Beta-adrenoceptor blocking agents and their effects on heart and blood vessels

Barbara J. Clark

The concept that a drug combines chemically with a "receptive substance" in a cell membrane in order to produce a tissue response was first suggested just over a century ago. It is generally agreed that "receptive substances", or receptors, are parts of macromolecular complexes which interact with drugs. Although some progress has been made in their isolation and characterization in chemical and physiochemical terms, for the most part, they must nevertheless still be regarded as hypothetical entities.

Responses involving a given type of receptor are only elicited by a comparatively marrow range of chemical substances with closely similar structural groupings and electronic properties. Consideration of the position of structural elements common to powerful stimulants can provide valuable information regarding the position of complementary sites on the receptor itself. Fig. 1 depicts the most important sites of attachment to the ß-adrenoceptor for isoproterenol. Isoproterenol can elicit the maximum response of which a tissue is capable, even when occupying only a small proportion of the receptors available, i.e., it is a full agonist. A partial agonist (e g., pindolol, oxprenolol, practolol, alprenolol) is a compound which may have a high affinity for the receptor, and can also stimulate it but fails to produce the maximum response of the tissue even when all the receptors are occupied (Figs. 1 and 2). Such compounds have a dual action, since by occupying the receptor, they prevent stronger stimulants from combining with it, and thus act as antagonists.

The apparent paradox of a compound producing two opposing actions at the same time, namely stimulation and blockade, is therefore nit a paradox at all, since receptor blockade is purely the passive result of receptor occupation.

The blocking activity of the partial agonists prenalterol and salbutamol is of no practical importance since their intrinsic activity is sufficiently pronounced to exert therapeutically beneficial effects. The intrinsic activity of a compound such as pindolol, on the other hand, 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 undesirable side effects such as bronchospasm, cold

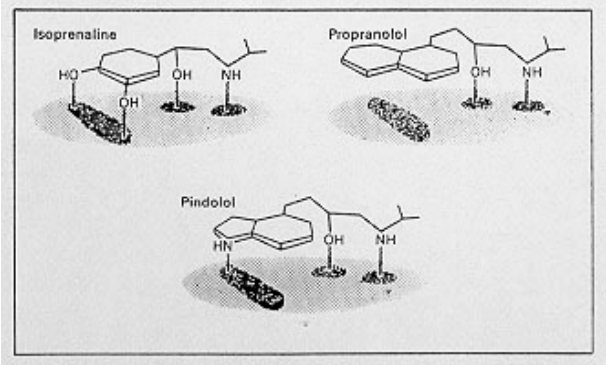

Fig. 1 - Diagrammatic representation of the β-adrenoreceptor showing the major points of attachment for na agonist (isoprenalone), a pure antagonist (propranolol) and partial agonist (pindolol).

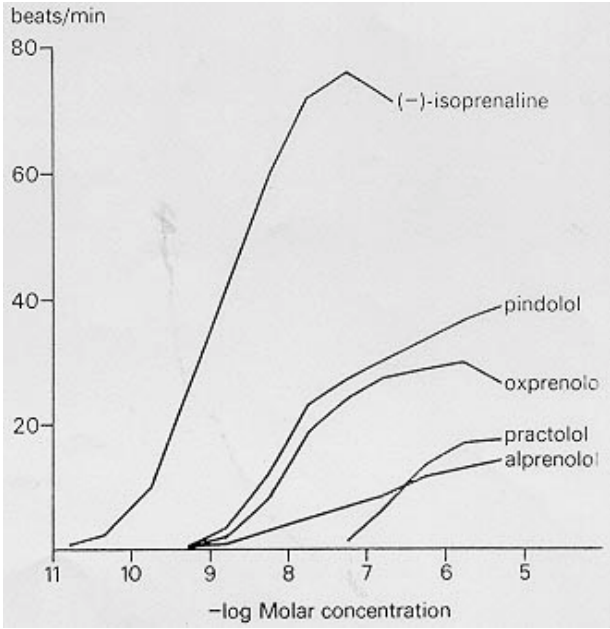

Fig. 2 - Positive chronotropic effects of 4 partial agonist compared with that of a full agonist in right atrial of kittens. Mean cumulative concentration response curves for (-)-isoprenaline and racemic mixtures of pindolol, oxprenolol, practolol and alprenolol (after Kaumann and Blinks[2]).

Member of the Royal College of Surgeons. Licentiated of the Royal College of Physicians.

extremities and bradycardia, which can occur as a result of β-adrenoceptor blockade [1].

Pharmacological and clinical findings have shown that the stimulant effects of pindolol exerted on ß-adrenoceptors in the heart and blood vessels result in a haemodynamic pattern which differs fundamentally from that produced by β-adrenoceptor blocking agents lacking this property. Moreover, experiments in isolated tissues have demonstrated that the degree of stimulation produced by pindolol is not identical in all tissues.

Effects on heart rate

Pindolol has more intrinsic activity than other ß-adrenoceptor blocking agents in clinical use; increases in the rate of contractions achieved in isolated kitten atria amount to approximately 50% of the maximum effect produced by isoproterenol [2] (Fig. 2). The response to pindolol (in beats/min) is quite considerable in the cat heart, both in vitro and in vivo, and far exceeds that which occurs in man. In patients with peripheral autonomic neuropathy, heart rate has been reported to increase from 70 ± 3 to 88 ± 4 beats/min following daily treatment with 15 mg pindolol [3]. These patients have pathologically denervated hearts. We have found that the increases in heart rate produced by pindolol in conscious, ganglion-blocked dogs (i.e., with chemically denervated hearts) correspond closely to those obtained in man (Fig. 3). We consider therefore that the dog is a suitable species to use for determining the influence of intrinsic activity on the cardiac and haemodynamic responses to β-adrenoceptor blockade.

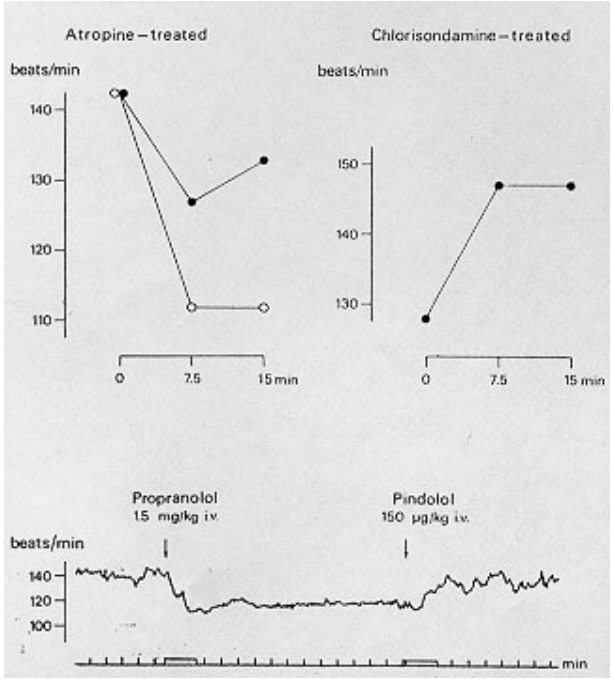

Fig. 3 - Mean changes in heart rate produced by propranolol 1.5 mg/kg i.v. (O-O) and pindolol 150 µg/Kg i.v. (•-•) in conscius dogs pretreated with atropine (n = 4) or chlorisondamine (pindolol only, n = 3). Lower panel shows a heart rate recording in an atropine-treated dog.

The effect of pindolol on heart rate in man has been shown to depend on the initial level of sympathetic nervous activity [4]. An analysis of the response to the drug in approximately 700 hypertensive patients has shown that at resting rates above 90 beats/min, heart rate will fall as the result of cardiac β-adrenoceptor blockade, when the resting rate is below 70 beats/min, intrinsic activity will be evident, and heart rate will increase. At rates between 70 and 90 beats/min, little change will occur. It appears that at these intermediate rates, the stimulant activity of pindolol is sufficien to compensate for the fall in heart rate which normally would result from inhibition of cardiac sympathetic drive [5].

We have attempted to confirm this in dogs in which vagal influences on heart rate were eliminatted with atropine (Fig. 3). 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 minutes to a rate 10 beats/min below the initial value. In a second group of animals treated with an equi-active blocking dose of propranolol (1.5 mg/kg i.v.), the mean fall in heart rate was 30 beats/min 15 minutes after administration.

The difference between the effect s 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 3 also illustrates an experiment in an atropinetreated dog in which pindolol was given 12 minutes 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.

Haemodynamic effects

The haemodynamic effects of three β-adrenoceptor blocking drugs were compared in anaesthetised 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 [1]. The compounds selected were pindolol (non-selective with intrinsic activity), propranolol (non-selective) and atenolol (β_1-selective). Increasing doses of each compound were administered intravenously at 30 minute intervals to groups of 5 dogs. A submaximal dose of isoprenaline was given 5 minutes 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.

The blocking agents lacking partial agonist activity (propranolol and atenolol) produced significant reductions in cardiac output, whereas pindolol produced small increases (Fig. 4). Changes in total peripheral resistance occurring in response to each drug were inversely proportional to the changes in cardiac output, since blood presure remained constant. The haemodynamic effects recorded in the dog were very similar to those obtained in healthy volunteers and patients with ischaemic heart disease [6,7] (Fig 5).

Femoral artery blood flow was continously measured in both hind limbs of the dogs by means of electromagnetic flow probes. One of the limbs was denervated by severing the femoral and sciatic nerves. Changes in femoral vascular resistance in the innervated limb parallelled those in total peripheral resistance the increases were eliminated or reduced by denervation. These experiments provided unequivocal evidence that resistance increases do not reflect blockade of vascular β -adrenoceptors, but represent neuronally-mediated reflex circulatory adjustments to an acutely depressed cardiac output. They also emphasise the value of partial agonism in minimising the haemodynamic disturbance consequent on blockade of cardiac sympathetic drive. The most interesting finding was the marked reduction in resistance which pindolol produced in the denervated hindlimb (Fig 4). Although blood pressure in these studies did not change significantly in response to pindolol at the doses used, falls of up to 15 mmHg had been observed in the conscious, ganglion-blocked dog at a dose (150 μg/Kg i.v.) equivalent to an oral therapeutic dose in man. It was therefore considered worthwhile examining the effect of pindolol on blood pressure in the hypertensive dog.

It is known that dogs with renal hypertension do not respond to β-adrenoceptor blocking agents despite the fact that the model is of proven value in evaluating the potential of practically all other classes of antihypertensive drugs [8]. We confirmed that propranolol (1.5 mg/wg i.v.) does not influence blood pressure in two-kidney perinephritic dogs despite the fact that it causes marked bradycardia [9]. By contrast, pindolol (150 μg/kg i.v.) produced progressive reductions in mean systemic blood pressure; the mean maximum fall obtained in 5 experiments was 25 mmHg (Fig. 6). In view of the lack of effect of propranolol, it was concluded that the fall in blood pressure in response to pindolol must be due to its vasodilator activity.

The mechanisms which may be involved in the antihypertensive effects of β-adrenoceptor blocking agents are numerous, and no single mechanism can be claimed to be wholly responsible. The degree to which they depress cardiac output and suppress renin secretion seems to be inversely proportional to the amount of intrinsic

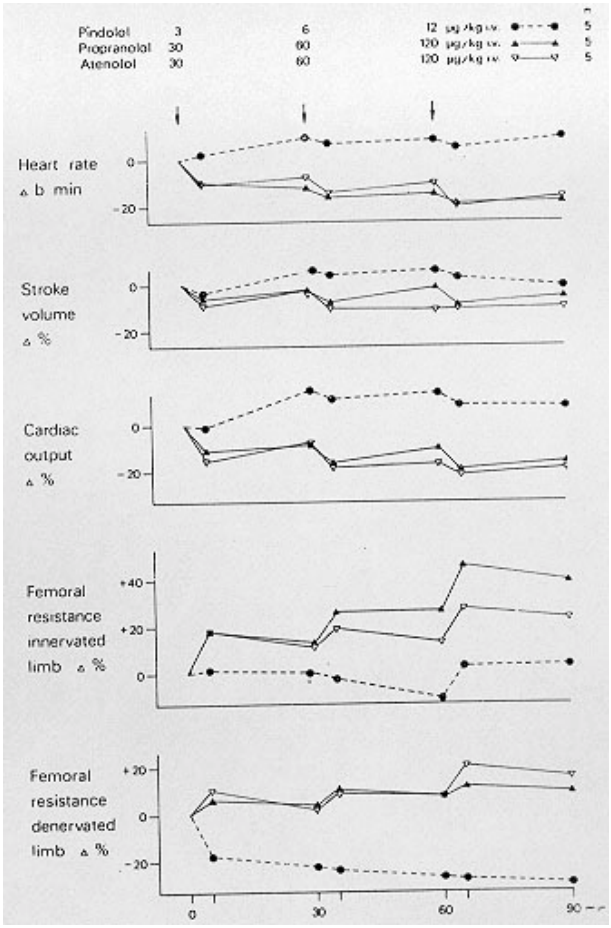

Fig. 4 - Haemodynamic effects of β-adrenoceptor blocking agents in chloraloseurethane anaesthetised dogs; mean changes produced in groups of 5 animals. Dose indicated are cumulative. Cardiac output determined by die dilution. One hindlimb denervated by cutting femoral and sciatic nerves. Femoral blood flow messured with electromagnetic flow probes.

activity which they possess [10]. Despite pharmacological differences, however they are all equally effective in lowering blood pressure in hypertensive patients. In man, compound lacking intrinsic activity produce an acute decrease. In cardiac output and a compensatory increase peripheral resistance. The blood pressure fall which occurs during long-term therapy is always associate with a reduction in vascular resistance even when cardiac output remains depressed. Resistance does not, however, fall below pretreatment levels (Fig. 7). In the case of pindolol, cardiac output undergoes little change in response to acute administration. Vascular resistance falls with time, but to levels below those before treatment began since no initial elevation occurred [10,11]. It is not. known whether the antihypertensive effect of pindolol is due to stimulation of vascular β-adrenoceptors or to the same (unknown) mechanism which reduces resistance with the pure antagonists. Both maybe involved.

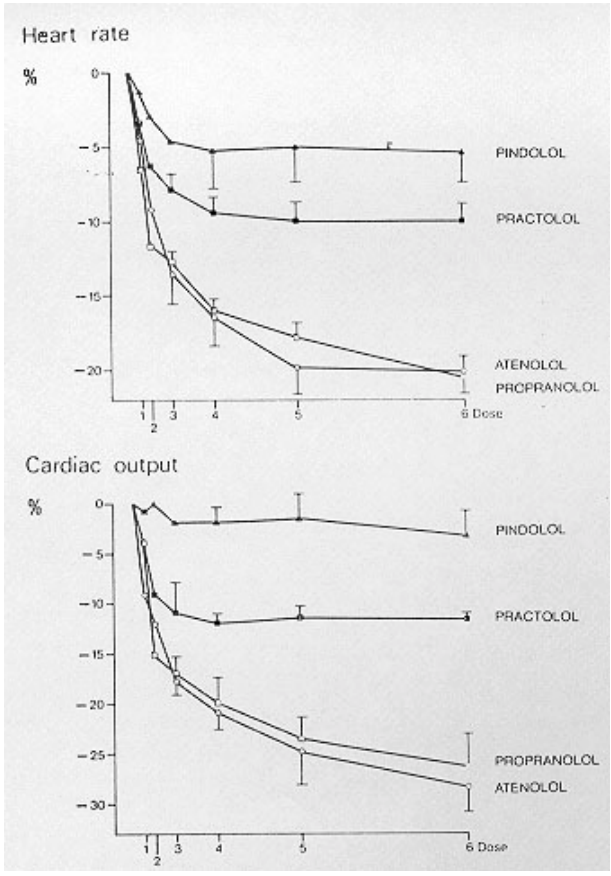

Fig. 5 - Reductions in heart rate and cardiac output after intravenus administration of 6 equipotent, logarithmically doses of β-adrenoceptor blocking agents in healthy volunteers (means ± S.E.M.) (after Svendsen et al.[6]).

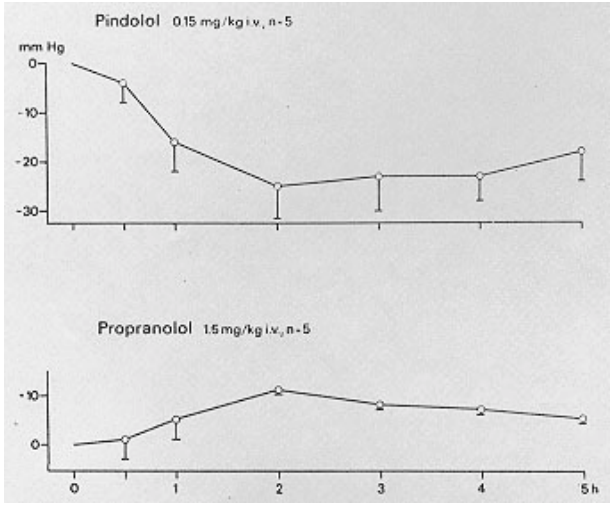

Fig. 6 - Effects of pindolol (150 µg/kg i.v.) and propranolol (1.5 mg/kg i.v.) on blood pressure in conscious dogs with renal hypertension (means ., N = 5).

Effects on vascular smooth muscle

We have found that the relaxant effect of pindolol on vascular smooth muscle is more pronounced than its simulant 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. Pressure within the system was increased by adding 40 mM potassium chloride to the perfusion fluid. Close arterial injections of pindolol produced reproducible, dose-dependent reductions in vascular resistance. In this tissue, pindolol behaved as a full agonist with maximum responses equalling those of isoprenaline [12].

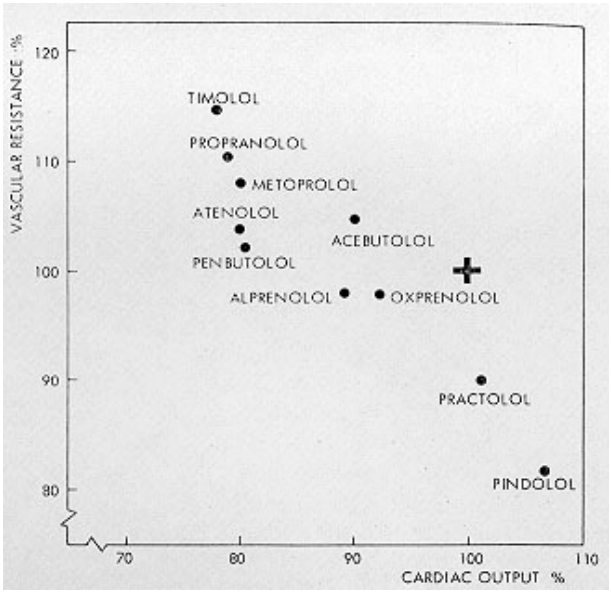

Fig. 7 - Relationship between cardiac output and vascular resistance following long-term treatment with β-adrenoceptor blocking agents values (Man in't Veld and Schalekamp [18]).

Our attempts to confirm that the vasodilator effect is due to activation of the β-adrenoceptor are incomplete and therefore not conclusive. Although propranolol reduced responses to pindolol, the concentration required (10^{-7} M) produced a much greater inhibition of responses to isoproterenol. This finding raised the question as to whether a part of the vasodilator effect of pindolol might be non-specific. This seems unlikely, since the splenic artery of the rabbit which appears to be devoid of β-adrenoceptors, does not relax in response to pindolol.

A disadvantage inherent in the vessel preparation employed in our studies is that drug concentrations present at the receptor cannot be determined. However, Thulesius and his colleages [13] have reported that pindolol relaxes isolated human arteries and veins at concentrations within the range of plasma levels detected in man following an oral dose of 15 mg. In these experiments, the maximum responses to pindolol were 78% (arteries) and 75% (veins) that of the maximum response to isoproterenol.

Effects in other tissues

Differences in the responsiveness of tissues bearing β-adrenoceptors to the stimulant effects of pindolol are not confined to the heart and blood vessels. Relaxant effects on guinea pig tracheal preparations are similar to those on the sinus mode of the cat, i.e., approximately 40% of the maximum beating guinea pig and rat atria hardly respond at all [2,15]. We have recently studied the effects of pindolol on the rate uterus. In anaesthetised animals, a dose of only 5 μg/kg i.v. pindolol produced a long-lasting depression of the spontaneous rhythimic contractions which occur during full oestrus. A dose of 40 μg/kg i.v. abolished the contractions completely for several hours (Fig. 8). The response to 5 μg/kg could be prevented by propranolol 300 μg/kg i.v., implying an effect on β-adrenoceptors. A quantitative estimate of efficacy made in isolated uteri contracted with potassium chloride 40 mM showed that the maximum relaxant effect of pindolol amounted to 78% that of isoproterenol.

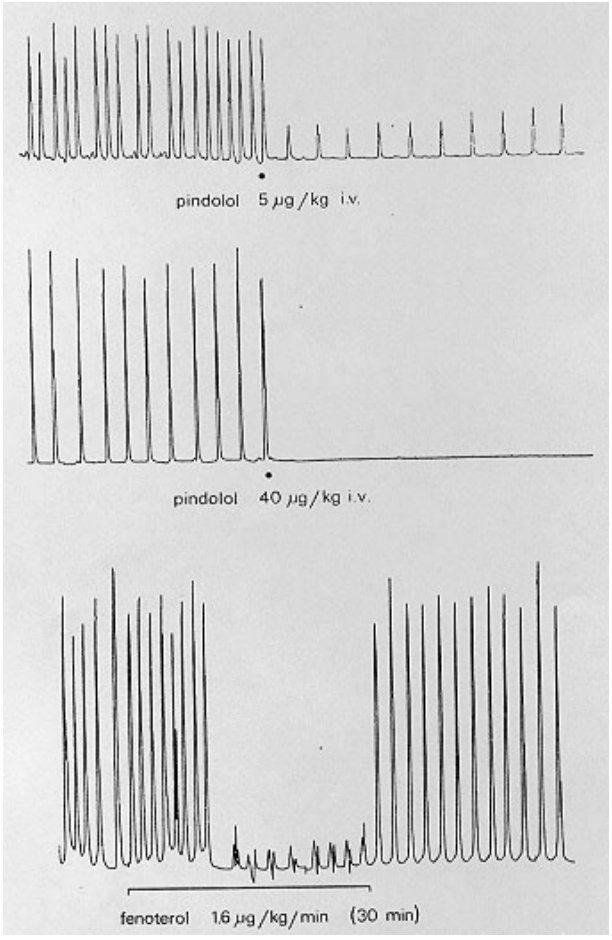

Fig. 8 - Effects of pindolol and the β-adrenoceptor stimulant, fenoterol, on spontaneous uterine activity in the rat. Pressure within one horn of the uterus was recorded via open-ended, fluid filled catheter.

The experiments are not only of pharmacological interest. They also suggest that pindolol might be useful in the treatment of premature labour. Not only has the drug a long duration of action, but it has an additional advantage in that it will not produce tachycardia - a problem commonly encountered in the use of ß-adrenoceptor stimulants in this indication.

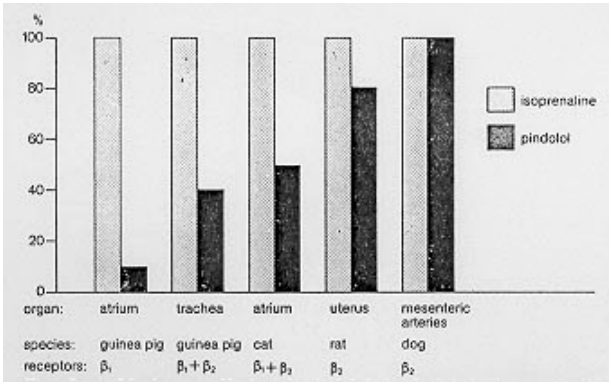

Fig. 9 - Maximum effects of pindolol in tissues (solid columns) compared with the maximum effects of isoproterenol (open columns).

Conclusions

The fact that the intrinsic stimulant activity of pindolol differs so much from one tissue to another could possibly be due to variations in the number of the number of β-adrenoceptors available for stimulation. Alternatively, the answer may lie in the distribution of β-adrenoceptor sub-types in different tissues. There is an impressive body of evidence showing that β_1,- and β_2 -adrenoceptors can occur together in a single organ or tissue. The β_1 sub-type responds preferentially to noradrenaline released from sympathetic nerves whereas the β_2 sub-type is more sensitive to adrenaline [16]. Isoproterenol-induced increases in the rate of contraction of cat atria, and relaxation of guinea pig tracheal smooth muscle are bronght about by activation of both β_1,- and β_2 -adrenoceptors [16]. In these two tissues, the maximum effects of pindolol are equivalent to 40-50% of those of isoproterenol [2,14]. The guinea pig and rat hearts differ from that of the cat in that increases in the rate of contraction appear to be mediated only by the β_1 -adrenoceptor [17]. In these tissues, pindolol produces negligible effects [2,15]. Its effects on vascular and uterine smooth muscle, however, approach that of a full agonist, and these tissues possess a pure population of β_2 -adrenoceptors (Fig. 9).

These findings are compatible with the hypothesis that, despite the fact that pindolol binds to and blocks both β-adrenoceptor sub-types non-selectively, the stimulant effects of the compound are exerted primarily on the β_2 -adrenoceptor.

References

1. Clark, B. J. - Beta-adrenoceptor blocking agents - are pharmacologic differences relevant? Am. Heart J. 104: 334, 1982.
2. Kaumann, A. J.; Blinks, J. R. - β-Adrenoceptor blocking agents as partial agonists; in isolated heart muscle: dissociation of stimulation and blockade. Naunyn-Schmiedeberg's Arch. Pharmacol. 311: 237, 1980.
3. Man in't Veld, A. J.; Boomsma, F.; Schalekamp, M. A. D. H - Effects of β-adrenoceptor agonists and antagonists in patients with peripheral autonomic neuropathy. Br. J. Pharmac13: 367, 1982.
4. Tanaka, N. et al - Dependence of the cardiovascular effects of pindolol on the individual sympathetic nervous activity. Europ. J. Clin. Pharmacol. 22: 383, 1982.
5. Rosenthal, J. et al. - Treatment of hypertension with a beta-adrenoceptor blocker. Br. J. Clin. Prac. 33: 165, 1979.
6. Svendsen, T. L.; Hartling, O.; Trap-Jensen, J. - Immediate haemodynamic, effects of propranolol, practolol, pindolol, atenolol and ICI 89,406 in healthy volunteers. Europ. J. Clin. Pharmacol. 15: 223, 1979.
7. Svendson, T. L. et al - Adrenergic beta-receptor blockade in man. The haemodynamic importance of intrinsic sympathomimetic activity at rest, Clin. Pharm. Ther. 29; 711, 1982.
8. Clark, B. J. - Pharmacology of beta-adrenoceptor blocking agents. In: Saxena, P. R.; Forsyth, R. P. ed Beta-Adrenoceptor Blocking Agents. North-Holland Publishing Company, Amsterdam, 1976. P. 45.
9. Clark, B. J.; Menninger, K.; Bertholet, A. - Pindolol -the pharmacology of a partial agonist. Br. J. clin. Pharmac. 13: 1495, 1982.
10. Man in't Veld, A. J.; Schalekamp, M. A. D. H. - Effects of 10 different β-adrenoceptor antagonists on haemodynamics, plasma renin activity and plasma norepirephrine in hypertension: the key role of vascular resistance changes in relation to partial agonist activity. J. Cardiovasc. Pharmac. 5: S30, 1983.
11. Weil, C.; Waite, R. - Haemodynamic differences in untreated hypertension and hypertension treated with various β-adrenoceptor antagonists. Br. J. clin. Pharmac. 13: 279S, 1982.
12. Clark, B. J.; Bertholet, A. - Effects of pindolol on vascular smooth muscle. Gen. Pharmacol. 14: 117, 1983.
13. Thulesius, O.; Gjores, J. E.; Berling, E. - Vasodilating properties of β-adrenoceptor blockers with intrinsic sympathomimetic activity. Br. J. clin. Pharmac. 13: 229S, 1982.
14. Waite, R - Activité sympathomimétique intrinsèque des bêta-bloquants. Nouv. Presse Med. 7: 2707, 1978.
15. Clark, B. J. - Unpublished results.
16. Daly, M. J.; Levy, G. P. - The subclassification of β-adrenoceptors: evidence in support of the dual β-adrenoceptor hypotesis. In: Kalsner, S. (ed.) - Trends in Autonomic Pharmacology, I., Urban and Schwarzenberg Baltimore-Munich: 1979. P. 347.
17. O'Donnell, S. R.; Wanstall, J. C. - pA_2, values of selective β-adrenoceptor antagonists on isolated atria demonstrate a species difference in the β_3-adrenoceptor populations mediating chronotropic responses in cat and guinea pig. J. Pharm. Pharmacol. 31: 686, 1979.
18. Man in't Veld, A. J.; Schalekamp, M. A. D. H. - How intrinsic sympathomimetic activity modulates the haemodynamic responses to β-adrenoceptor antagonists. A clue to the nature of their antihypertensive mechanism. Br. J. clin. Pharmac. 13; 245S, 1982.