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VASODILATING PROPERTIES OF β-ADRENOCEPTOR BLOCKERS WITH INTRINSIC SYMPATHOMIMETIC ACTIVITY

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1 *In vitro* experiments have been performed using 33 preparations of human arteries and veins and 10 human umbilical artery preparations. Changes in the tone of helical strips of vasculature were recorded isometrically following contraction of the tissues by exposure to 5-hydroxytryptamine (10^{-6}–10^{-5} M) or potassium (127 mM).

2 Isoprenaline induced concentration-dependent relaxation and this effect could be competitively antagonized by propranolol or sotalol.

3 The β-adrenoceptor antagonists pindolol and celiprolol, both of which possess intrinsic sympathomimetic activity, produced concentration-dependent relaxations of arteries and veins but not of umbilical vessels.

4 The relaxation produced by pindolol or celiprolol could be antagonized but not abolished by pretreatment with propranolol or sotalol.

5 It is concluded that the vascular relaxation produced by β-adrenoceptor antagonists with intrinsic sympathomimetic activity is the result of β_2-adrenoceptor stimulation. In the case of pindolol the relaxant effects were seen at concentrations within the range encountered after administration of normal therapeutic doses suggesting that this effect may contribute to the haemodynamic responses to pindolol seen in man.

Introduction

Treatment with β-adrenoceptor blockers is associated with an initial increase in peripheral resistance, concomitant with a reduction in cardiac output. This is probably due to a compensatory augmentation in sympathetic vasoconstrictor activity and α-adrenoceptor stimulation. Such a response pattern is, however, not seen during the first 2 months of treatment with pindolol. With prolonged treatment there is even a reduction of peripheral resistance below the initial level (Atterhög *et al.*, 1977).

The question is whether this mechanism is simply due to a reduction in sympathetic vasoconstrictor activity or if it is an expression of a direct vasodilator effect of pindolol. The object of the present study was to investigate if pindolol affects smooth muscle tone in human isolated blood vessel preparations.

Methods

Thirty-three vascular preparations were tested in an organ bath, monitoring isometric contraction. Twenty-three specimens (arteries and veins), were obtained during abdominal surgery (herniotomies) and vascular surgery (stripping of varicose veins). Ten umbilical arteries were received from the maternity hospital. All vessels were freshly prepared by dissection and stored in chilled Krebs-Ringer solution. Small helical strips were cut from each vessel (length 10–20 mm) and suspended in an organ bath of 20 ml capacity equipped with a system for recording isometric tension. The organ bath was filled with Krebs-Ringer solution, kept at a constant temperature of 37°C and treated with a gas mixture of 95% oxygen and 5% carbon dioxide. Tension was recorded continuously and cumulative dose-response curves for relaxation were calculated for isoprenaline and pindolol after precontraction with 5-hydroxytryptamine or 127 mM potassium chloride solution.

The dose-response curves were calculated using a special program adapted for an Apple II computer connected to a plotter (Thulesius & Stephen, 1982).

Drugs used were 5-hydroxytryptamine creatine sulphate (Sigma), isoprenaline hydrochloride (B.P.), pindolol (Sandoz) phentolamine mesylate (Ciba),

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Table 1 Mean values for threshold (Th) and ED_{50} concentrations (M) and relaxation (Rlx) (%)

	Arteries				*Veins*			
	Th	ED_{50}	*Rlx*	n	*Th*	ED_{50}	*Rlx*	n
Isoprenaline	1×10^{-7}	2×10^{-6}	43	4	1×10^{-6}	1×10^{-5}	16	3
Pindolol	2×10^{-7}	4.5×10^{-6}	33.5	9	2×10^{-6}	1×10^{-5}	12	6
Celiprolol	7.5×10^{-6}	5×10^{-5}	22.5	5	8×10^{-6}	4×10^{-5}	8	3

atenolol (I.C.I.), (±)-propranolol (I.C.I.), celiprolol (Chemie Linz), sotalol (Bristol), and noradrenaline (Sigma).

Results

The activity of each vascular preparation was first tested with a standard agonist known to induce maximal contraction (noradrenaline for arteries and veins and 5-hydroxytryptamine for umbilical vessels) in order to test the responsiveness. Thereafter contraction was induced by 5-hydroxytryptamine (10^{-6}–10^{-5} M) or potassium chloride (127 mM). During this precontracted state isoprenaline was administered in increasing concentrations. This induced a dose-dependent relaxation which could be blocked by propranolol and sotalol, indicating that is was the result of a β_2-adrenoceptor stimulation (cf. Table 1).

The administration of pindolol and celiprolol similarly gave rise to a dose-dependent reduction in vascular tone with a threshold value of 2×10^{-7} M in arteries and 2×10^{-6} M in veins. In umbilical arteries no such response could be detected. This relaxant response was inhibited but not completely abolished by propranolol and sotalol. The administration of atenolol and sotalol did not change the level of smooth muscle contraction, whereas propranolol itself induced some relaxation.

Discussion

The results show that both pindolol and celiprolol, β-adrenoceptor blockers with intrinsic sympathomimetic activity (ISA) are capable of inducing a dose-dependent relaxation of human arteries and veins *in vitro*. The concentration at which these responses were observed are within the therapeutic dose range observed after a single oral dose of 15 mg pindolol (Bangah *et al.*, 1980). Therefore, there is a possibility that β-adrenoceptor blockers with ISA may have vasodilating properties.

The most likely explanation for the vasodilatory response is a β_2-adrenoceptor stimulation, similar to that induced by isoprenaline. The vasodilation was, however, not entirely blocked by the non-selective β-adrenoceptor blockers propranolol and sotalol. The pindolol-induced dilatation was not the result of α-adrenoceptor blockade, since the response was not altered after phentolamine. The residual relaxation seen after pretreatment with sotalol could have resulted from an additive membrane stabilizing effect although the concentrations of pindolol seems to have been too low. In experiments on spontaneously beating guinea-pig atria negative chronotropic and inotropic effects have only been observed with threshold concentrations of 5.10^{-5} M (Waite, personal communication).

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