PHARMACOLOGY OF BETA-ADRENERGIC BLOCKERS

MECHANISM OF ACTION AND PHARMACOLOGICAL CLASSIFICATION OF β-ADRENERGIC RECEPTOR BLOCKING DRUGS

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No less than twenty beta-receptor blocking drugs have been synthesized and pharmacologically characterised since the original description of the dichloro analogue of isoprenaline (Powell & Slater, 1958) clearly vindicated Ahlquist's (1948) dual receptor hypothesis to account for the action of catecholamines. Beta-receptor blockade already has an established place in the management of a wide variety of clinical conditions and is becoming recognised as one of the major advances in cardiovascular therapeutics in recent times. However, beta-receptor antagonists do not constitute a homogeneous group. The individual compounds in the group differ markedly in specificity and blocking potencies. They undergo differing pathways of breakdown and metabolism in the body, and they may have dissimilar protein-binding characteristics and renal excretion patterns. Many of them have important additional pharmacological properties. A rational use of these drugs therefore requires a detailed appreciation of their overall pharmacological effects.

It is the purpose of this paper to discuss at length some of these features which are relevant to the therapeutic use of beta-blockers in disorders of the cardiovascular system. It is, however, not intended to review the effects of beta-blockade on cardiovascular and coronary dynamics as these will be discussed by other speakers in this symposium. The chemical structures of some representative compounds are shown in Fig. 1.

COMPARATIVE BETA-BLOCKING POTENCY

The competitive antagonism between beta-blockers and agonists (e.g. isoprenaline) is best quantitated by measuring the degree of the parallel shift to the right of the dose-response curve. The result is then most conveniently expressed was pA_2 which may be defined as the negative logarithm of the molar concentration of the antagonist which just doubles the concentration of the agonist to produce a given effect (Schild, 1947).

pA_2 values for a number of beta-blocking drugs are shown in Table I. In this group, LB_{46} is the most potent, having at least four times the activity of propranolol. Agents with even greater potency than LB^{46} have now been synthesized and are undergoing clinical and experimental evaluation. It must, however, be mentioned that the potency ratios of beta-blockers can differ under different conditions of evaluation such as *in vitro* and *in vivo* experimental procedures and this has been found to be largely due to sequestration of certain agents by serum proteins, For example, propranolol loses its *in vitro* potency by a factor of 25 when it comes into contact with blood (Barrett, 1971) and this naturally has a bearing on comparative potency ratios when propranolol is used as the 'reference' compound.

INTRINSIC SYMPATHOMIMETIC ACTIVITY (ISA)

Most, but not all, beta-receptor blocking drugs have some ISA in concentrations which produce significant beta-receptor blockade (Table I). It is still debated whether the presence of ISA in a beta-receptor antagonist constitutes an advantage in cardiac therapy. From time to time, it has been claimed that ISA protects against cardiac failure (Ablad, Brogard & Ek, 1967) when beta-blockers are used in patients with diminished cardiac function but comparative studies with compounds with and without ISA have produced conflicting reports (Lund-Larsen & Sivertssen, 1969; Wassermann, Proctor, Allen & Kemp, 1970). It is, however, known that compounds with ISA produce less depression of atrio-ventricular conduction and cause smaller elevations of peripheral vascular resistance for a given degree of cardiac beta-receptor blockade. Similarly, agents which are devoid of ISA (propranolol, sotalol, procinolol, MK-950) depress the heart rate more markedly than those with ISA (LB^{46}, alprenolol, oxprenolol, practolol) and this difference may govern the choice of an agent in situations where depression of heart rate (e.g. thyrotoxic crisis) is of prime importance.

CARDIO-SELECTIVE BETA-BLOCKADE

Experimental evidence is sufficiently convincing to suggest a sub-classification of beta-adrenergic receptors into (a) beta-1—subserving lipolysis and cardiac stimulation and (b) beta-2—subserving bronchodilatation and vasodepression (Lands, Arnold, McHuliff, Luduena, & Brown, 1967). Selective beta-2 stimulants (e.g. salbutamol) as well as beta-1 antagonists (e.g. practolol) have now been synthesized. It must, however, be stressed that cardio-selectivity as exhibited by these compounds is a relative one and that absolute specificity has not been achieved. Nevertheless, preliminary investigations with the ortho-and para-analogues of several beta-blockers allows the hope of a further improvement in cardio-specificity (Vaughan Williams, Bagwell & Singh, 1972; Åblad, Brogard, Carlsson & Ek, 1970). In addition, our own studies have revealed that propranolol has a 'reverse specificity' in that it blocks beta-2 receptors more markedly than it does beta-1 for any particular concentration of the compound used. This may well explain, why, for a given degree of beta-blockade of the heart, it has a greater propensity to aggravate cardiac failure than practolol, for by blocking the peripheral receptors in patients with cardiac decompensation, it increases the afterload whereas a cardio-specific agent (e.g. practolol) does not.

LOCAL ANAESTHETIC AND CARDIAC MEMBRANE DEPRESSANT EFFECT OF BETA-BLOCKING DRUGS

Many beta-receptor antagonists are also potent local anaesthetics on nerve. For example, propranolol has local anaesthetic potency twice that of lignocaine; potency ratios for some other beta-receptor blocking compounds in relation to that of propranolol are shown in Table II. It will be seen at once that the local anaesthetic effect of the compounds is associated with a quantitatively similar action on the cardiac membrane although very much smaller concentrations (1/100-1/300th) are required to produce comparable changes.

The 'local anaesthetic' action of the beta-blocking drugs on cardiac muscle has been variously called 'quinidine-like', 'membrane stabilising', and 'membrane depressant' and to get over the semantic confusion we have called the effect simply 'Class 1' anti-arrhythmic action (Singh & Vaughan Williams, 1971; 1972). Such an effect is characterised by (i) a marked reduction in the maximal rate of depolarisation (MRD) of the cardiac action potential (ii) reduction in the overshoot potential with no change in the resting membrane voltage (iii) little or no change in the time course of the repolarisation phase of the action potential and lastly (iv) a reduction in the steepness of the slope of the pacemaker potential in the automatic myocardial cells. These features were most clearly established for the therapeutic concentrations of quinidine (Vaughan Williams, 1958) and were found to be associated with an elevation of the electrical threshold of excitability and delay in conduction velocity together with a very great increase in the effective refractory period of cardiac muscle. Collectively, these actions form the basis of anti-arrhythmic actions of not only many beta-

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TABLE I

COMPARATIVE AGONIST AND ANTAGONIST ACTIVITIES OF ß-RECEPTOR BLOCKING DRUGS

	Agonist Activity* (maximal response to isoprenaline = 1)	pA2 (combined rate and force)	Approximate relative *in vitro* activity as ß-blockers (Propranolol = 1)
Propranolol	0	8·55	1·0
Alprenolol	0·16	8·49	1·0
Oxprenolol	0·29	8·25	0·5
Practolol	0·35	6·50	0·01
LB_{46}	0·56	9·17	4·0
Inpea	0·34	6·05	<0·01
Solatol	0	6·30	<0·01

*These figures are taken from Barrett and Carter (Brit. J. Pharmacol. 40, 373, 1970) and refer to relative activities with respect to positive chronotropic actions of the compounds in reserpinized rats.

TABLE II

LOCAL ANAESTHETIC AND CARDIAC MEMBRANE DEPRESSANT PROPERTIES OF ß-RECEPTOR ANTAGONISTS IN RELATION TO THOSE OF PROPRANOLOL

	Local Anaesthetic Potency (Propranolol = 1)	Cardiac Membrane Depressant Property (Propranolol = 1)
1. Propranolol	1·0	1·0
2. Alprenolol	1·07	1·38
3. Oxprenolol	0·39	0·31
4. Practolol	0·011	0·008
5. LB_{46}	0·095	0·088
6. Inpea	0·049	0·029
7. Sotalol	0·0033	0·0059

The collected data were obtained under identical experimental conditions. The figures relating to propranolol, oxprenolol, and practolol are from Papp (1969), the remainder from Singh (1971).

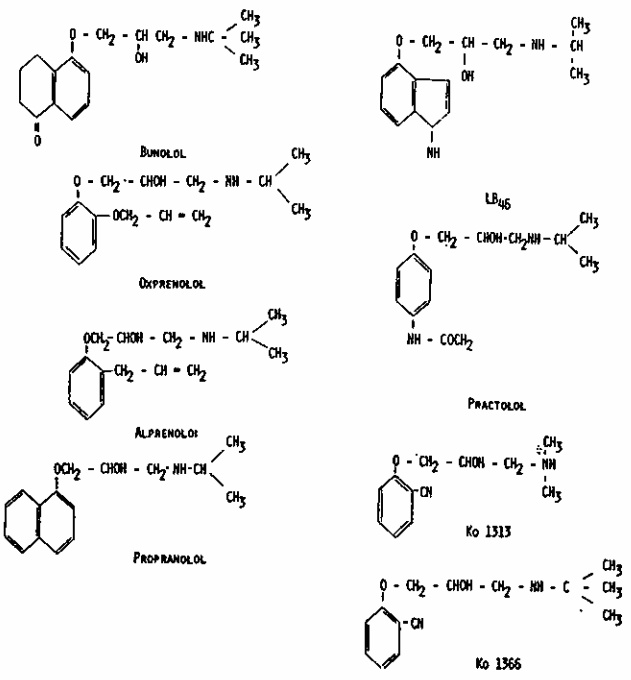

Fig. 1. Structures of some of the beta-receptor blocking drugs discussed.

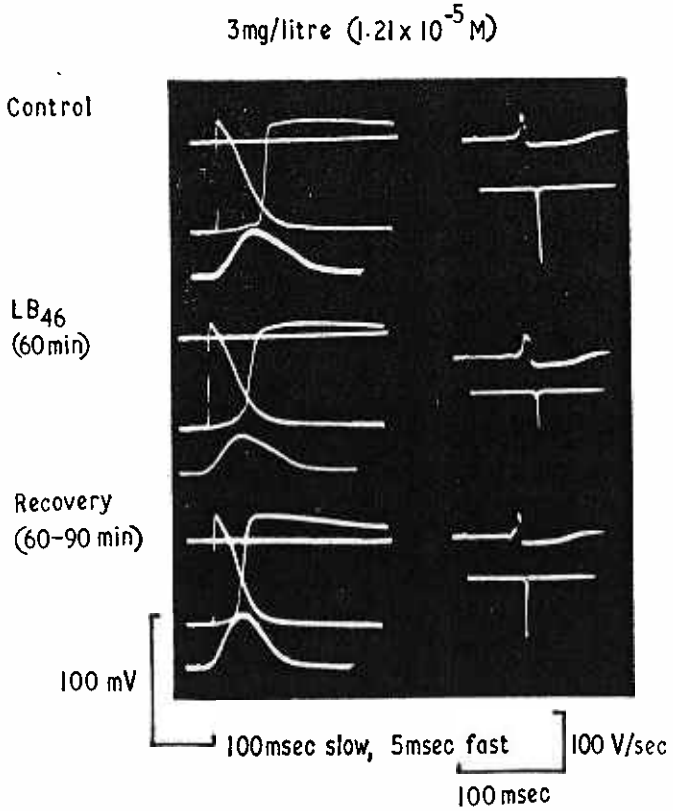

Fig. 2. The effects of LB_{46} (Pindolol) on rabbit atrial intracellular potentials, demonstrating membrane depressant action. In each frame on the left, the horizontal line indicates zero potential; the superimposed traces depict intracellular potentials at slow and fast sweep speeds. Bottom trace: isometric tension. The right upper trace shows surface electrogram recorded with bipolar electrodes; upstroke velocity of the intracellular potential (dV/dt of phase O) is indicated by the depth of the differential signal in the lower trace (Singh, 1971). The overall changes depicted are quantitatively similar to those found with propranolol at 1/10th concentration of LB_{46}.

TABLE III
A CLASSIFICATION OF THE PHARMACOLOGICAL ACTIONS OF ß-RECEPTOR ANTAGONISTS

	ß-blockade (Propranolol = 1) In Vitro	ß-blockade (Propranolol = 1) In vivo	Intrinsic Sympathomimetic Action (Isoprenaline = 1)	Local Anaesthesia on nerve (Propranolol = 1)	Class 1 Membrane Depressant action (Propranolol = 1)
A. **CARDIO-SELECTIVE**					
(i) *Weak Local Anaesthetics*					
Practolol	0·01	0·3-0·4	0·35	0·011	0·088
(ii) *Potent Local Anaesthetics*					
Para-oxprenolol	0·5	0·5-1·0	0·30	0·25	not known
Para-alprenolol	1·0	0·5-1·0	0·20	1·00	not known
B. **NON CARDIO-SELECTIVE**					
(i) *Potent Local Anaesthetics*					
Propranolol	1·0	1·0	0	1·0	1·0
Alprenolol	0·5-1·0	0·5-1·0	0·16	1·07	1·38
Oxprenolol	0·5-1·0	0·5-1·0	0·29	0·39	0·31
(ii) *Weak Local Anaesthetics*					
LB_{46}	4-10	4-40	0·56	0·095	0·088
Bunolol	not known	20	0	not known	not known
Procinolol	5-10	5-40	0	not known	not known
MK-950	not known	8-10	0	not known	not known
Kö 1316	1	1	0·15	0·05	not known
Kö 1366	not known	20-100	0·15	0·05	not known
Inpea	<0·001	<0·01	0·34	0·049	0·029
Sotalol	<0·01	0·3	0	0·0033	0·0059

receptor antagonists but also of major anti-arrhythmic drugs in common clinical practice (Fig. 2).

In this context, one further point needs emphasis. Much confusion still prevails concerning the relationship between the phenomenon of 'direct myocardial depression' following the use of beta-receptor blocking drugs and their Class I electrophysiological ('quinidine-like' or older terminology) effect. In terms of the plasma concentrations of beta-blocking drugs actually achieved in clinical practice, it is highly probable that their direct myocardial depressant actions demonstrated in isolated heart muscle in the organ bath is only of theoretical importance. In any event, it needs to be remembered that the electrophysiological effects of beta-blocking drugs on heart muscle are not automatically linked to effects on cardiac contractility.

A PHARMACOLOGICAL CLASSIFICATION OF ACTIONS

Based on the above considerations a classification of the actions of the beta-receptor antagonists which might have a therapeutic potential can now be presented. This is outlined in Table III, which is largely self-explanatory but a few additional comments may be worthwhile.

It will be noted that there is still a paucity of cardio-selective agents and practolol is the only compound which has undergone extensive experimental and clinical evaluation. There are marked differences between the *in vitro* and *in vivo* activities of some of the agents shown in Table III. These differences may reflect differences in protein binding in the blood but other as yet unidentified factors may be involved. It will also be seen that the intrinsic sympathomimetic actions of the compounds which have this property is not in any systematic way related to their actions as beta-blockers and the property is also independent of their local anaesthetic potencies either on nerve or on the cardiac membrane. A good correlation is, however, demonstrated between the cardiac membrane depressant action and the local anaesthetic activities on nerve of all the beta-receptor blocking drugs so far studied.

It is likely that future advances in beta-receptor blockade will depend on the precise knowledge of the relationships of the known beneficial and deleterious effects of the existing compounds to their structural characteristics and pharmacological actions.

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