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PINDOLOL – THE PHARMACOLOGY OF A PARTIAL AGONIST

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1 Pindolol is a non-selective β-adrenoceptor blocking agent; its affinity to adrenoceptors in guinea pig atria (β_1) is not significantly different from that in guinea pig trachea ($\beta_1 + \beta_2$) and canine vascular smooth muscle (β_2).

2 Pindolol displays a striking diversity of agonist activities in isolated tissues. Stimulant effects correspond to 40–50% of the maximum effects of isoprenaline in isolated kitten atria and guinea pig trachea and to only 10% in guinea pig atria. Effects in canine isolated mesenteric vessels are those of a full agonist, maximum responses equalling those of isoprenaline. These findings suggest that the stimulant effects of pindolol are exerted principally on β_2-adrenoceptors.

3 Cardiac stimulation produced by pindolol in the dog is sufficient to compensate for the cardiac depression resulting from blockade of β-adrenoceptors in the heart. Reductions in cardiac output and compensatory increases in total peripheral resistance do not occur or are much smaller than those produced by β-adrenoceptor blocking agents lacking sympathomimetic activity.

4 Pindolol-induced relaxation of bronchial smooth muscle prevents or minimizes the bronchoconstrictor effects of injected spasmogens in the cat.

5 Pindolol has marked vasodilator activity, small doses reducing femoral and mesenteric vascular resistance by approximately 30%. Doses comparable to those used in hypertensive patients lower blood pressure by 20 mmHg in non-anaesthetized dogs.

Introduction

How can a molecule stimulate and block a receptor at the same time? This apparent paradox can be explained by considering events involved in the stimulation and blockade of a β-adrenoceptor (Clark, 1982).

The β-adrenoceptor is a small region of the cell surface membrane which combines chemically with a drug. The three major sites for attachment of the agonist isoprenaline are shown schematically in Figure 1a. The catechol moiety of isoprenaline represents that portion of the molecule which is important for triggering the complex series of intracellular events which lead to the characteristic response of the cell. A pure agonist has a chemical structure which is optimal for activating the receptor. When present in sufficient concentration, it will evoke the maximum physiological response of the cell since it stimulates all the receptors with which it combines. A partial agonist, e.g. pindolol, has a chemical structure which is not optimal (Figure 1b) and the process of activation is consequently slow and inefficient. Even when all the receptors are occupied, the maximum response achieved will be smaller than that produced by a full agonist. A partial agonist must combine with the receptor in order to produce its stimulant effect, and during the time that the drug/receptor combination exists, access of other molecules to the receptor will be prevented. The pharmacological effect of a partial agonist is therefore not only that of stimulation but also of receptor occupation, i.e. blockade. The blocking activity of partial agonists such as prenalterol and salbutamol is of minor importance since their intrinsic activity predominates, being sufficiently pronounced to exert therapeutically beneficial effects. The intrinsic activity of pindolol is too weak to be of use in cardiac failure or obstructive lung disease, but is nevertheless sufficient to reduce the frequency and severity of side effects (bronchospasm, cold extremeties, cardiac failure) which may occur as a result of β-adrenoceptor blockade (Clark, 1982).

Effects on the heart

Kaumann & Blinks (1980) compared the intrinsic activities of nine β-adrenoceptor blocking agents in kitten isolated atria. Increases in the rate of spontaneous contraction produced by pindolol, oxprenolol, practolol and alprenolol are shown in Figure 2. Pindolol has the most marked activity of the four compounds, the maximum increase in rate amounting to approximately 50% of the maximum effect of (−)-isoprenaline.

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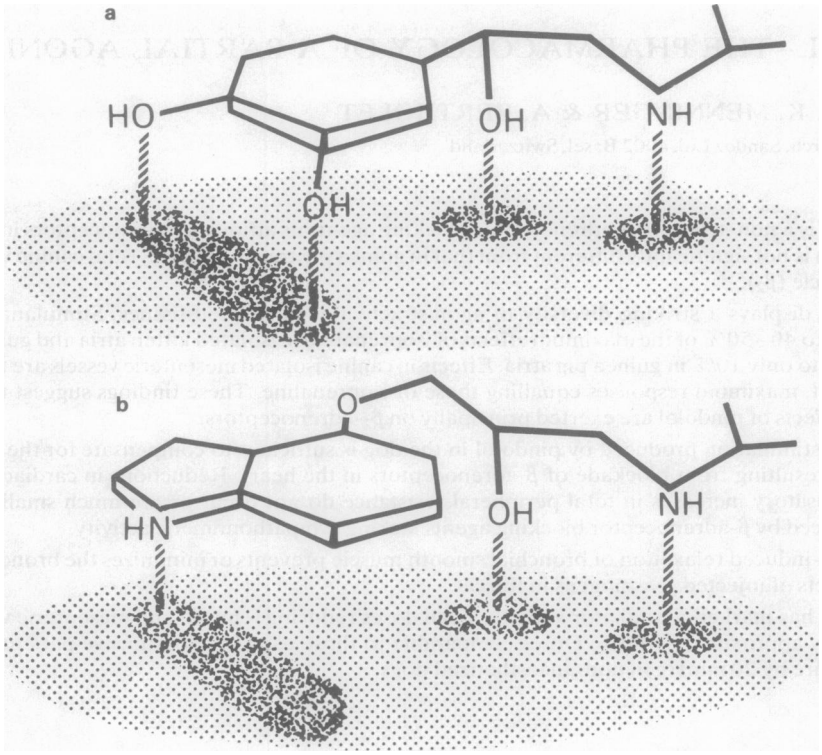

Figure 1 Diagrammatic representation of the β-adrenoceptor showing the major points of attachment for a) an agonist (isoprenaline) and b) a partial agonist (pindolol), (Clark, 1982.)

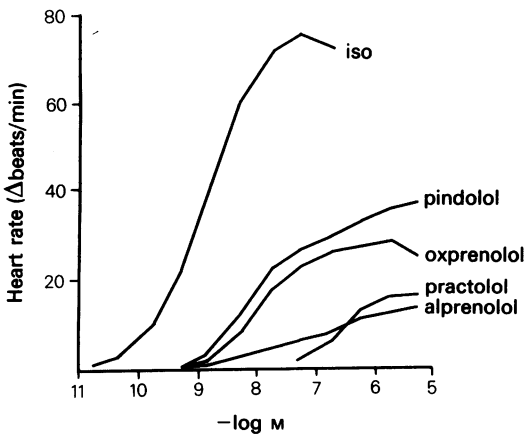

Figure 2 Positive chronotropic effects of four partial agonists compared with that of a full agonist in right atria of kittens. Mean cumulative concentration-response curves for (−)-isoprenaline (iso) and racemic mixtures of pindolol, oxprenolol, practolol and alprenolol (after Kaumann & Blinks, 1980).

The maximum increase in the rate of contraction produced by pindolol *in vivo* is very similar to that occurring in the isolated tissue. Figure 3 depicts results obtained with pindolol and its enantiomers in vagotomized cats in which sympathetic control of the heart was eliminated by ligating the spinal cord in the cervical region. Intravenous doses of the test compounds were given at 30 min intervals; a submaximal dose of isoprenaline was administered 10 min after each dose to establish the degree of blockade produced. Pindolol inhibited the positive chronotropic effects of isoprenaline dose-dependently, and also increased heart rate and myocardial contractile force. The effects of (−)-pindolol were similar. An unexpected finding was that (+)-pindolol, which was at least 100 times less potent than the racemate in inhibiting isoprenaline effects, was only about five times less potent in increasing heart rate. The effects of (+)-pindolol on myocardial contractility are rather variable in this preparation, and no positive inotropic effects were observed in the series of experiments illustrated in Figure 3.

It was assumed that the stimulant effects of pindolol must reflect an action on cardiac β-

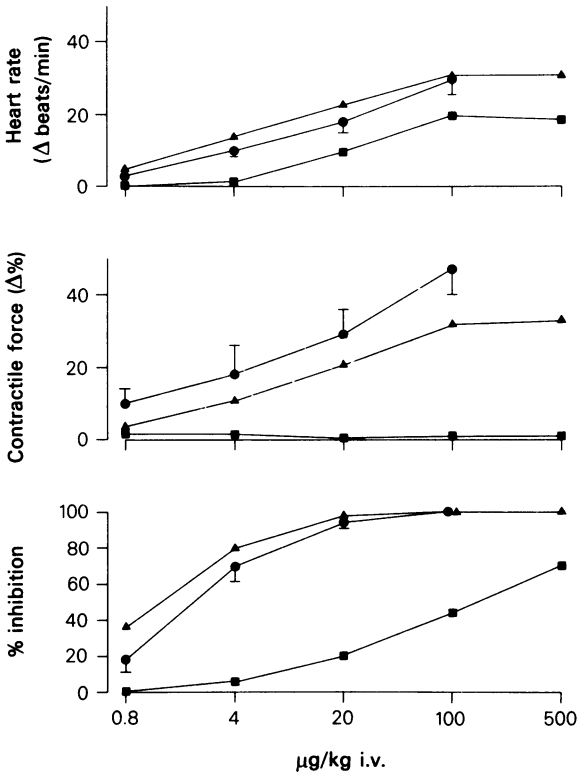

Figure 3 Increases in heart rate and myocardial contractile force, and inhibition of positive chronotropic effects of isoprenaline 0.1 μg/kg i.v. produced by pindolol and its enantiomers in vagotomized, spinal cats. Intravenous doses of (−)-pindolol (▲), (+)-pindolol (■), and the racemic mixture (●) were given at 30 min intervals. Means ± s.e.mean, $n = 4$.

adrenoceptors but we have been unable to confirm this in the spinal cat. Three animals were given propranolol 1 mg/kg i.v. 10 min before beginning the experiment; pindolol produced increases in rate and contractile force which were not significantly different from those obtained in the absence of propranolol. Higher doses of propranolol were not used since they are known to exert membrane-stabilizing activity.

Pindolol has been reported to increase heart rate by up to 120 beats/min in syrosingopine-treated rats (Barrett & Carter, 1970; Bilski *et al.*, 1979) and by 60 beats/min in reserpinized cats (Clark, 1976). In the spinal cat, heart rate can increase by up to 40 beats/min. These models are useful tools for comparing the activities of different drugs but are of little value in predicting the degree of cardiac stimulation which a compound might produce in man. The conscious dog appears to be a more reliable model. Man in't Veld & Schalenkamp (1981) reported that oral administration of pindolol 5 mg three times daily increases heart rate by 10–21 beats/min in patients with efferent or afferent lesions of the baroreflex arc, a clinical picture resembling that of ganglion blockade. We have administered pindolol at a dose of 150 μg/kg i.v. to three dogs treated with the ganglion blocking agent, chlorisondamine (Ecolid). The heart rate increases recorded were similar to those in patients with chronic autonomic failure, i.e., 16, 17 and 26 beats/min (Figure 4).

The effect of pindolol on heart rate in subjects with normal autonomic control depends on the initial level. In general, heart rate increases when resting rate is below 70 beats/min, and decreases at resting rates in excess of 90 beats/min. At rates between 70 and 90 beats/min, little change will occur (Rosenthal *et al.*, 1979). It appears that at these intermediate rates, the intrinsic activity of pindolol is sufficient to compensate for the fall in heart rate which would result from inhibition of cardiac sympathetic drive. We have attempted to confirm this in dogs in which vagal influences on heart rate were eliminated with atropine (Figure 4). Mean heart rate at the beginning of the experiments was 72 beats/min. Atropine infusion caused marked tachycardia, which settled to a steady level of 143 beats/min (mean of 8 experiments). Intravenous administration of pindolol 150 μg/kg resulted in an abrupt fall in heart rate followed by a slight increase, settling within 15 min to a rate 10 beats/min below the initial value. In a second group of animals treated with propranolol 1.5 mg/kg i.v., the mean fall in heart rate was 30 beats/min 15 min after administration. The difference between the effects of pindolol and propranolol (20 beats/min) was equal to the mean increase in rate which occurred in response to pindolol in the ganglion-blocked animals. Figure 4 also illustrates an experiment in an atropine-treated dog in which pindolol was given 12 min after administering propranolol. The intrinsic activity of pindolol exactly compensated for the reduction in cardiac sympathetic drive produced by propranolol, and heart rate was restored to its initial level.

Effects on vascular smooth muscle

The relaxant effect of pindolol on vascular smooth muscle is more pronounced than its stimulant effect on the heart, when maximum responses are compared with those of isoprenaline. Vasodilator activity was studied in isolated mesenteric vessels of the dog perfused under constant flow conditions according to the method described by Clark & Bertholet (1982). Pressure within the system was increased by adding 40 mM potassium chloride to the perfusion fluid. Close arterial injections of pindolol produced repro-

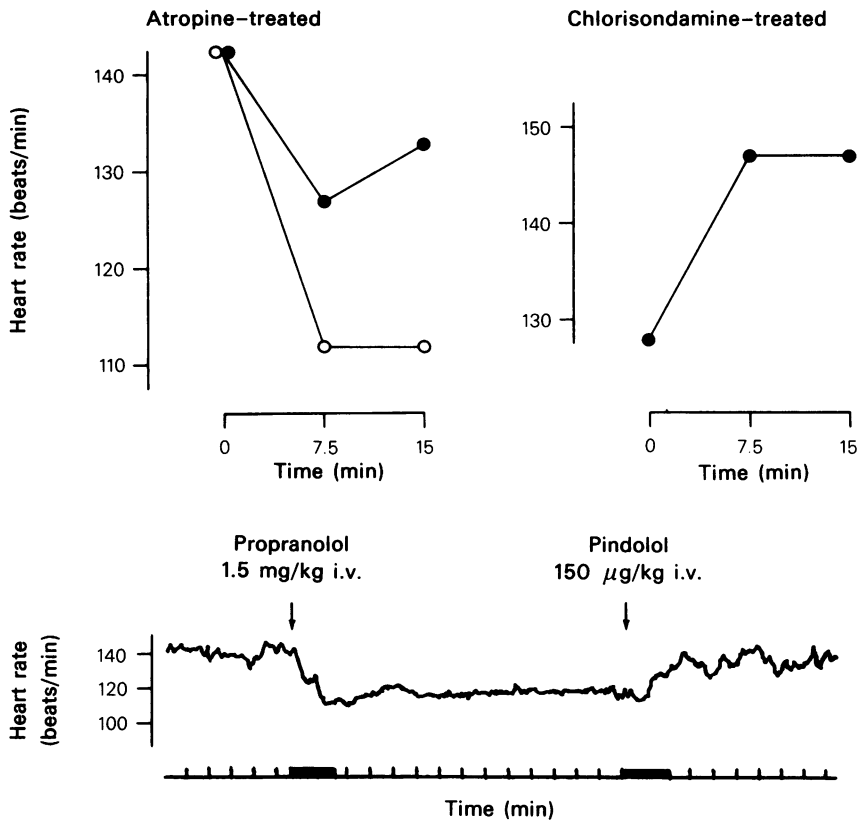

Figure 4 Mean changes in heart rate produced by propranolol 1.5 mg/kg i.v. (O——O) and pindolol 150 μg/kg i.v. (●——●) in conscious dogs pretreated with atropine ($n = 4$) or chlorisondamine (pindolol only, $n = 3$). Lower panel shows a heart rate recording in an atropine-treated dog.

ducible, dose-dependent reductions in vascular resistance. In this tissue, pindolol behaved as a full agonist with maximum responses equalling those of isoprenaline (Figure 5).

The similarity in response to the two enantiomers was even more remarkable in the isolated vessel preparation than on the heart in the spinal cat. The effects produced were not significantly different from each other or from the racemate. The latter finding raised the question as to whether the vasodilator effects of pindolol might be non-specific. This seems unlikely, since only compounds known to possess intrinsic activity (e.g., oxprenolol and alprenolol) have vasodilator activity in this preparation; propranolol and atenolol are inactive. In addition, the dose-response curve for pindolol was displaced to the right by a relatively high concentration of propranolol (10^{-7} M) added to the perfusion fluid 30 min before the first dose of pindolol (Figure 5) indicating that vasodilation occurred as the result of β-adrenoceptor stimulation.

A reduction in resistance in the femoral vascular bed has been demonstrated for pindolol in chloralose-urethane anaesthetized dogs following close arterial administration. A cannula was introduced into the right iliac artery via the ipsilateral femoral artery. Blood flow in the right femoral artery was measured by means of an electromagnetic flow probe. Flow increased transiently and dose-dependently in response to bolus injections of isoprenaline and pindolol. Corresponding volumes of 0.9% sodium chloride solution produced negligible changes. In the experiment illustrated in Figure 6, the maximum reduction in resistance obtained in response to pindolol was 86% of the maximum effect obtained in response to isoprenaline. Reductions in femoral vascular resistance in a denervated limb have also been obtained following intravenous administration of very small doses (3–12 μg/kg) of pindolol (*vide infra*). In addition, a dose comparable to that used therapeutically (150 μg/kg i.v.) reduced mean blood pressure by 20 mmHg in four of six conscious

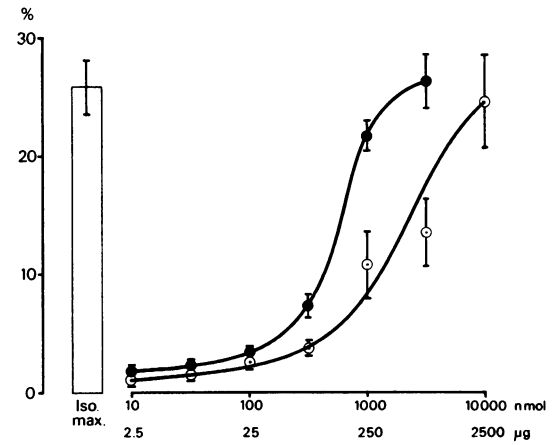

Figure 5 Mean ± s.e.mean decreases in resistance in isolated, perfused mesenteric vessels of the dog, produced by intra-arterial injections of pindolol alone (●——●, $n=5$) and in the presence of propranolol 10^{-7} M (○——○, $n=5$). Open column represents the mean maximum effect of isoprenaline ($n=7$).

dogs pretreated with atropine. Blood pressure remained constant in five dogs given propranolol 1.5 mg/kg i.v.

Effects on bronchial smooth muscle

Spirally-cut strips of guinea pig trachea or single tracheal rings incubated for 30 min in Krebs-Henseleit solution develop spontaneous tone without the addition of constrictor substances (Bertholet *et al.*, 1981). Although reproducible dose-response curves can always be obtained with isoprenaline in this preparation, increasing concentrations of pindolol fail to produce dose-dependent effects. Reliable estimates of the tracheal smooth muscle relaxant activity of the compound can be obtained, however, by comparing the response to a single concentration with that obtained with a supramaximal dose of isoprenaline (Waite, 1978). The maximum effect obtained with racemic pindolol amounted to approximately 40% of the maximum response to isoprenaline (Figure 7). Significant relaxation occurred at concentrations within the range of therapeutic plasma levels found in man, i.e., 10–50 ng/ml. Similarity between responses to the two enantiomers was observed again. The laevoenantiomer of pindolol is approximately 300 times more potent than the dextroenantiomer in inhibiting the relaxant effect of isoprenaline in the preparation. The two enantiomers are equipotent, however, in relaxing tracheal smooth muscle (Waite, 1978). The intrinsic activity of pindolol is clearly not a stereospecific property of the molecule.

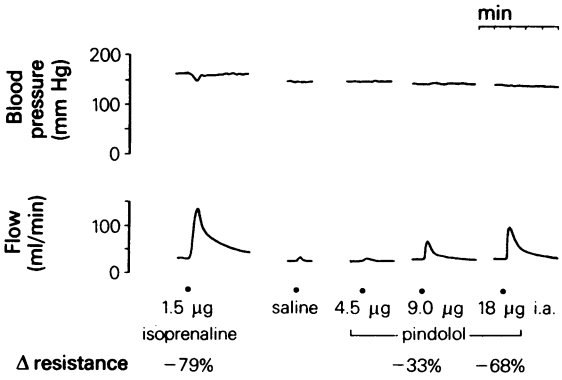

Figure 6 Effects of intra-arterial doses of isoprenaline and pindolol on femoral artery blood flow and resistance in a chloralose-urethane anaesthetized dog.

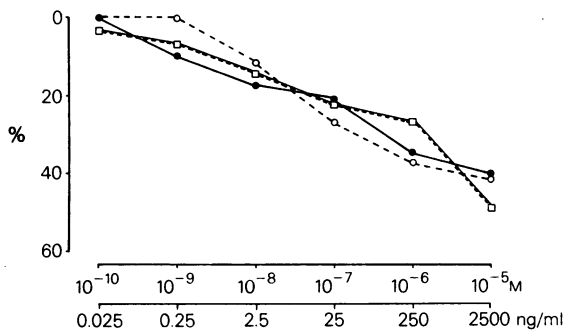

Figure 7 Relaxant effects of (−)-pindolol (□), (+)-pindolol (○) and the racemic mixture (●) in the guinea pig isolated trachea expressed as percentages of the response to a supramaximal dose of isoprenaline (10^{-7} M). Each point is the mean of 4 experiments (after Waite, 1978).

Experiments in anaesthetized cats indicate that the relaxant effect observed in isolated tracheal smooth muscle is of relevance in the whole animal. Air overflow during constant pressure ventilation was recorded using the Konzett-Rössler technique in cats anaesthetized with Numal ®. Intravenous doses of histamine, acetylcholine and serotonin produced reproducible, transient increases in air overflow i.e., bronchoconstriction. Administration of pindolol 10 and 1000 µg/kg by the intravenous or the intraduodenal route produced long-lasting inhibition of the bronchoconstrictor effects of all three stimuli, but did not alter resting bronchial tone. In contrast, intravenous administration of propranolol produced a small increase in air overflow and failed to reduce responses to histamine (D. Römer, personal communication).

Haemodynamic effects

The haemodynamic effects of five β-adrenoceptor blocking drugs were compared in anaesthetized dogs. Our objective was to determine the degree to which intrinsic sympathomimetic activity might modify the alterations in cardiac function and vascular resistance resulting from β-adrenoceptor blockade (Clark, 1982). The compounds selected were pindolol (non-selective with intrinsic activity), propranolol (non-selective), practolol (β_1-selective with intrinsic activity), metoprolol (β_1-selective) and atenolol (β_1-selective). Myocardial contractility was measured by means of a strain gauge arch sutured to the right ventricle; cardiac output was registered by an electromagnetic flow probe placed around the ascending aorta. Increasing doses of each compound were administered intravenously at 30 min intervals to groups of four to five dogs. A submaximal dose of isoprenaline was given 5 min after each dose to assess the degree of blockade. The dose range chosen for each compound produced equivalent blockade of isoprenaline-induced tachycardia, but isoprenaline-induced hypotension was inhibited only by propranolol and pindolol.

Decreases in heart rate produced by the five β-adrenoceptor blocking drugs were relatively small considering the high initial rate (115–180 beats/min). We have shown that reflex withdrawal of vagal tone is an important compensatory mechanism when sympathetic drive to the sinus node is depressed. Decreases in myocardial contractility were more pronounced, especially with compounds lacking sympathomimetic activity (Figure 8). Atenolol depressed contractility by $57 \pm 4\%$, metoprolol by $54 \pm 12\%$ and propranolol by $41 \pm 9\%$ (mean±s.e.mean). The effects of practolol and pindolol were smaller, i.e., $26 \pm 6\%$ and $30 \pm 6\%$ respectively. The difference between compounds with and without sympathomimetic activity was evident again in the changes occurring in cardiac output. Pindolol reduced cardiac output by only $14 \pm 2\%$, compared with 38.5% for atenolol. Reductions in cardiac output produced by each compound were associated with proportional increases in total peripheral resistance regardless of whether vascular β_2-adrenoceptors were blocked or not (Figure 8). These experiments provide unequivocal evidence that the increases in total peripheral resistance which occur in response to most β-adrenoceptor blocking agents do not reflect blockade of vascular β-adrenoceptors, but represent a reflex circulatory adjustment to a depressed cardiac output. They also emphasize the value of partial agonism in minimizing the haemodynamic disturbances resulting from inhibition of cardiac sympathetic drive.

In a second series of experiments, femoral blood flow was recorded in both hind limbs by means of electromagnetic flow probes; one limb was denervated by dividing the sciatic and femoral nerves. Cardiac output was measured by dye dilution in order to keep surgical intervention to a minimum. Haemodynamic changes resulting from cardiac β-adrenoceptor blockade were less pronounced in these animals than in dogs with an open thorax, but the general pattern was similar (Figure 9). Compounds lacking intrinsic activity again produced reductions in cardiac output; maximum effects were $-19 \pm 6\%$ for propranolol, $-22 \pm 8\%$ for atenolol and $-25 \pm 5\%$ for metoprolol. These effects are significantly greater than the spontaneous changes which occur in untreated control animals (*viz.*, $-6 \pm 6\%$, mean of five observations ±s.e.mean). Total peripheral resistance increases were again proportional to the decreases in cardiac output. Administration of pindolol resulted in small increases in cardiac output which were associated with a maximum mean reduction of $13 \pm 3\%$ in total peripheral resistance. This effect, although relatively small, was considered to reflect active dilation since resistance tends to increase ($\Delta = +9 \pm 9\%$) in untreated animals. A dilator effect was clearly evident in the denervated hind limb; resistance fell by $30 \pm 10\%$ during the course of the experiment. A similar effect was not observed with practolol since this compound was tested at doses which were shown to be selective for β_1-adrenoceptors.

Discussion

There is an impressive body of evidence showing that β_1- and β_2-adrenoceptors can occur together in a single organ or tissue, and that the $\beta_1 : \beta_2$ ratio can vary for the same tissue in different species. Dog mesenteric vessels possess only β_2-adrenoceptors whereas the cat sinus node and guinea pig trachea contain a mixture of β_1- and β_2-adrenoceptors, both types mediating the same response (Daly & Levy, 1979; Minneman *et al.*, 1981). The two subtypes are also present in guinea pig atria, but the rate of contraction in this species appears to be mediated only by the β_1-adrenoceptor (Hedberg *et al.*, 1980; O'Donnell & Wanstall, 1979). Pindolol is a non-selective β-adrenoceptor antagonist; its potency in inhibiting isoprenaline effects in guinea pig atria is similar to that in guinea pig trachea and dog mesenteric vessels. In contrast, the stimulant effects of pindolol differ considerably from one tissue to another. Increases in heart rate in guinea pig atria (β_1) and cat atria ($\beta_1 + \beta_2$) amount to 10% and 50% of the maximum effect produced by isoprenaline (Kaumann & Blinks, 1980). In guinea pig tracheal preparations ($\beta_1 + \beta_2$), the maximum relaxant effect

is approximately 40% that of isoprenaline, whereas in dog mesenteric vessels (β_2), pindolol acts as a full agonist. These findings suggest that the stimulant effects of pindolol are due principally to an action on β_2-adrenoceptors. Pindolol, therefore, resembles the partial agonists soterenol and salbutamol (Malta & Raper, 1980) in that it exerts functionally selective agonist effects without binding selectively to either β-adrenoceptor subpopulation.

An unexpected characteristic of the stimulant action of pindolol is the lack of stereospecificity. The two enantiomers are equiactive in relaxing vascular

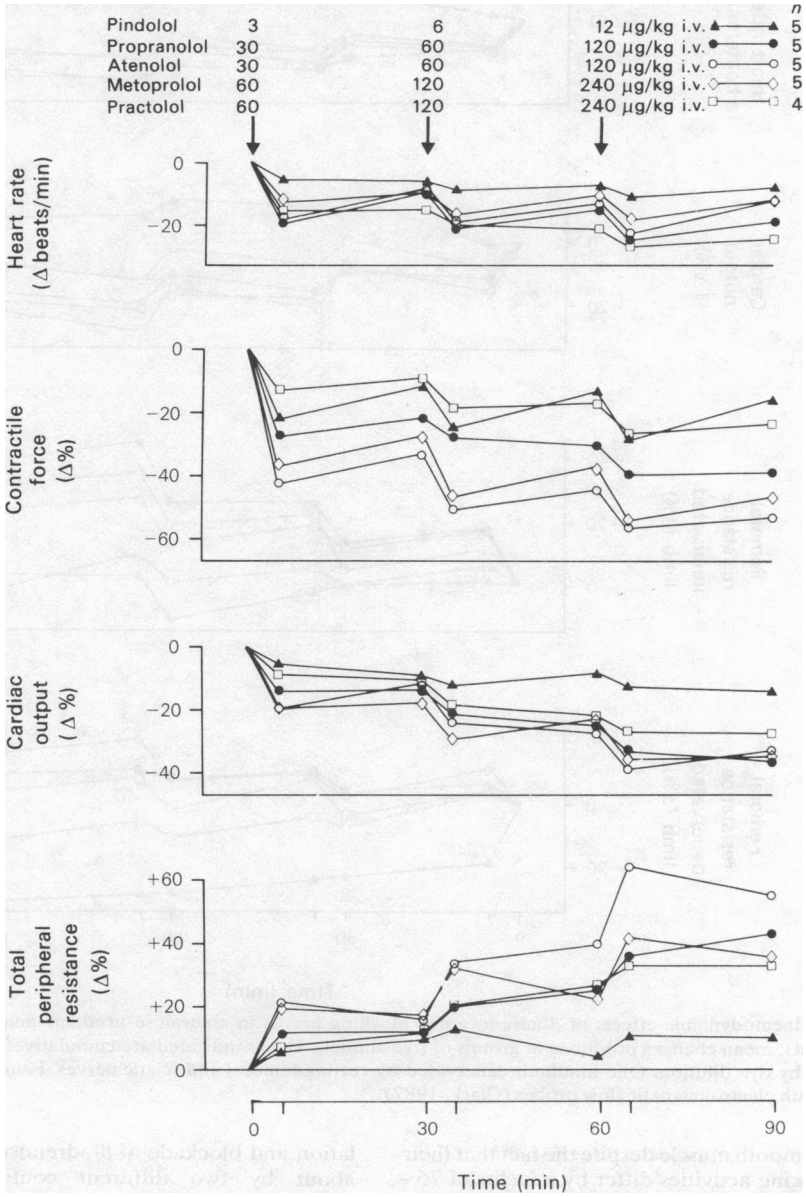

Figure 8 Haemodynamic effects of β-adrenoceptor blocking agents in chloralose-urethane anaesthetized dogs (open thorax); mean changes obtained in groups of four to five animals. Doses indicated are cumulative. Myocardial contractile force measured by means of a strain gauge arch sutured to the right ventricle; cardiac output measured with an electromagnetic flow probe on the ascending aorta. Submaximal doses of isoprenaline (0.05 or 0.1 μg/kg i.v.) were given 5 min after administration of each dose of blocking agent (Clark, 1982).

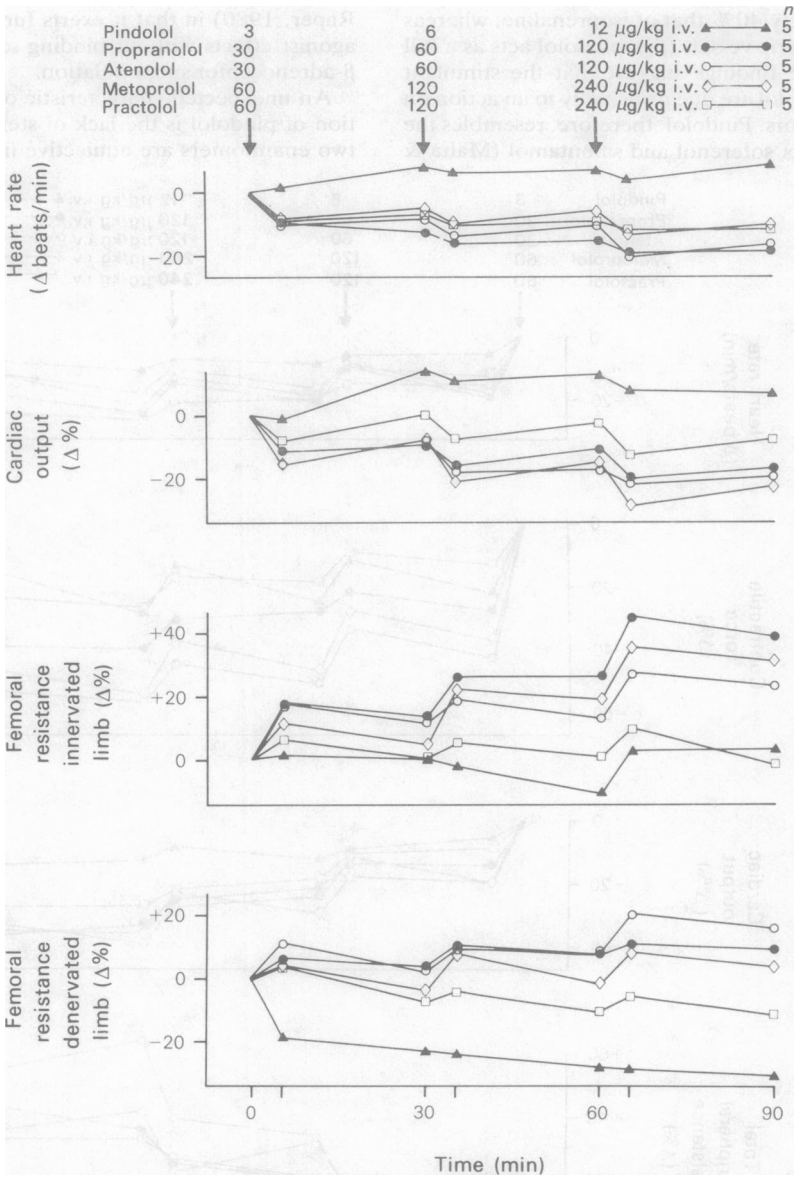

Figure 9 Haemodynamic effects of β-adrenoceptor blocking agents in chloralose-urethane anaesthetized dogs (closed chest); mean changes produced in groups of five animals. Doses indicated are cumulative. Cardiac output determined by dye dilution. One hindlimb denervated by cutting femoral and sciatic nerves. Femoral blood flow measured with electromagnetic flow probes (Clark, 1982).

and tracheal smooth muscle despite the fact that their receptor blocking activities differ by a factor of 76–300 (Waite, 1978; Clark & Bertholet, 1982). This could be interpreted as indicating that the drug produces its effects by stimulating a population of receptors which are different from those stimulated by isoprenaline. An alternative possibility is that stimulation and blockade of β-adrenoceptors are brought about by two different configurations of the molecule, the side chain hydroxyl group being an important point of attachment to the receptor for blockade but not for stimulation. A further unexplained observation is that the concentration of propranolol necessary to antagonize the relaxant effect of

pindolol in isolated vessels was at least ten times higher than that which produces substantial inhibition of the effects of isoprenaline in the same preparation. In addition, high doses of propranolol failed to influence the positive chronotropic effects of pindolol in the cat and dog. A similar phenomenon has been observed in a patient with acute dysautonomia in whom plasma noradrenaline levels were undetectable (<25 pg/ml). Intravenous doses of 12 mg propranolol and 14 mg metoprolol, given over a period of 2.5 h, had no effect on heart rate, but subsequent administration of 1.2 mg pindolol increased rate by 15 beats/min (A.M. Man in't Veld, personal communication). The effect was not different from that occurring in patients given pindolol alone (Man in't Veld & Schalenkamp, 1981). The processes involved in generating the sympathomimetic effects of pindolol seem to be more complex than has been considered hitherto. Difficulties encountered in antagonizing these effects with other β-adrenoceptor blocking agents indicate that the kinetics of the interaction of pindolol with the receptor may be fundamentally different from those governing the interaction of a pure agonist with the receptor.

The pharmacological profile of pindolol differs considerably from that of other β-adrenoceptor blocking agents, due to the fact that this compound possesses more sympathomimetic activity than other blocking drugs in clinical use. The stimulant effects are sufficiently pronounced to be not only of pharmacological interest but also of clinical relevance. We have demonstrated that effects exerted on the heart minimize or prevent the haemodynamic disturbances resulting from cardiac β-adrenoceptor blockade in the dog. Comparable results have been obtained in healthy volunteers and patients with ischaemic heart disease (Svendsen *et al.*, 1979, 1982). Stimulation of receptors in bronchial smooth muscle diminishes or prevents the bronchoconstrictor effects of injected spasmogens in the cat. This finding also has a parallel in man in that the incidence of dyspnoea occurring during therapy with pindolol is lower than that reported for a β_1-selective antagonist lacking sympathomimetic activity (Simpson, 1977; Rosenthal *et al.*, 1979). The effect of pindolol on blood vessels is of even greater interest than those on heart and bronchi. Reductions in resistance have been shown to equal those of isoprenaline in isolated mesenteric vessels, and a 30% reduction in resistance occurs in the denervated hind limb of anaesthetized dogs following a total cumulative dose of only 12 μg/kg i.v. Cutaneous hyperaemia is invariably observed in the course of experiments with pindolol in the rat and dog. It is probable that the vasodilator activity of pindolol is responsible for the relatively low incidence of peripheral vascular disturbances (cold extremities, Raynaud's phenomenon) occurring in man. Finally, a 20 mmHg reduction in blood pressure was recorded in atropinized conscious dogs in response to 150 μg/kg i.v. pindolol, an effect which cannot be attributed to a fall in cardiac output since the mean fall in heart rate in these animals was only 10 beats/min. In similar experiments, propranolol 1.5 mg/kg i.v. reduced heart rate by a mean of 30 beats/min but did not influence blood pressure. The assumption can be made that the vascular actions of pindolol contribute to its antihypertensive effect in man. It is interesting to note that pindolol is the only β-adrenoceptor blocking agent which has been reported to reduce total peripheral resistance during long term therapy in hypertensive patients (Lang & Holtmann, 1974; Torres *et al.*, 1975; Atterhög *et al.*, 1976; Tsukiyama *et al.*, 1976; Velasco *et al.*, 1980).

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