Br. J. Pharmac. (1984), **83**, 419–426

Electrophysiological effects of α-adrenoceptor antagonists in rabbit sino-atrial node, cardiac Purkinje cells and papillary muscles

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1 The effects of prazosin, labetalol, and medroxalol were studied in the rabbit sino-atrial node, Purkinje cells and papillary muscles.

2 At concentrations producing similar bradycardia, labetalol and medroxalol reduced the maximum rate of depolarization (*Vmax*) and overshoot potential in the sinus node. Prazosin had no such effects.

3 These large and highly significant reductions in *Vmax* and overshoot in sinus node cells were observed at concentrations of medroxalol and labetalol which had no negative inotropic effect. If depolarization in the sinus node was due to the second inward current, this would imply that such currents in the sinus node and contracting cardiac muscle are pharmacologically distinct.

4 All three drugs prolonged action potential duration in the sinus node, Purkinje cells and papillary muscles in a dose-related manner. Recovery after 1 h in drug-free solution from the effects of medroxalol and labetalol was only partial in the sinus node, but almost complete in Purkinje cells and papillary muscle. Recovery from prazosin was complete in all tissues.

5 All three drugs depressed *Vmax* in Purkinje cells and papillary muscles in a dose-related manner, and recovery was complete.

6 It is concluded that all three drugs had class 1 and class 3 antiarrhythmic actions, which could contribute to their protective effects in ischaemia and reperfusion independently of blockade of myocardial α-adrenoceptors.

Introduction

The availability of selective α_1- and α_2-, and β_1- and β_2-adrenoceptor agonists and antagonists has permitted an analysis of the cardiac electrophysiological effects mediated by the individual types of adrenoceptor (Dukes & Vaughan Williams, 1984a,b). In the rabbit sinoatrial node, stimulation individually of β_1- or β_2-adrenoceptors induces tachycardia by accelerating repolarization and increasing the slope of the slow diastolic depolarization. In addition β_1-, but not β_2-, adrenoceptor stimulation increases the maximum rate of depolarization (*Vmax*) in the sinus node, and increases contractions in papillary muscle. α_2-Adrenoceptor stimulation has no electrophysiological effects in any cardiac tissue but α_1-adrenoceptor stimulation causes bradycardia by delaying repolarization in the sinus node. In papillary muscle, α_1-stimulation causes a small increase in developed tension, and prolongs both action potential duration (APD) and contraction.

It might have been expected, therefore, that α_1-adrenoceptor blocking drugs would shorten APD, by nullifying the agonist effect, which would be an arrhythmogenic action of particular current interest, since it would be out of line with recent evidence that α-adrenoceptor stimulation may exacerbate arrhythmias induced by ischaemia and reperfusion in cats (Sheridan *et al.*, 1980). Phentolamine and prazosin reduced these arrhythmias, but propranolol did not. The antiarrhythmic effect was attributed to blockade of α-adrenoceptors, although it is possible that other actions contributed, because it is known that phentolamine restricts fast inward current (Rosen *et al.*, 1971; Northover, 1983). In dogs, phentolamine had no effect on early post-occlusion arrhythmias (Stewart *et al.*, 1980), but reduced the arrhythmias occurring on reperfusion in association with a reduction in the dispersion of ventricular refractoriness, though it was not clear whether the latter was an

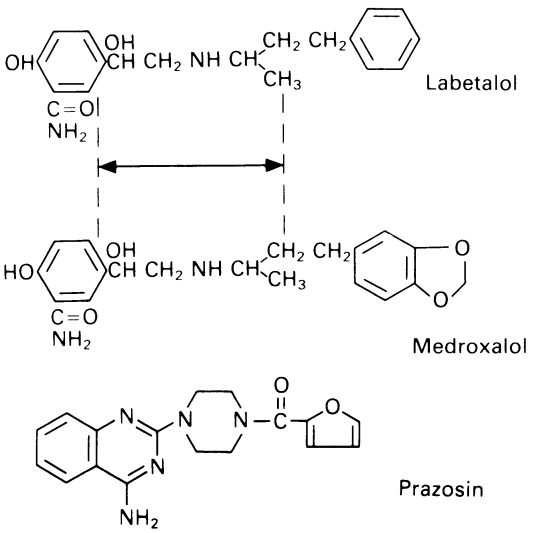

Figure 1 Structures of labetalol, medroxalol and prazosin. Medroxalol differs from labetalol only in the substitution of the ring attached to the N-ethyl, and both drugs contain a segment (indicated by the arrows) which is common to most β-blockers.

effect of alpha-blockade or represented a direct membrane effect of the drug.

It was thought worth while, therefore, to study the direct electrophysiological actions of some other α-adrenoceptor antagonists, in addition to phentolamine, those chosen being prazosin (Davey, 1980), labetalol (Richards & Turner, 1976; Vaughan Williams *et al.*, 1982), and a new antiarrhythmic drug structurally related to labetalol, medroxalol (Figure 1) which not only blocks α- and β-adrenoceptors, but has been reported to exhibit partial agonist activity on β_2-adrenoceptors in bronchial, vascular and uterine muscle (Spedding, 1981; Dage, *et al.*, 1981; 1983).

Methods

Rabbits of either sex, weighing 1 to 1.5 kg were stunned and their hearts were rapidly removed. After separating the atria from the ventricles, dissection was continued to leave a portion of the vena cava containing the sinus node bordered by the ring bundle. The preparation was pinned to the silastic base of a 12 ml bath and superfused with modified Locke solution (Composition, mM: NaCl 125, KCl 5.6, $CaCl_2$ 2.16, $NaHCO_3$ 25, $MgCl_2$ 1.0, NaH_2PO_4 0.8 and glucose 11) at pH 7.4.

Action potentials were recorded with conventional glass microelectrodes filled with 3 M KCl, coupled to a high input impedance d.c. amplifier with variable capacity compensation. Action potentials were displayed on a Tektronix 5103N storage oscilloscope and recorded at will on tape (Racal Store 4). The stored records were measured and analysed statistically by a computer programme (Vaughan Williams, 1977) which incorporated Student's *t* test. Individual values in each set of control and treated results were expressed as percentages of the mean in each experiment. These percentages were then used to recalculate absolute values from the appropriate mean of all the experiments. The statistical significance of differences could be calculated on a sounder basis because the irrelevant element of between-animal differences was eliminated. The actual means were, of course, unchanged. The normalisation procedure merely adjusted the individual variations to the common mean from the experimental mean.

Records of Purkinje cell and papillary muscle potentials were made at 32°C as previously described (Millar & Vaughan Williams, 1982). Sino-atrial records were made at 36.5°C. The sinus node was explored and cells were accepted as 'sino-atrial' if there was a slow diastolic depolarization merging into an action potential upstroke with *Vmax* not greater than 15 V s^{-1} (i.e. unlikely to contain a component of

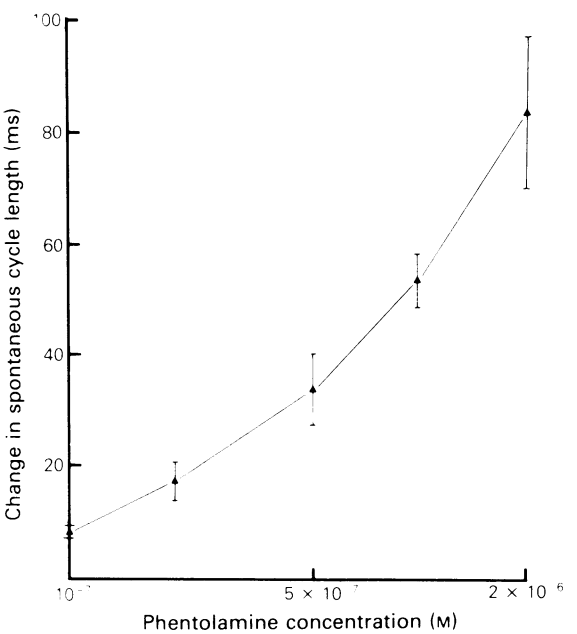

Figure 2 The effect of phentolamine on spontaneous frequency in rabbit isolated atria. Ordinate scale: increase in peak-to-peak (P-P) interval (ms). Abscissa scale: concentration in mol l^{-1}, on logarithmic scale. The mean initial frequency was 209.4 ± 3.1 beats min^{-1} (at 36.5°C).

fast inward current). In the prazosin experiments the criterion was lowered to a *Vmax* not greater than $10 V s^{-1}$. It was usually possible to maintain impalement of a single cell throughout control and drug-exposure periods in the sinus node. The important comparisons were between the control and treatment periods, not between different controls in different animals.

Intracellular records were made from at least six cells at each drug concentration in four or five hearts in the atrium and ventricle. Separate animals were used for each drug, and for the experiments on atria and on ventricles. The animals in each group of 4 or 5 animals were usually littermates. The standard errors of the means of observations from each set of animals were small, and have not, therefore, been given in the tables for the sake of clarity. In respect of the effects of the drugs on *Vmax* and on the slope of the slow diastolic depolarization, the actual values have been presented in the tables. Other effects have been expressed as changes from control, since the main point of interest was quantitative comparisons between drug potencies.

The drugs used were gifts from the manufacturers as follows: medroxalol, Merrell; labetalol, Glaxo; prazosin, Pfizer. Other drugs were obtained commercially.

Results

Sino-atrial node

Bradycardia Medroxalol and labetalol both caused a substantial dose-related bradycardia *in vitro*, concentrations of 5×10^{-6} mol l^{-1} causing reductions in heart rate of 22 and 17 beats min^{-1} respectively. The non-selective α-adrenoceptor blocking drug phentolamine also produced a dose-related bradycardia (Figure 2), as did the α_1-adrenoceptor selective antagonist prazosin. This was surprising because α_1-adrenoceptor stimulation caused bradycardia (Dukes & Vaughan Williams, 1984a,b). Prazosin was a little more potent than medroxalol and labetalol, so that the concentrations selected of the latter were 10^{-6}, 5×10^{-6} and 10^{-5} mol l^{-1}, for comparison with concentrations of prazosin causing approximately similar bradycardia, namely 10^{-6}, 2×10^{-6} and

Table 1 Effects of medroxalol, labetalol and prazosin on depolarization in the sinus node

Medroxalol					
Conc (mol l^{-1})	0	10^{-6}	5×10^{-6} *	10^{-5} ***	0. Recovery
Max. rate of depolarization (Vs^{-1}, *Vmax*)	9.1	8.6	6.4	2.6	4.1
Change in peak amplitude (mV)		*** −2.1	*** −5.7	*** −8.9	++ −2.8
Change in take-off potential (mV)		+0.8	* +4.4	*** +7.3	+6.4
Labetalol					
$Vmax_1$ (Vs^{-1})	10.7	8.8	*** 6.8	*** 5.0	6.8
Change in peak amplitude (mV)		*** −0.7	*** −2.8	*** −5.0	++ −1.4
Change in take-off potential (mV)		+1.7	*** +3.0	*** +4.5	+3.0
Prazosin					
Conc (mol l^{-1})	0	10^{-6}	2×10^{-6}	4×10^{-6} *	0. Recovery +
$Vmax_1$ (Vs^{-1})	5.7	5.2	5.3	4.6	5.8
Change in peak amplitude (mV)		−0.1	−0.18	0.0	−0.21
Change in take-off potential (mV)		+1.6	*** +4.7	*** +7.1	+++ +0.7

In this and subsequent tables the statistical significance of differences is indicated thus: * $P<0.05$; **, $P<0.01$; ***, $P<0.001$: difference from control $^{+}P<0.05$, $^{++}P<0.01$, $^{+++}P<0.001$; difference of recovery value from that of highest drug concentration used. Each measurement is an overall mean derived from the data obtained in all the experiments, as described in methods.

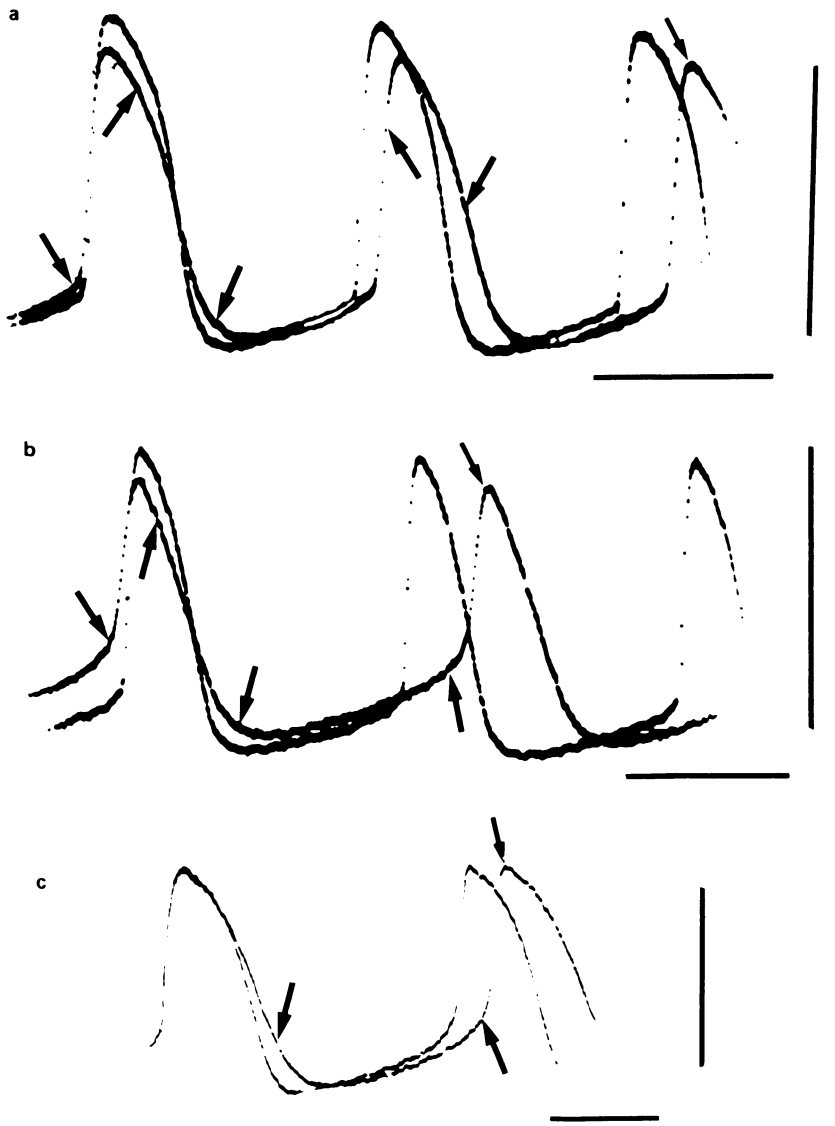

Figure 3 Effects of medroxalol (a) and labetalol (b) at concentrations of 5×10^{-6} mol l^{-1}, and of prazosin (c) at 2×10^{-6} mol l^{-1} on intracellular potentials recorded from the sinoatrial node. The bradycardia induced by all three drugs was similar. Labetalol and medroxalol decreased *Vmax*, but prazosin did not. The arrows indicate the trace taken in the presence of the drugs superimposed on control traces. Vertical bars; 60 mV. Horizontal bars; (a) and (b) 200 ms; (c) 100 ms.

4×10^{-6} mol l^{-1}. The effects of higher concentrations of prazosin were also examined, but they caused sinus node arrest.

Intracellular potentials The effects of medroxalol and labetalol on sinus node potentials were very similar. Both drugs decreased the maximum rate of depolarization (*Vmax*) and depressed the peak amplitude (APA) of the action potential (Figure 3a,b) implying restriction of the second inward (calcium) current. The mean initial overshoot potential was 4.6 ± 2.1 mV in the medroxalol group, and 9.2 ± 1.0 mV in the labetalol group. In contrast, prazosin had no effect on action potential amplitude (initial mean overshoot 6.0 ± 0.1 mV) and only slightly depressed *Vmax* at the highest concentration

Table 2 Effects of medroxalol, labetalol and prazosin on repolarization and diastolic potentials in the sinus node

Medroxalol					
Conc (mol l^{-1})	0	10^{-6}	5×10^{-6}	10^{-5}	0.Recovery
Increase in P-P interval (from peak to max. diastolic potential) and APD (ms)		7.9	32.4 ***	69.1 ***	69.2 ++
		3.6	25.4 ***	39.0 ***	26.6 +++
Slope of slow diastolic, depolarization (mV s^{-1})	82.7	73.1	70.44	59.7	73.35
Decreased negativity of maximum diastolic potential (mV)		1.61	2.42 ***	3.79 ***	2.14
Labetalol					
Increase in P-P interval		12.7	26.5 ***	36.2 ***	26.9 ++
and APD (ms)		11.0	15.5 **	30.4 ***	19.6 ++
Slope of slow diastolic depolarization (mV s^{-1})	91.8	94.8	83.7	73.8 ***	84.3
Decreased negativity of maximum diastolic potential (mV)		0.31	1.72	2.74 ***	1.25
Prazosin					
Conc (mol l^{-1})	0	10^{-6}	2×10^{-6}	4×10^{-6}	0
Increase in P-P interval		7.13	22.6 ***	93.0 ***	17.2 +++
and APD (ms)		0.9	22.7 **	42.1 ***	3.0 ++
Slope of slow diastolic depolarization (mV s^{-1})	81.6	82.7	75.8	71.5	79.2
Decreased negativity of maximum diastolic potential (mV)		0.40	1.46 *	3.33 ***	0.15

used (Figure 3c). All three drugs, however, significantly shifted in a positive direction the potential at which the upstroke of the action potential 'took off', (Table 1). The take-off potential was the point at which extrapolation forwards of the slow diastolic depolarization intersected extrapolation backwards of the action potential upstroke. The initial values in the medroxalol and labetalol groups were -51 ± 3.2 and -55 ± 0.8 mV respectively. In the prazosin group, in which stricter criteria for selection of potentials were applied, it was -24.3 ± 0.4 mV. The initial P-P intervals were 215.5, 202.2 and 308.3 ms in the medroxalol, labetolol and prazosin groups respectively, and the initial APDs, measured from the peak to the point of maximum diastolic potential were 109 ± 9.1, 113 ± 4.1 and 137.8 ± 1.8 ms.

The effects of the drugs on repolarization are presented in Table 2, which shows that all three drugs delayed repolarization in a dose-related manner. Indeed this delay wholly accounted for the bradycardia induced by the lower two doses of prazosin, the additional increase in the interval between successive action potential peaks (P-P) being due to the more positive take-off potential, as there was little effect on *Vmax* or slow diastolic depolarization. Even with medroxalol and labetalol, the delayed repolarization contributed substantially to the bradycardia, especially at the lower concentrations. The initial maximum diastolic potentials were -65.0 ± 2.4, -71.1 ± 0.5 and -58.6 ± 0.2 mV in the medroxalol, labetalol and prazosin groups, respectively. It can be seen from Table 2 that all three drugs also shifted the maximum diastolic potentials in a positive direction, which, taken with the delayed repolarization, would be consistent with restriction of potassium outward current.

After measurements had been made at the highest concentration, the drugs were washed out for an hour, and the measurements were repeated (recovery column). It was noteworthy in both Tables 1 and

Table 3 Effects on depolarization and repolarization in Purkinje cells

Medroxalol					
Conc ($mol\,l^{-1}$)	0	10^{-6}	5×10^{-6}	10^{-5}	0.Recovery
			**	***	+++
Vmax ($V\,s^{-1}$)	347	340	327	300	341
Increases			**	***	+++
in APD_{50} (ms)		1.9	7.5	25.2	2.5
			***	***	+++
and APD_{90} (ms)		2.1	15.6	27.5	2.1
Labetalol			***	***	+++
Vmax ($V\,s^{-1}$)	326	335	300	280	322
Increases			***	***	+++
in APD_{50} (ms)		1.7	12.6	22.8	6
			***	***	+++
and APD_{90} (ms)		1.7	13.0	26.0	5
Prazosin					
Conc ($mol\,l^{-1}$)	0	10^{-6}	2×10^{-6}	4×10^{-6}	0.Recovery
			**	***	+++
Vmax ($V\,s^{-1}$)	375	370	362	342	379
Increases			***	***	+++
in APD_{50} (ms)		2.2	10.6	17.2	−1.4
			***	***	+++
and APD_{90} (ms)		1.5	13.1	18.0	−2.8

The initial values for APD_{50} and APD_{90} were 145.7 ± 2.8 and 205.1 ± 4.3 in the medroxalol group, 150 ± 2.0 and 209.7 ± 3.2 in the labetalol group, and 156.2 ± 1.8 and 213.7 ± 3.9 ms in the prazosin group.

Table 4 Effects on depolarization and repolarization in papillary muscle

Medroxalol					
Conc ($mol\,l^{-1}$)	0	10^{-6}	5×10^{-6}	10^{-5}	0.Recovery
			***	***	+++
Vmax ($V\,s^{-1}$)	151	155	126	111	149
Increase			**	***	+++
in APD_{50} (ms)		2.6	5.2	17.5	2.4
			**	***	+++
and APD_{90} (ms)		2.7	8.1	17.5	−1.3
Labetalol			***	***	+++
Vmax ($V\,s^{-1}$)	162	158	137	120	166
Increase			*	***	+++
in APD_{50} (ms)		2.1	4.4	18.3	1.4
			***	***	+++
and APD_{90} (ms)		3.8	9.4	17.9	3.7
Prazosin					
Conc ($mol\,l^{-1}$)	0	10^{-6}	2×10^{-6}	4×10^{-6}	0.Recovery
			**	***	+++
Vmax ($V\,s^{-1}$)	185	180	173	163	179
Increase			***	***	+++
in APD_{50} (ms)		3	11.4	23.4	2.1
			***	***	+++
and APD_{90} (ms)		6.5	17.8	29.9	1.1

The initial values for APD_{50} and APD_{90} were 95.2 ± 2.7 and 138.7 ± 2.5 in the medroxalol group, 97.3 ± 2.0 and 142.7 ± 2.0 in the labetalol group, and 105.6 ± 1.8 and 150.4 ± 4.2 ms in the prazosin group.

2 that recovery from prazosin was greater than that from medroxalol or labetalol.

Ventricle

Distal Purkinje cells None of the drugs had any effect on resting potential in distal Purkinje cells, or on the overshoot potential, except for a small depression by the highest concentration of prazosin from 34.8 ± 0.7 to 31 ± 0.8 mV ($P < 0.001$), recovering on washout to 34.1 ± 0.6 mV. All three drugs, however, depressed the maximum rate of depolarization (*Vmax*) and prolonged action potential duration in a dose-related fashion (Table 3), and recovery was complete after washing for 1 h. Recovery of APD was nearly complete with medroxalol and labetalol, illustrating that the duration of action of these compounds was less persistent in Purkinje cells than in the sinoatrial node, and implying that the more negative diastolic potential of the Purkinje cells contributed to more rapid detachment of the drugs.

Papillary muscle The effects on papillary muscle were similar to those on Purkinje cells. None of the drugs had any effect on resting potential, or on overshoot potential, except for a very small depression by prazosin at the highest concentration (reduced from 32.4 ± 0.4 to 31 ± 0.3 mV ($P < 0.001$), recovering on washout to 32.5 ± 0.9 mV). All three compounds depressed *Vmax* and prolonged APD in a dose-related manner. Recovery of *Vmax* was complete after 60 min for all three drugs, and recovery of APD almost complete.

Medroxalol had no significant effect on contractions, except at the highest concentration. Labetalol, likewise, had been found in previous experiments to have no negative inotropic effect at a concentration of 4×10^{-6} mol l^{-1} in atrial muscle, and even at 11×10^{-6} mol l^{-1} a small depression (−12.6%) of contraction was not statistically significant (Vaughan Williams *et al.*, 1982).

Discussion

Medroxalol and labetalol caused bradycardia in rabbit isolated atria. Since both drugs are β-blockers, this effect might have been due to abolition of the effect of locally released catecholamines, but for the fact that atenolol 10^{-6} mol l^{-1} has no effect on spontaneous frequency in this preparation (Dukes & Vaughan Williams, 1984b). Prazosin also caused bradycardia, but in the sino-atrial node the effects of prazosin differed from those of medroxalol and labetalol, because although the prolongation of APD by all three drugs was similar, prazosin had no effect on *Vmax* or overshoot potential. In contrast, medroxalol and labetalol reduced both *Vmax* and overshoot in a dose-dependent manner, which implies that they restricted the second inward (calcium) current (i_{si}). This difference might be attributed to the fact that the criterion for the selection of sinus node cells was more rigorous in the prazosin group, and the effect on *Vmax* in the medroxalol and labetalol groups could be attributed to a depression of fast inward current. Even in the medroxalol and labetalol groups, however, the take-off potential was only −55 and −51 mV respectively, voltages at which sodium channels would have been inactivated. At the concentration of 5×10^{-6} mol l^{-1} labetalol depressed *Vmax* and overshoot potential by 36.4% and 2.8 mV respectively, and medroxalol by 30% and 5.7 mV ($P < 0.001$ in both cases), but at these concentrations neither drug had any negative inotropic effect on contracting myocardium. It would appear, therefore, if it can be accepted that depolarization in sinus node cells is due to the second inward current, that the second inward current in the sinus node is different pharmacologically from the calcium inward current regulating contractions in cardiac muscle.

The structures of labetalol and medroxalol are very similar, whereas that of prazosin is quite different. Nevertheless all three compounds are α-blockers, and all have in common the property of causing bradycardia in the sinus node, largely by delaying repolarization. All three drugs reduced fast inward current and prolonged action potential duration in distal Purkinje cells and papillary muscles in a dose-dependent manner. It seems doubtful, however, whether these effects could be related to blockade of the α-adrenoceptors, because stimulation of α_1-adrenoceptors also causes bradycardia, and prolongs action potential duration in Purkinje cells and papillary muscles (Dukes & Vaughan Williams, 1984a,b).

The depression of *Vmax*, and a uniform delay of repolarization, would constitute antiarrhythmic actions (Class1 and Class 3 respectively), which reinforces the suggestion that the efficacy of α-adrenoceptor blocking drugs in protecting against ischaemia- and reperfusion-induced arrhythmias might be unrelated to blockade of myocardial α-adrenoceptors. Since stimulation of α_1-adrenoceptors uniformly prolonged APD in all the cardiac tissues studied, this itself would be antiarrhythmic rather than arrhythmogenic. Although Sheridan *et al.* (1980) reported that phentolamine did not cause any significant shift in the distribution or magnitude of total post-occlusion hyperaemia, the hyperaemic flow was 2.5 times the control value, and small, but arrhythmogenic, heterogeneities of perfusion caused by α-adrenoceptor-mediated local vasoconstrictions in the untreated myocardium could have gone undetected (Vaughan Williams *et al.*, 1982). Thus it seems possible that the antiarrhythmic

action of α-blockers in ischaemia and reperfusion could be attributed partly to elimination of local vasoconstriction induced by ischaemically-released catecholamines responsible for heterogeneity of the distribution of blood in the myocardial microcirculation, and partly to the direct class 1 and 3 antiarrhythmic actions unrelated to α-adrenoceptor blockade.

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(Received February 10, 1984. Revised May 2, 1984.)