min. Figure 1 shows the effects of pretreatment with amosulalol (10^{-10}–10^{-5}M) on membrane depolarizations produced by exogenously applied noradrenaline. In the absence of amosulalol, exgenously applied noradrenaline depolarized the smooth muscle membrane by about 10 mV in both mesenteric and main pulmonary arteries. In the mesenteric artery, the noradrenaline-induced depolarization was inhibited significantly by amosulalol in concentrations over 10^{-8}M, and the depolarization ceased by amosulalol in concentrations over 10^{-7}M (Figure 1a). In the pulmonary artery, membrane depolarizations produced by 5×10^{-6}M noradrenaline were significantly reduced by amosulalol in concentrations over 10^{-7}M, and ceased after pretreatment with 10^{-5}M amosulalol (Figure 1b).

In the mesenteric vein, membrane depolarization produced by exogenously applied noradrenaline (10^{-5}M) was not blocked by amosulalol, up to 10^{-5}M (resting potential, -66.9 ± 2.3 mV, $n = 23$; 10^{-5}M noradrenaline, -55.0 ± 2.6 mV, $n = 10$; 10^{-5}M noradrenaline plus 10^{-5}M amosulalol, -55.9 ± 2.2 mV, $n = 16$).

In the guinea-pig portal vein, exogenously applied noradrenaline depolarized the membrane and increased the frequency of spike discharges (von Loh, 1971). Figure 2 shows effects of amosulalol (10^{-8}–10^{-6}M) on electrical responses produced by exogenously applied noradrenaline (10^{-7}M) in the guinea-pig portal vein. Membrane depolarization and increase in spike discharges induced by noradrenaline were inhibited by pretreatment with 10^{-8}M amosulalol, and ceased in the presence of 10^{-7}M amosulalol. In tissues pretreated with 10^{-7}–10^{-6}M amosulalol, application of noradrenaline did not alter the pattern of periodic appearances of spontaneous burst discharges.

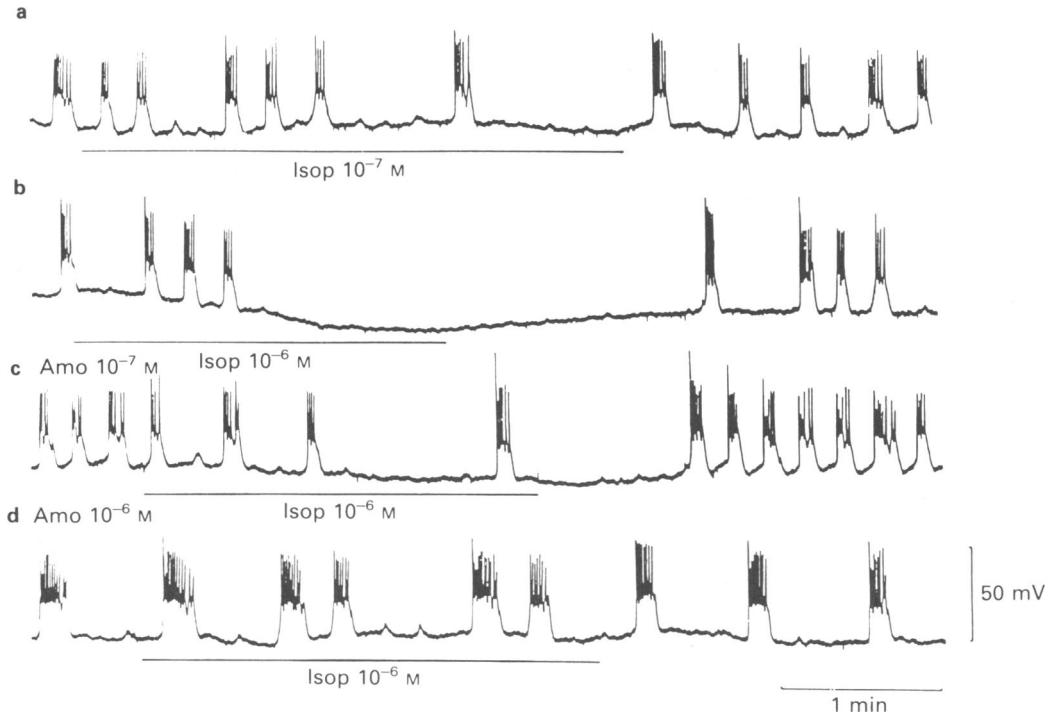

Figure 3 Effects of amosulalol (Amo) on isoprenaline (Isop)-induced electrical responses in the portal vein. Isoprenaline (10^{-7}M or 10^{-6}M) was applied at the bar under each record, before (a) and (b) or after treatment with 10^{-7}M amosulalol (c) or 10^{-6}M amosulalol (d). All the responses were recorded from a single cell.

Effects of amosulalol on isoprenaline-induced responses

Isoprenaline ($10^{-8}-5\times10^{-6}$M) hyperpolarized the smooth muscle membrane of the guinea-pig portal vein but not the mesenteric artery (Takata, 1980). Effects of amosulalol on the isoprenaline-induced hyperpolarization were observed in the portal vein. As shown in Figure 3a, application of isoprenaline 10^{-7}M increased the silent periods between burst spike discharges with no change in the membrane potential. Increase in the concentration of isoprenaline to 10^{-6}M resulted in hyperpolarizations of the membrane and cessation of spontaneous spike discharges (Figure 3b). In tissues pretreated with amosulalol 10^{-7}M, this concentration of isoprenaline increased the duration of burst spike discharges, and the effects of isoprenaline were blocked after pretreatment with amosulalol 10^{-6}M for 5 min (Figure 3d).

Figure 4 shows the dose-response relationship between concentrations of isoprenaline and membrane potentials of smooth muscle cells of the portal vein. The experiments were carried out in the presence of phentolamine (10^{-7}M) throughout, and in these condi-

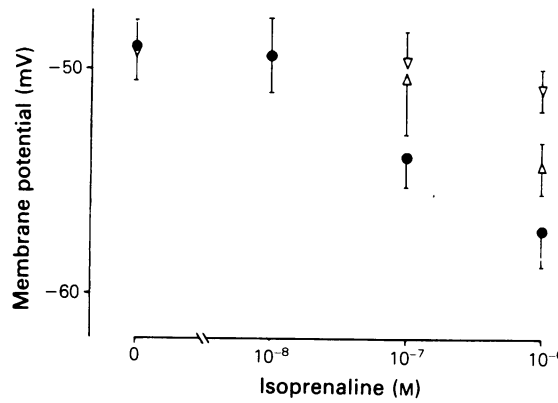

Figure 4 Modification by amosulalol of the effect of isoprenaline (in the presence of phentolamine 10^{-7}M) on the membrane potential of muscle cells in guinea-pig portal vein. (●) Control (no amosulalol); after pretreatment (5 min) with 10^{-8}M (△) and 10^{-7}M (▽) amosulalol. Mean of 5–8 observations is shown; vertical lines indicate s.d.

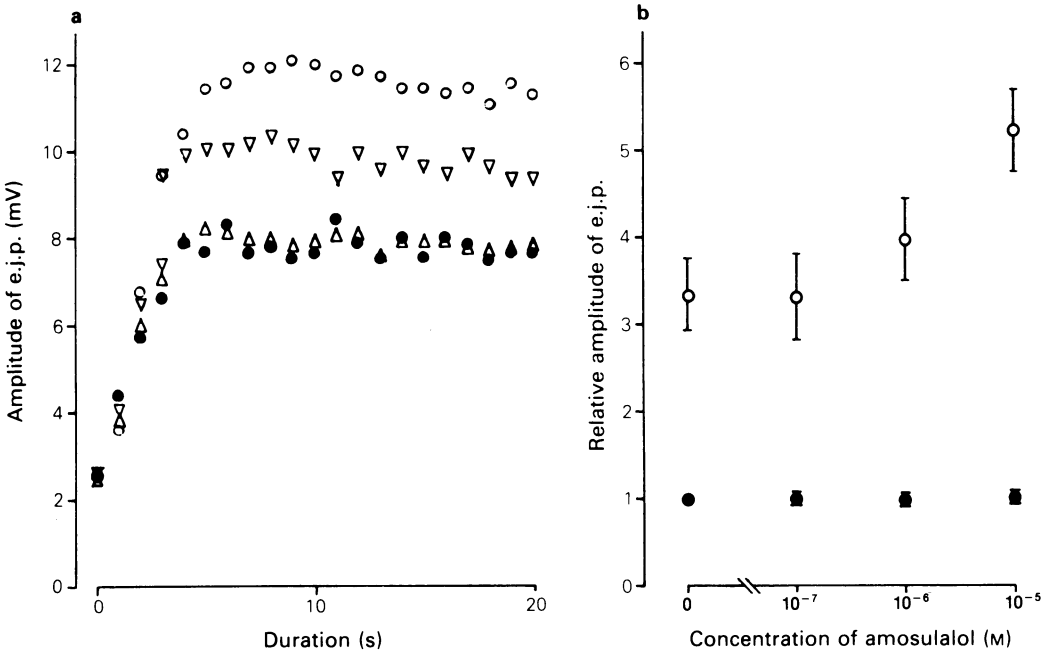

Figure 5 (a) Effects of amosulalol (Δ, 10^{-7}M; ∇, 10^{-6}M; ○, 10^{-5}M) on the e.j.p. amplitudes produced by perivascular nerve stimulation (0.1 ms duration, 50 V intensity) for 20 s with 1 Hz frequency of guinea-pig mesenteric artery. (●) Control response obtained before application of amosulalol. Each point is a mean value of 5–7 observation; s.d. did not exceed ± 10% of the mean. (b) Dose-response relationship of the effects of amosulalol on the e.j.p. amplitudes in the first (●) and the fully facilitated condition (○). Stimulation; 1 Hz frequency, 20 stimuli. Mean is shown, with vertical lines indicating s.d.

tions the threshold concentration of isoprenaline required to produce the hyperpolarization was decreased to 10^{-7}M. When the effects of amosulalol (10^{-7}M) were observed on this relationship, it was found to block the isoprenaline-induced hyperpolarization, up to 10^{-6}M.

Effects of amosulalol on adrenergic transmission

In the guinea-pig mesenteric artery, perivascular nerve stimulation with a brief current pulse (0.05–0.1 ms duration, 30–50 V intensity) generated an excitatory junction potential (e.j.p.). The e.j.p. amplitude increased, when the intensity was increased or when the nerves were stimulated repetitively at 0.1–1.0 Hz frequency (Kuriyama & Suzuki, 1981).

Figure 5 shows the effects of amosulalol (10^{-7}–10^{-5}M) on the e.j.ps produced by perivascular nerve stimulation for 20 s with 1 Hz frequency. The e.j.p. amplitude increased by successive stimuli during the initial 4–5 s (facilitation process), then reached a steady amplitude which was 3–4 times larger than the first of the train. When the mean amplitudes of e.j.ps produced by 1 Hz stimulation, in the absence or presence of amosulalol (10^{-7}–10^{-5}M), were compared, the amplitude of the first e.j.p. generated by a train of nerve stimulation (1 Hz frequency, 21 times) was not modified by application of amosulalol (10^{-7}–10^{-5}M). The e.j.p. amplitude after the facilitation had been completed was enhanced by application of amosulalol in concentrations over 10^{-6}M.

The e.j.p. emplitude was reduced by application of noradrenaline, and the effects of noradrenaline were antagonized by phentolamine in the guinea-pig mesenteric artery (Kuriyama & Makita, 1983). As shown in Figure 6 the e.j.p. amplitude which had been reduced by application of noradrenaline (10^{-7}M), was increased slightly by application of 3×10^{-6}M amosulalol. Additional application of phentolamine 10^{-7}M further enhanced the e.j.p. amplitude over the control.

Effects of amosulalol on β-adrenoceptors located in the nerve terminals were estimated by recording the e.j.ps from smooth muscles of the guinea-pig mesenteric artery. Figure 7 shows the effects of amosulalol on the e.j.p. in the presence of isoprenaline. Phen-

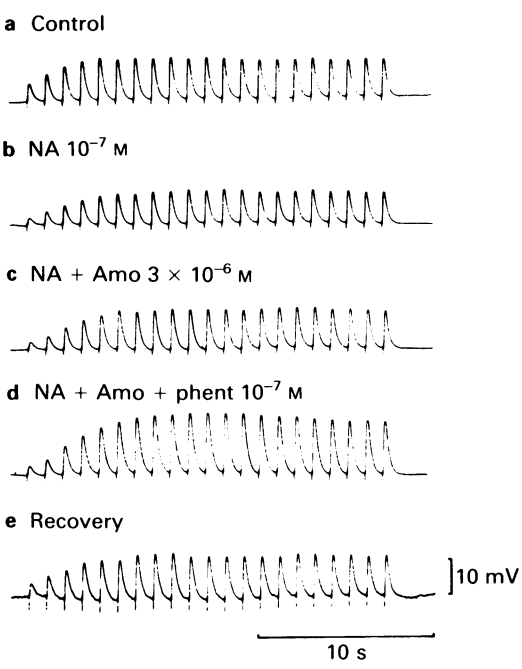

Figure 6 Effects of additive applications of 10^{-7}M noradrenaline (NA, b), 3×10^{-6}M amosulalol (Amo, c) and 10^{-7}M phentolamine (Phent, d), on e.j.ps produced by perivascular nerve stimulation (21 stimuli at 1 Hz frequency) in the guinea-pig mesenteric artery. (a) Control response recorded before application of drugs; (e) recovery responses recorded after 2 h washing period. Each train of responses was recorded at 1.5–2 min intervals, and all of the responses were recorded from the same cell.

tolamine (10^{-7}M) was added to the superfusate throughout the experiment, to block α-adrenoceptors. Application of isoprenaline (10^{-7}M) enhanced the e.j.p. amplitudes, and the enhanced amplitude of e.j.ps was again reduced by additional application of amosulalol 3×10^{-6}M.

Figure 8 shows the dose-response relationship between concentrations of isoprenaline and e.j.p. amplitudes, in the absence or presence of various concentrations of amosulalol (10^{-8}–10^{-6}M). Perivascular nerves were stimulated for 20 s at a 1 Hz frequency and the effects of isoprenaline on the first and the fully facilitated e.j.ps were observed. Amplitudes of e.j.ps (the first, and after full facilitation) increased with applications of isoprenaline in concentrations over 10^{-7}M, dose-dependently. These effects of isoprenaline were depressed by pretreatment (5 min) with amosulalol (10^{-7}M), and abolished by pretreatment with 10^{-6}M amosulalol.

In the guinea-pig mesenteric vein, a train of perivascular nerve stimulation generates slow depolarization which is sensitive to tetrodotoxin, guanethidine or phentolamine (Suzuki, 1981). Figure 9 shows effects of different types of α-adrenoceptor antagonists (i.e., prazosin, yohimbine and phentolamine) on the slow depolarizations produced by perivascular nerve stimulation in the guinea-pig mesenteric vein. When a fixed concentration (10^{-6}M) of each of these α-adrenoceptor antagonists was applied (3–5 min pretreatment), the slow depolarization was almost completely blocked by phentolamine and was depressed to about half the amplitude of the control by prazosin or yohimbine. Application of amosulalol showed a weak inhibitory effect on the slow depolarization. Effects of each of these drugs were irreversible and wash out of the drug for over 2 h produced a recovery of only 20–30% of the control.

The dose-response relationship of the effects of prazosin, yohimbine, phentolamine and amosulalol on the amplitude of the slow depolarization is shown in Figure 10. Perivascular nerves were stimulated by a train of 30 stimuli at 1 Hz frequency, and the amplitude of the slow depolarization observed in the presence of various concentrations (10^{-8}–10^{-5}M) of these drugs is expressed relative to the control. The amplitude of the slow depolarization was dose-dependently decreased by application of these drugs and the effects were the strongest in the case of phentolamine. Yohimbine showed stronger inhibitory effects on the slow depolarization than prazosin. Amosulalol showed weak inhibitory effects on the slow depolarization, and the amplitude of the slow depolarization decreased to about 50% of the control on application of 10^{-5}M amosulalol.

Discussion

The present experiments revealed that in the guinea-pig mesenteric artery, main pulmonary artery and portal vein, the noradrenaline-induced depolarization was inhibited by amosulalol, with no change in the membrane properties (i.e., the resting membrane potential, membrane resistance or spontaneous electrical activities). In the mesenteric artery (Takata, 1980), the main pulmonary artery (Suzuki, 1983) or the portal vein (Takata, 1980), exogenously applied noradrenaline depolarizes the smooth muscle membrane through activation of α_1-adrenoceptors. Thus, amosulalol has properties of a α_1-adrenoceptor antagonist.

In the guinea-pig mesenteric vein, the slow depolarization induced by perivascular nerve stimulation may be generated by noradrenaline through activation of α-adrenoceptors (Suzuki, 1981). We found that the slow depolarization is inhibited by

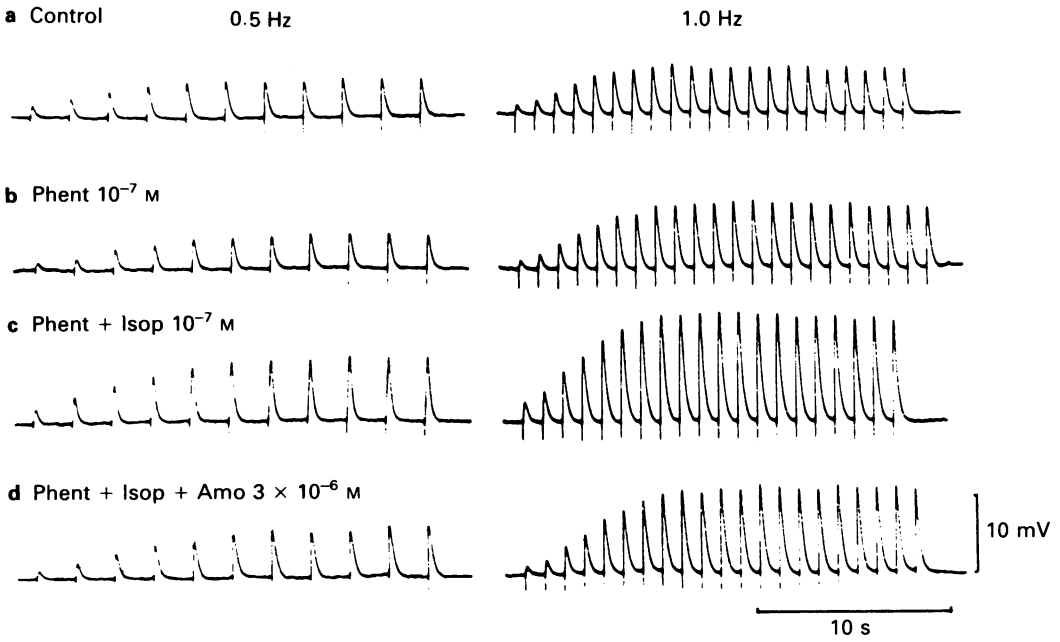

Figure 7 Effects of additive applications of 10^{-7}M phentolamine (Phent, b), 10^{-7}M isoprenaline (Isop, c) and 3×10^{-6}M amosulalol (Amo, d) on e.j.ps in the guinea-pig mesenteric artery. (a) Control responses. Perivascular nerves were stimulated 11 times at 0.5 Hz frequency (left) or 21 times at 1 Hz frequency (right). All the responses were recorded from the same cell.

phentolamine more selectively than by yohimbine or prazosin. The inhibitory effects of yohimbine were slightly stronger than those of prazosin. These observations suggest that the smooth muscle membrane of the guinea-pig mesenteric vein possesses both α_1- and α_2-adrenoceptors. This finding is slightly different from that seen in the guinea-pig renal vein (Makita, 1983) or the dog mesenteric vein (Suzuki, 1984; Kou *et al.*, 1984) in which noradrenaline depolarizes the smooth muscle membrane mainly through activation of α_2-adrenoceptors. Amosulalol showed weak inhibitory effects on the membrane depolarizations produced by both endogenous and exogenous noradrenaline, thereby suggesting that amosulalol has only a small inhibitory effect on the α_2-adrenoceptors.

Amplitudes of e.j.ps generated by single stimuli of perivascular nerves were not modified by application of amosulalol, but those seen after the facilitation was completed with repetitive stimulation of nerves were enhanced by high concentrations (over 10^{-6}M) of amosulalol. Application of α-adrenoceptor antagonists such as phentolamine, yohimbine or phenoxybenzamine enhances the e.j.p. amplitude generated by repetitive stimulation of nerves, presumably due to inhibition of α-autoinhibition mechanisms at the prejunctional membrane (Kuriyama & Makita, 1983). Activation of the α-autoinhibition mechanism by exogenously applied noradrenaline decreased the e.j.p. amplitude, and the effects of noradrenaline were inhibited by amosulalol. Therefore, the enhancement of the e.j.p. amplitude by amosulalol may be due to the inhibition of α_2-adrenoceptors at perivascular nerve endings. However, the inhibitory effects of amosulalol on the α_2-adrenoceptor may be very weak, since additional application of phentolamine further enhanced the e.j.p. amplitude.

In vascular tissues, β-adrenoceptors are located both in the pre- and post-junctional membranes, and activation of the latter relaxes the smooth muscles while that of the former enhances the release of transmitter (Vanhoutte *et al.*, 1981). The smooth muscle membrane of the guinea-pig portal vein is hyperpolarized by application of isoprenaline and the effect is antagonized by available β-adrenoceptor antagonists (Takata, 1980). Amosulalol also blocked the isoprenaline-induced hyperpolarization in this tissue. Thus, amosulalol possesses a property which blocks β-adrenoceptors. A similar conclusion is derived from evidence that amosulalol blocks the enhancement of e.j.p. amplitude by isoprenaline in the mesenteric artery.

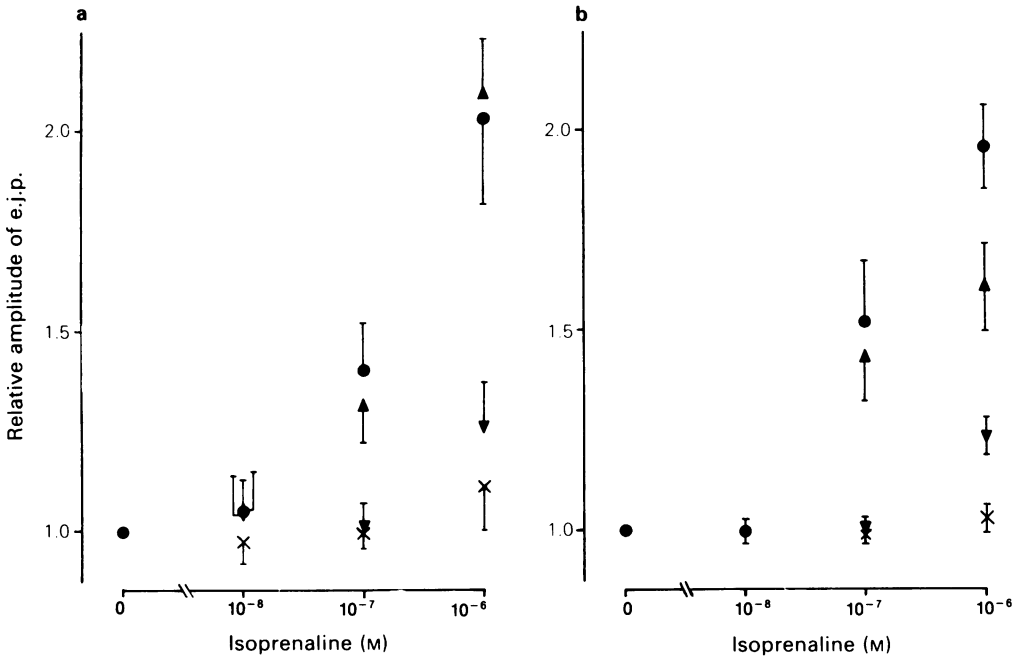

Figure 8 Dose-response relationship of the effects of isoprenaline on the amplitudes of the first (a) and the fully facilitated e.j.ps (b), recorded in the guinea-pig mesenteric arteries pretreated for 5 min with various concentrations of amosulalol (●, control; ▲, 10^{-8}M; ▼, 10^{-7}M; x, 10^{-6}M). Phentolamine (10^{-7}M) was present throughout the experiment. Perivascular nerves were stimulated 21 times with 1 Hz frequency, at 1.5–2 min intervals. Mean of 5–8 observations is shown as relative to the control value obtained before application of isoprenaline; s.d. shown by vertical lines.

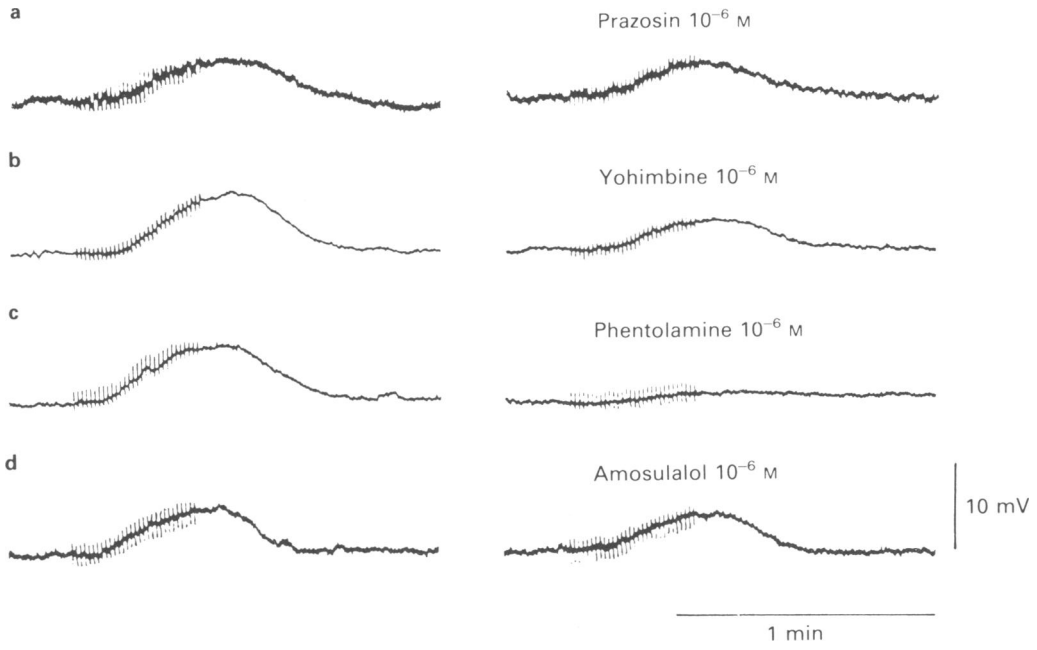

Figure 9 Effects of prazosin (a), yohimbine (b), phentolamine (c) and amosulalol (d) on the slow depolarization produced by perivascular nerve stimulation in the guinea-pig mesenteric vein. Perivascular nerves were stimulated by a train of 30 pulses (0.05 ms in duration and 100 V in intensity) at 1 Hz frequency. The nerve stimulation was repeated at 3–5 min intervals and each drug (at a concentration of 10^{-6}M) was applied for 5–8 min before recording the second response (control response is shown at left hand side). The effects of each of these drugs were observed in different tissues.

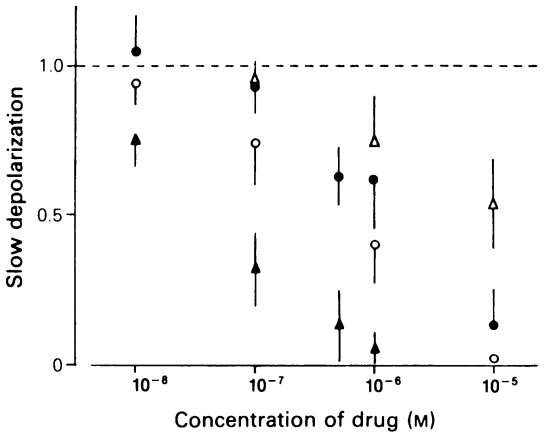

Figure 10 Dose-response relationship of the effects of α-adrenoceptor antagonists on the slow depolarizations produced by perivascular nerve stimulation in the guinea-pig mesenteric vein. (●) Prazosin; (○) yohimbine; (▲) phentolamine; (△) amosulalol. Perivascular nerve stimulation (0.05 ms in duration, 100 V, 1 Hz frequency, 30 stimuli) was applied repetitively every 3–5 min, while each drug was applied cumulatively from lower (10^{-8}M) doses. Each point is a mean of 8–14 observations obtained from 3–5 different tissues; vertical lines show s.d. The amplitude of the slow depolarization is expressed relative to the control which was obtained before application of drugs. Dotted line shows relative amplitude of 1.0 (= control value).

In summary, in the guinea-pig vascular tissues, amosulalol blocked the actions of noradrenaline and isoprenaline at pre- and post-junctional membranes, with no change in the membrane properties of the smooth muscle cells. The inhibitory effects of amosulalol may be due to inhibition of α_1- and β-adrenoceptors. High concentrations of amosulalol had only weak inhibitory actions on α_2-adrenoceptors located in perivascular adrenergic nerve endings and in smooth muscle membrane of the mesenteric vein.

This combination of α- and β-adrenoceptor blockade may be effective for the clinical control of blood pressure, because β-blockade would overcome the reflex cardioacceleration resulting from α-blockade and α-blockade would eliminate the peripheral vasoconstriction resulting from nonselective β-blockade.

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