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A comparison of the anti-arrhythmic actions of I.C.I. 50172 and (—)-propranolol and their effects on intracellular cardiac action potentials and other features of cardiac function

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1. I.C.I. 50172 had marked quinidine-like effects on intracellular cardiac action potentials at concentrations above 20 mg/l. ($6{\cdot}61 \times 10^{-5}$M). The rate of rise and overshoot of the action potential, conduction velocity and contractions were decreased. (−)-Propranolol had similar effects at less than 1/30 this concentration.

2. I.C.I. 50172 had 1/100 the activity of (−)-propranolol as a local anaesthetic. Since this is also the ratio of their *in vitro* β-receptor blocking activities, I.C.I. 50172 provides no net increase in specificity of β-receptor blockade.

3. In contrast, the *in vivo* activity of I.C.I. 50172 in protecting anaesthetized guinea-pigs against ouabain-induced ventricular fibrillation was 40% that of (−)-propranolol.

4. Structure-activity relations of β-receptor blocking drugs are discussed.

The β-receptor blocking drug pronethalol, introduced by Black & Stephenson (1962), is capable of preventing ouabain-induced ventricular fibrillation, and of restoring a regular rhythm when fibrillation has been already established (Vaughan Williams & Sekiya, 1963). It was soon discovered, however, that both pronethalol (Gill & Vaughan Williams, 1964) and its successor propranolol (Morales-Aguilerá & Vaughan Williams, 1965) were powerful local anaesthetics, and shared with quinidine the property of reducing in atrial muscle the rate of rise of the intracellularly recorded action potential, without altering resting potential or repolarization time. The disadvantage of β-receptor blocking drugs with "non-specific" actions is that they may depress contractions as well as membrane excitability, though the two effects are not necessarily present in the same degree. To improve specificity of β-receptor blockade either β-receptor blocking potency must be increased or non-specific activity reduced.

The first approach is exemplified by the isolation of the laevo-isomer of propranolol, which relative to (±)-propranolol doubles specificity because it has about one hundred times the β-blocking activity of the dextro-compound (Howe & Shanks, 1966; Barrett & Cullum, 1968). It is well known that the activity of local anaesthetics is reduced by the introduction of certain electron-withdrawing groups into the ring, and β-receptor blocking drugs of this type are, INPEA (Murmann &

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Gamba, 1966 ; Murmann, Saccani-Guelfi & Gamba, 1966 ; Somani & Lum, 1966) and MJ1999 (Lish, Weikel & Dungan, 1965 ; Somani & Lum, 1966 ; Levy, 1968). One of the most recently introduced β-receptor blocking drugs with a ring-substitution is I.C.I. 50172 (Barrett, Crowther, Dunlop, Shanks & Smith, 1967 ; Dunlop & Shanks, 1968), and since this compound and (−)-propranolol represent the two approaches to greater specificity, decrease of non-specific and increase of specific activities respectively, it was of interest to make a direct quantitative comparison of the effects of these drugs on intracellular potential, local anaesthetic activity, and some other actions. We have also studied the effects of I.C.I. 50172 and (−)-propranolol in protecting against ouabain-induced arrhythmias.

Methods

Protection against ouabain-induced arrhythmias

The method used was similar to that described by Vaughan Williams & Sekiya (1963) but was automated by a 0·5 rev./min motor, closing contacts for 5 and 30 sec per revolution. Guinea-pigs of either sex were given 1·6 g/kg of urethane intraperitoneally, and were respired artificially. Body temperature was maintained at 37° C by a heated copper plate controlled by an intra-rectal thermistor (Mullard, VA 3410). The electrocardiogram (lead II) was recorded for 5 sec every 2 min. Ouabain, 3·6 μg, was infused over 30 sec from a motor-driven syringe every 2 min.

Intracellular potentials

These were recorded (Vaughan Williams, 1958 ; Szekeres & Vaughan Williams, 1962) with fine glass pipettes from the interior of atria, taken from young rabbits of either sex, and suspended horizontally in a bath through which nutrient solution flowed continuously at 32° C. The fluid was recirculated rapidly by the gas mixture, and the flexibly mounted microelectrodes were inserted under visual observation at $\times 25$ to $\times 40$ magnification in transmitted light. Contractions were recorded by an RCA 5734 transducer actuated by a long lever which permitted 2–3 mm movement of the atrium under light stretch (0·5 g approximately). Conduction velocity was calculated from records obtained with bipolar surface electrodes placed on the left and right atrium. The left atrium was stimulated by 1 msec square shocks, of at least twice threshold strength. The solution contained (mM): NaCl, 125 ; KCl, 5·6 ; $CaCl_2$, 2·16 ; $NaHCO_3$, 25 and glucose, 11, and was gassed with 95% oxygen and 5% carbon dioxide ; pH 7·4.

Local anaesthesia

The sciatic nerve of a frog (*Rana pipiens*) was stripped of its sheath for 2 cm and mounted in a Perspex bath with three chambers ; in the end chambers the nerve rested in moist air on pairs of platinum wires connected to stimulating and recording assemblies respectively. In the central chamber grounded by a platinum wire the nerve was immersed in frog Ringer (mM): NaCl, 120 ; KCl, 1·88 ; $CaCl_2$, 1·08 and $NaHCO_3$, 2·38, with or without drug, buffered by 10 ml./l. Tris (Sigma) at pH 7·5. It was stimulated by square 1·0 msec pulses, at 1/sec, strength twice supramaximal. The height of the fastest wave of action potentials was measured on a graduated oscilloscope screen, before and after 30 min exposure to each concentration of the drugs used.

Drugs used

I.C.I. 50172 HCl, 4-(2-hydroxy-3-isopropylaminopropoxy) acetanilide; (−)-propranolol HCl (I.C.I. 47320); procaine HCl (B.D.H.); strophanthin G (ouabain) (B.D.H.); urethane (Hopkin and Williams). Weights are expressed in terms of the salt. Statistical evaluation was by Student's t test, and χ^2 test (for incidence of fibrillation).

Results

Ouabain-induced arrhythmias

Ouabain caused ventricular fibrillation in thirty out of thirty controls. A statistically significant reduction in the incidence of ventricular fibrillation induced by ouabain was produced by as little as 0·375 mg/kg of (−)-propranolol, given intravenously to anaesthetized guinea-pigs. It has previously been found (Dohadwalla, Freedberg & Vaughan Williams, 1969) that (±)-propranolol was more effective than the dextro-isomer in protecting guinea-pigs against ouabain-induced arrhythmias, which indicates that at least part of this effect was due to β-receptor blockade. In contrast, the lowest dose of I.C.I. 50172 which would produce a significant decrease in the incidence of ouabain-induced ventricular fibrillation was 1·5 mg/kg. Details of the results of the ouabain-infusion experiments are given in Table 1.

The incidence of ouabain-induced ventricular fibrillation was significantly reduced by concentrations of both I.C.I. 50172 and (−)-propranolol that were lower than those necessary to reduce the dose of ouabain required to produce ectopic extrasystoles or a purely ventricular rhythm. Reduction in the incidence of ventricular fibrillation was also closely related to the dose of β-receptor blocking drug, and it was possible to draw a dose-response curve with reasonable parallelism which indicated that I.C.I. 50172 had 40% of the activity of (−)-propranolol.

TABLE 1. *Effect of I.C.I.* 50172 *and (−)-propranolol on the toxicity to the heart of ouabain (guinea-pig experiments)*

Compound and dose (mg/kg i.v.) (M × 10^{-6})			Amount of ouabain (μg/kg i.v.) required to produce			
		n	Ectopic extrasystoles	Ventricular rhythm	Ventricular fibrillo-flutter	Cardiac arrest
Control		30	194·8±8·2	238·6±8·8	277·6±10·5	327·0±12·2
I.C.I. 50172	0·75 (2·48)	10	209·7±15·0	242·3±21·9	299·0±20·8 (9/10)	343·0±25·0
	1·5 (4·96)	10	211·0±19·4	258·4±18·1	318·1±17·5 (7/10†)	344·0±23·5
	3 (9·92)	10	215·0±16·5	259·6±13·9	351·7±12·0* (3/10‡)	351·2±22·0
	6 (19·83)	10	239·4±16·7†	271·0±17·2	None	346·7±18·4
	12 (39·67)	8	244·3±16·9†	276·4±16·6	None	355·5±28·9
(−)-Propranolol	0·375 (1·26)	10	198·4±14·5	244·2±11·6	275·9±17·9 (8/10†)	315·5±14·9
	0·75 (2·53)	10	245·4±25·4†	263·3±23·0	323·8±37·3 (4/10‡)	341·6±23·1
	1·5 (5·06)	10	235·0±10·2†	271·6±23·2	396·4±45·6 (2/10‡)	338·0±25·5
	3 (10·12)	10	279·1±23·1‡	291·0±22·3†	None	356·8±21·7
	6	9	303·7±28·5‡	370·2±45·5‡	None	427·7±41·8†

The values given are the means and standard errors of the amounts of ouabain required to produce the stated effects. The incidence of the effects is given in brackets, when this was less than 100%. Statistical significance of the difference from control: * $P<0·05$; † $P<0·01$; ‡ $P<0·001$.

TABLE 2. *Effect of I.C.I. 50172 and (−)-propranolol on intracellular atrial potentials*

Compound and concentration mg/l. (M × 10^{-6})			Resting potential		Action potential		Maximum rate of rise		Mean rate of rise		Repolarization to 50%		Repolarization to 90%	
			mV	Difference (%)	mV	Difference (%)	V/sec	Difference (%)	V/sec	Difference (%)	msec	Difference (%)	msec	Difference (%)
I.C.I. 50172	0·75	C	65·6 (27)	−2·1	85·0 (33)	+0·8	83·1 (32)	+8·7	41·4 (32)	+14·2	57·8 (31)	−4·5	106·4 (31)	−0·2
	(2·48)	E	64·2 (57)		85·7 (62)		90·3 (61)		47·3 (59)		55·2 (59)		106·2 (59)	
	24	C	65·0 (37)	+1·1	89·3 (37)	−3·3	109·1 (36)	−22·8†	64·2 (36)	−24·6†	57·6 (37)	−6·8†	102·3 (37)	−4·9†
	(79·4)	E	65·7 (52)		86·3 (52)		84·2 (52)		48·4 (52)		53·7 (52)		97·3 (52)	
	100	C	64·0 (11)	+0·6	94·1 (11)	−15·2†	145·5 (11)	−30·8‡	77·0 (11)	−30·2†	61·4 (11)	+5·7	112·3 (11)	+1·1
	(331)	E	64·4 (13)		79·8 (13)		100·7 (13)		53·7 (13)		64·9 (13)		113·5 (13)	
(−)-Propranolol	0·075	C	64·4 (22)	−0·8	84·6 (23)	−2·7	88·7 (23)	+1·5	46·3 (23)	+10·4	52·0 (23)	+0·2	102·0 (23)	−4·5
	(0·25)	E	63·9 (20)		82·3 (22)		90·0 (22)		51·1 (22)		52·1 (22)		97·4 (22)	
	0·15	C	67·1 (26)	−1·8	91·6 (26)	−4·2	95·0 (26)	−12·6‡	58·0 (26)	−13·8‡	48·0 (26)	−5·4†	97·0 (26)	+2·8
	(0·51)	E	65·9 (27)		87·7 (27)		83·0 (27)		50·0 (27)		45·4 (27)		99·7 (27)	
	0·3	C	60·7 (12)	+0·5	84·3 (14)	−10·1‡	82·1 (14)	−14·4‡	45·9 (14)	−14·6†	53·1 (14)	−5·8†	110 0 (14)	−3·1*
	(1·01)	E	61·0 (12)		75·8 (12)		70·3 (12)		39·2 (12)		50·0 (12)		106·6 (12)	
	1	C	66·3 (20)	−1·0	85·8 (21)	−9·8‡	83·1 (21)	−28·0‡	51·6 (21)	−25·4‡	54·5 (21)	−4·9*	106·9 (21)	−3·8*
	(3·37)	E	65·6 (20)		77·4 (20)		59·8 (20)		38·5 (20)		51·8 (20)		102·8 (20)	
	3	C	68·7 (25)	+1·0	87·4 (28)	−15·9‡	81·7 (28)	−75·8‡	35·9 (28)	−71·3‡	55·6 (28)	−2·5	110·3 (28)	−1·4
	(10·12)	E	69·4 (16)		73·5 (17)		19·8 (17)		10·3 (17)		54·2 (17)		108·7 (17)	

The values given are the means and standard errors with number of records in brackets. C, Control; E, effect of drug after 60-90 min exposure.
Statistical significance of difference from control: * $P<0·05$; † $P<0·01$; ‡ $P<0·001$.

Intracellular potentials

I.C.I. 50172, in spite of reports that it was devoid of local anaesthetic activity, proved to have marked "quinidine-like" properties at high concentrations. A concentration of 24 mg/l. ($7{\cdot}93 \times 10^{-5}$M) produced a highly significant reduction in the rate of rise of the intracellular action potential of isolated rabbit atria. The complexity of the technique, and the wide scatter of control values, makes such

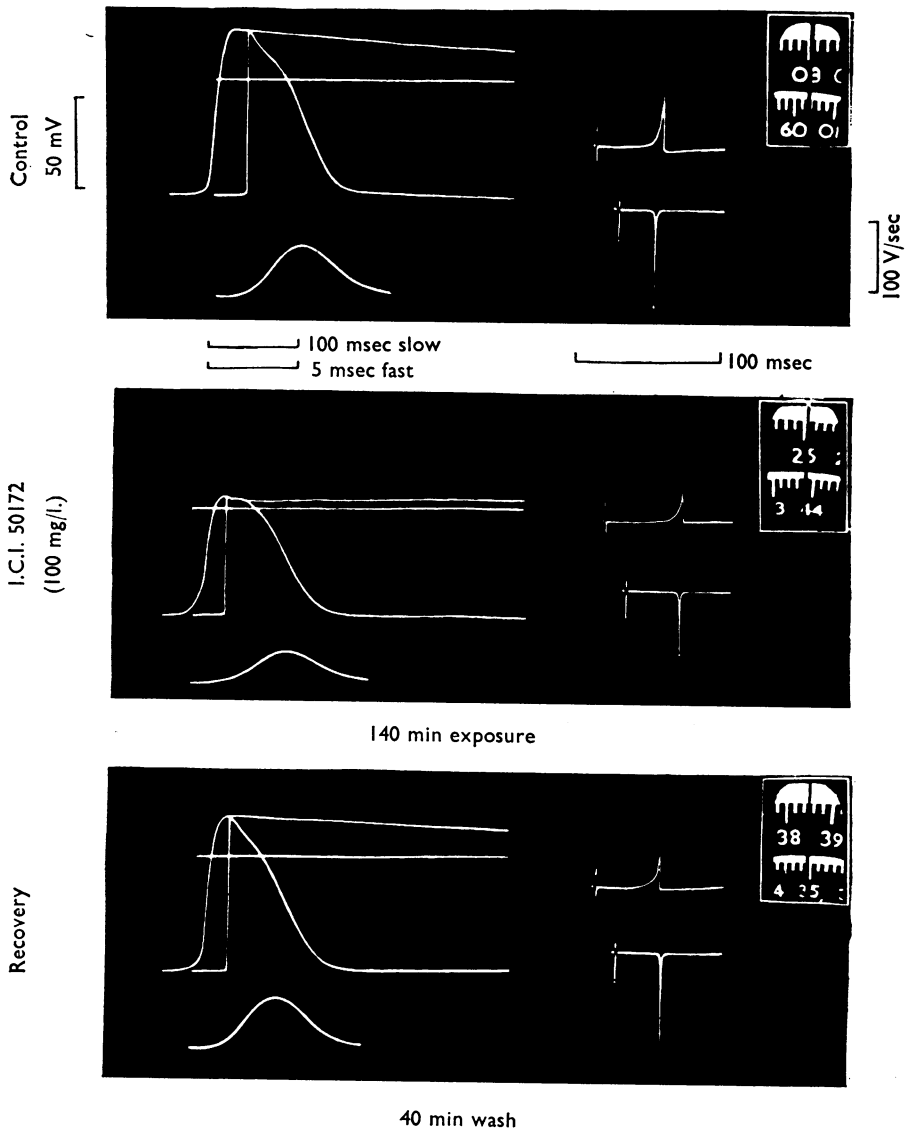

FIG. 1. Quinidine-like effects of I.C.I. 50172. In each panel: upper left, zero potential, and intracellular records at slow and fast sweep speeds; lower left, contractions; upper right, stimulus artefact and action potential from surface of atrium; lower right, differential of intracellular potential (depth of spike $= dV/dt$). Inset, time at which last of superimposed traces was exposed in minutes (above) and seconds (below). I.C.I. 50172 reduced rate of rise of action potential and overshoot, without altering resting potential or repolarization time. Conduction velocity and contractions were reduced.

measurements unsuitable for accurate assay. Nevertheless, it can be seen from Table 2 that (−)-propranolol produced comparable effects at less than one-thirtieth the concentration of I.C.I. 50172. Neither compound had any effect on the resting potential, so that reduction in the total action potential height represents depression of the overshoot (Na potential). Neither compound prolonged the duration of the action potential; in fact, at the lower effective concentrations, both compounds produced a small but significant shortening of the repolarization phase and a flattening of the plateau. Recovery from the quinidine-like action of I.C.I. 50172 was rapid (Fig. 1).

Local anaesthesia

As measured by depression of the frog nerve action potential, I.C.I. 50172 was found to possess appreciable local anaesthetic activity, a little less than one-twentieth that of procaine, and just more than 1% of the potency of (−)-propranolol (Table 3), on a molar basis.

Other effects

Measurements of spontaneous frequency, maximum driven frequency, electrical threshold, contractions and conduction velocity in atria were also made. I.C.I. 50172 had very little effect on any of these parameters. A concentration of 24 mg/l. ($7{\cdot}93 \times 10^{-5}$M) reduced contractions and the maximum driven frequency by less than 5%, and caused no significant change in the other measurements. 100 mg./l. ($3{\cdot}31 \times 10^{-4}$M), however, reduced contractions by 34%, spontaneous frequency by 16%, and conduction velocity by 18%. Electrical threshold and maximum driving frequency were raised by 16% and 14% respectively. All these effects are consistent with weak quinidine-like or non-specific actions of the drug, exhibited also by (−)-propranolol at about one-hundredth of the concentration of I.C.I. 50172.

Discussion

Pronethalol, the first β-receptor blocking drug without significant β-receptor excitatory activity (Black & Stephenson, 1962) was found to be a local anaesthetic, with twice the activity of procaine (Gill & Vaughan Williams, 1964) and to possess, like quinidine, the property of reducing the rate of rise of the cardiac action potential in the absence of a change in resting potential or action potential duration (Vaughan Williams, 1964). To increase specificity it was necessary either to increase β-receptor blocking activity or to reduce non-specific activity. The introduction of propranolol (Black, Crowther, Shanks, Smith & Dornhorst, 1964), involving a lengthening of the side chain by the interposition of an O–CH_2-link between the isopropylaminoethanol side-chain and the naphthalene ring, increased β-receptor blockade by a much larger factor than it increased quinidine-like actions, with a resultant gain in specificity by a factor of at least ten (Morales-Aguilerá & Vaughan Williams, 1965; Blinks, 1967). The isolation of the laevo-isomer of

TABLE 3. *Local anaesthetic effect of* (−)*-propranolol, I.C.I.* 50172 *and procaine (desheathed sciatic nerves of the frog)*

Compound	*n*	ED25 (mM)	Relative activity	ED50 (mM)	Relative activity	ED75 (mM)	Relative activity
(−)-Propranolol	5	0·13±0·01	100	0·14±0·01	100	0·16±0·02	100
I.C.I. 50172	10	10·70±0·60	1·2	12·10±0·63	1·1	13·72±0·81	1·2
Procaine	30	0·42±0·02	30·9	0·53±0·02	26·4	0·67±0·03	23·9

Concentrations required to produce 25, 50 and 75% decrease in the spike amplitude of frog nerve action potential are given (mean±S.E.).

propranolol (Howe & Shanks, 1966) has again doubled specificity in comparison with the racemic drug, for the β-receptor blocking action of (−)-propranolol is eighty to one hundred times that of the dextro-isomer, whereas the non-specific properties of the two isomers are the same (Whitsitt & Lucchesi, 1967 ; Barrett & Cullum, 1968).

To account for such a large difference between the activities of the dextro- and laevo-isomers it must be assumed that there are not less than three points of attachment to the β-receptor, and that firm fixation at two of them (probably by the ring and the β-hydroxyl group) results in the side-chain of the laevo-isomer pointing towards a third site, while that of the dextro-compound points away from it (Vaughan Williams, 1968). If this hypothesis is correct, it would be expected that substitutions introduced into the ring with the object of reducing local anaesthetic and non-specific potency would also obstruct attachment to the β-receptor. Consequently a reduction of β-receptor blocking action in the same proportion as the loss of local anaesthesia would lead to no net gain in specificity.

A quantitative comparison of the local anaesthetic properties of I.C.I. 50172 and (−)-propranolol (Table 3) has indicated that the latter is one hundred times more active. In other actions commonly considered " non-specific " (reduction in conduction velocity, raising of electrical threshold and maximum driving frequency) the ratio of activities was similar. I.C.I. 50172 had less than one-thirtieth the activity of (−)-propranolol in reducing the rate of rise of the intracellularly recorded action potentials of isolated rabbit atria.

An accurate assessment of the relative activities of different drugs as β-receptor blocking agents is difficult to obtain for several reasons: (1) a non-specific action may appear as doses increase ; (2) some drugs may themselves have a positive chronotropic or inotropic action (Dunlop & Shanks, 1968 ; Brunner, Hedwall & Meier, 1968) ; (3) the time-course of action may vary (Fitzgerald & Scales, 1968) ; (4) different ratios of activities may be found *in vitro* and *in vivo* (Blinks, 1967 ; Farmer & Levy, 1968 ; Jackson, 1968 ; Dunlop & Shanks, 1968). It is highly probable, however, that the particular effect of β-receptor excitation which increases the probability of cardiac arrhythmias involves an alteration in the voltage-dependence of the same ionic channel (controlled by a factor designated *s*) which also determines pacemaker activity (Noble & Tsien, 1968 ; Hauswirth, Noble & Tsien, 1968). If this is so, then measurement of the antagonism by drugs of the cardiac chronotropic action of catecholamines would be the method of comparing β-receptor blocking potencies which would be the most appropriate in relation to protection against arrhythmias. By this criterion the pA_2 value for I.C.I. 50172 was found to be 6·4 (on a molar basis) in contrast to 8·2 for (±)-propranolol (equivalent to about 8·5 for the pure laevo-isomer), an activity ratio of 1 : 100 (Foo, Jowett & Stafford, 1968). So far as this action is concerned, therefore, the modification of the ring of propranolol to that of I.C.I. 50172 had diminished β-receptor blockade to the same extent as it has reduced local anaesthetic potency. If this is because the side-chain obstructs access of the ring to the β-receptor, then it would be expected that the ratio between the activities as β-receptor blockers of the dextro- and laevo-isomers of I.C.I. 50172 would be smaller than that of the isomers of propranolol (1 : 100).

On the other hand, I.C.I. 50172 is a clinically effective anti-arrthythmic drug (Gibson, Balcon & Sowton, 1968 ; Johnstone, 1969) and the *in vivo* protective effect of I.C.I. 50172 against ouabain-induced ventricular fibrillation was 40% that of

(−)-propranolol. It is of particular relevance that bretylium, which is virtually devoid of a quinidine-like action on the heart, also protects against ouabain-induced fibrillation (Papp & Vaughan Williams, 1969). The relevance of β-receptor blockade to protection against digitalis-induced arrhythmias has been questioned (Lucchesi, 1965 ; Somani & Lum, 1965, 1966 ; Benfey & Varma, 1966 ; Parmley & Braunwald, 1967), but there is now much evidence (discussed by Dohadwalla *et al.*, 1969) that elimination of a sympathetic component reduces the probability of fibrillation, and if I.C.I. 50172 is not achieving this effect by β-blockade, it is possible that it too, like bretylium, interferes with transmitter release. In this context the finding by Foo *et al.* (1968) that I.C.I. 50172 can reduce noradrenaline release by tyramine is of special interest, as is the report of Brick, Hutchison, McDevitt, Roddie & Shanks (1968), that *in vivo* I.C.I. 50172 is much more effective in reducing sympathetic cardiac reflex responses than would be expected from its *in vitro* activity as a β-receptor blocking agent.

This *in vivo* anti-sympathetic action apart, it is apparent that in I.C.I. 50172 no net gain has been achieved in β-receptor blockade, since the ring-substitution has diminished β-receptor blocking activity in the same proportion as local anaesthetic potency has been reduced. On the other hand, (−)-propranolol is close to being a pure β-receptor blocking drug. The minimum effective dose that decreases the rate of rise of the cardiac action potential, 0·15 mg/l. (5×10^{-7}M), although 250 times less than that required to reduce the action potential of frog nerve, is nevertheless fifty times greater than the concentration which will cause a substantial decrease in the chronotropic effect of noradrenaline (Blinks, 1967). Thus, virtually complete β-receptor blockade can be achieved by (−)-propranolol without any significant quinidine-like action. A further increase in anti-arrhythmic specificity might be achieved by a drug which blocked chronotropic more than inotropic effects, but there is no firm evidence that the β-receptors subserving these two functions are different. In any case many arrhythmias cannot be controlled by sympatholytic action alone, and require a drug which will reduce depolarizing current. In this direction there is a reasonable hope of further advances, because quinidine-like potency does not run parallel with effects on contractions (Vaughan Williams & Szekeres, 1961).

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