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Effect of α-adrenoceptor antagonists (phentolamine, nicergoline and prazosin) on reperfusion arrhythmias and noradrenaline release in perfused rat heart

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1 Rat isolated hearts were perfused through the left atrium with a modified Krebs-Henseleit solution or mounted on a Langendorff perfusion system. The hearts were prelabelled with [^{3}H]-noradrenaline ([^{3}H]-NA) and the left main coronary artery was ligated for 10 min after which reperfusion followed. The liberation of [^{3}H]-NA and the development of ventricular tachycardia and fibrillation were monitored throughout.

2 During the occlusion period, ventricular arrhythmias did not occur and heart rate was not significantly altered in the control series. In contrast, reperfusion was followed by ventricular fibrillation and ventricular tachycardia in all the hearts in the control series (Langendorff or 'working' models).

3 The α-adrenoceptor antagonists phentolamine (7.1×10^{-6} M and 7.1×10^{-5} M) and nicergoline (3.1×10^{-6} M) diminished or prevented reperfusion arrhythmias. However, prazosin (5.2×10^{-6} M) was not effective. The lower concentration of phentolamine did not alter the pattern of [^{3}H]-NA release, whereas, high doses of phentolamine and nicergoline increased the release of [^{3}H]-NA. Prazosin (5.2×10^{-6} M) caused a very marked increase in release of [^{3}H]-NA but was not antiarrhythmic.

4 A 'membrane-stabilizing' effect seems the most appropriate explanation for these antiarrhythmic effects of α-antagonist agents.

Introduction

The role of α-myocardial adrenoceptors remains ill-defined (Benfey, 1982). One recent hypothesis is that activation of α-adrenoceptors changes cell calcium fluxes by an enhanced slow inward calcium current (Exton, 1982) and facilitates an increase of cytosolic Ca^{2+}. However, the mechanisms by which α-adrenoceptor stimulation raise cytosolic Ca^{2+} is not well understood. There may be an influx of extracellular Ca^{2+} through 'gates' in the plasma membrane and a release of Ca^{2+} from mitochondria. Calcium ions are important mediators of electrical activity in cardiac cells. Calcium-dependent ionic currents may be implicated in the genesis of ischaemic ventricular arrhythmias (Opie & Thandroyen, 1983). For example after potentials are sensitive to calcium channel inhibitors (Cranefield *et al.*, 1974). The electrophysiological basis of reperfusion arrhythmias remains unknown but increased automaticity may play a role (Bigger *et al.*, 1977). Accordingly we attempted to test the effect of α-adrenoceptor antagonist agents on reperfusion arrhythmias. The model used was the isolated perfused working heart of the rat in which ventricular arrhythmias are consistently obtained soon after release of a coronary ligature and in which the rate of release of [^{3}H]-NA can be followed in the coronary effluent.

Methods

Experimental animals and isolated heart procedures

Experiments were performed in the isolated perfused heart of the rat. Male Sprague-Dawley rats (Iffa-

Credo, 250–300 g) were lightly anaesthetized with ether and heparin (600 iu) was injected into the femoral vein. The hearts were rapidly excised, arrested by immersion in ice-cold Krebs-Henseleit solution and mounted by the aorta on a cannula and perfused according to the method of Langendorff ('non-working heart') or the working heart technique (Neely *et al.*, 1967).

Langendorff technique

With the Langendorff method hearts were mounted on an aortic retrograde perfusion system modified to contain two perfusate reservoirs and perfused at a constant filling pressure of 100 cmH_2O (9.8 kPa).

Working heart technique

In the rat isolated working heart technique, each heart was quickly cannulated via the aorta and initially perfused as a Langendorff preparation with Krebs-Henseleit buffer at 37°C. Perfusion in this way was carried out for 10 min to clear the coronary bed of blood and to permit the cannulation of the left atrium. During this period the perfusate passing through the heart was discarded. At the end of this preperfusion the perfusion of the heart by the left atrium was commenced. The pressure in the left atrium (preload) was fixed at 10 cmH_2O (0.98 kPa) and the heart ejected against a hydrostatic pressure of 80 cmH_2O (postload) (7.8 kPa).

Measurement of cardiac function and heart rhythm

During the major series of experiments, the coronary flow of 'non-working' or working hearts was measured minute by minute by collecting the effluent into tared tubes. The electrocardiogram was continuously recorded on a Racia apparatus and the heart rate was determined. Atrial, ventricular and nodal arrhythmias were analyzed. The criteria for ventricular arrhythmias were those reported by Lubbe *et al.* (1978). Ventricular tachycardia (VT) was diagnosed when more than three consecutive morphologically similar ventricular premature extrasystoles (VPEs) occurred. Ventricular fibrillation (VF) was diagnosed when there was total irregularity of the morphology of repetitive ectopic complexes for at least six cycles. In the working rat heart experiments, the following indices of cardiac function was recorded during perfusion: aortic pressure, aortic flow and cardiac output. The coronary flow was measured min by min and the effluent weighed. The aortic output was measured by a timed collection. The cardiac output was the sum of the aortic output and the coronary flow. When the aortic output fell to zero, as occurred during ventricular fibrillation, then the perfusion fluid was recirculated by a pump and the heart perfused by the Langendorff technique until normal rhythm resumed.

Perfusion medium and time sequence of perfusion

The hearts were perfused with a modified Krebs-Henseleit bicarbonate buffer equilibrated with O_2/CO_2 (95:5) at 37°C and containing (mM): NaCl 118, KCl 1.8, $CaCl_2$ 2.5, $MgSO_4$ 1.2, KH_2PO_4 1.2 and $NaHCO_3$ 25; plus ascorbic acid 10 mg; disodium EDTA 10 mg; distilled water to 1 litre. Glucose (11 mM) was included as a substrate. The chosen low cencentration of K^+ (3 mM) has previously been demonstrated to increase arrhythmias (Lubbe *et al.*, 1978). Immediately after mounting on the perfusion system, the hearts were subjected to a 5 min perfusion by the Langendorff method.

In the main series of experiments, the NA stores of the hearts were labelled by perfusion between 5 and 15 min after mounting with a Krebs-Henseleit buffer containing 30 μCi of [^{3}H]-NA ([1-7-^{3}H]-noradrenaline (norepinephrine), specific activity 15 Ci mM^{-1}, Radiochemical Centre, Amersham). The final concentration of NA (about 16 nM) was appropriate for selective labelling of neuronal stores (Iversen, 1963). At 30 min, the left ventricular work was started and 30 min after the start of the heart work the left main coronary artery was tied (Bajusz, 1963; Kannengiesser *et al.*, 1975). The ligature was maintained for 10 min, the coronary ligature was cut and the reperfusion was continued for 10 min. α-Blocking agents were added 15 min before coronary artery ligation and the concentration maintained for the rest of the perfusion period.

In another series of hearts not subject to coronary ligation and perfused by the Langendorff method, the effect of α-blockers on the uptake of [^{3}H]-NA was examined. The α-blocking drugs were added after 10 min of perfusion, then 5 min later [^{3}H]-NA was added to the perfusate for a period of 10 min (2 μCi of [1-7-^{3}H] noradrenaline; specific activity: 15 Ci mM^{-1}) and at 27 min the experiment was terminated. The amount of [^{3}H]-NA liberated and retained during the 15–27 min period was compared with that remaining in the heart.

Isotopic techniques

The efflux of ^{3}H-labelled compounds was measured by collection of coronary effluent min by min into tubes containing 1 ml $HClO_4$ (5 N) added 0.1% of sodium bisulphite and 0.1% disodium EDTA to inhibit the oxidation of NA. The total radioactivity ([^{3}H]-NA and metabolites containing ^{3}H) was measured in a liquid scintillation counter (Packard 3385)

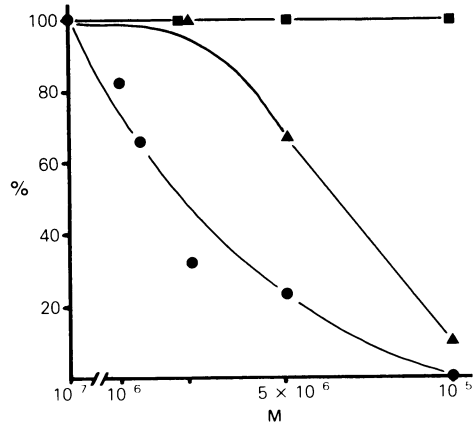

Figure 1 Antiarrhythmic action of α-blocking agents in rat isolated heart (Langendorff). The effect of increased concentration of phentolamine (▲), nicergoline (●) and prazosin (■) in the perfusate on the percentage of hearts developing ventricular arrhythmias during reperfusion. Number of hearts in each series = 10.

by addition of 2 ml of effluent to 15 ml scintillation mixture (dimethyl-POPOP, 0.1 g; PPO, 4 g; Triton X100 500 ml and 1 litre of toluene). Quenching was monitored by the external standard technique. At the end of the experiment the hearts were removed from the apparatus and the 'ischaemic' and 'non ischaemic' zones were separated, weighed and homogenized in 10 ml $HCLO_4$ (0.4 N) containing 0.1% sodium bisulphite and 0.1% disodium EDTA. Total radioactivity and [^{3}H]-NA were measured as already described (Didier *et al.*, 1980; Rochette *et al.*, 1980). The amount of radioactivity liberated per min into the coronary effluent was expressed as a percentage of the total radioactivity present in the heart at the beginning of the experiment. This last value was calculated by adding the radioactivity liberated into the coronary effluent during the perfusion period to the radioactivity remaining in the heart at the end of the experiment.

Drugs

The following drugs were used: phentolamine methane sulphonate (Ciba-Geigy), prazosin chlorhydrate (Pfizer), nicergoline tartrate = dimethyl-1,6 (bromo-5 nicotinoyl-oxymethyl)-8 β methoxy-10 α ergoline (Specia).

Statistical analysis

Results are expressed as means ± s.e.mean. Student's *t* test was used to determine the significance between mean values of different experiments.

Results

Effect of coronary ligation and reperfusion on ventricular functions

Ligation of the coronary artery resulted in a 25% reduction in coronary flow which remained relatively constant during the occlusion period. In the working rat heart model the aortic flow fell from 39.3 ± 1.5 to 21.5 ± 3.4 ml min^{-1}. Reperfusion was followed by a return of the coronary flow to a value similar to the flow before ligation. During the occlusion period, heart rate was not significantly altered. Reperfusion was followed by ventricular fibrillation and ventricular tachycardia in all the hearts in the control series (Langendorff series and 'working' series). These arrhythmias caused the cardiac output to drop temporarily to zero aortic flow (Figure 2).

Effect of α-blocking agents on cardiac functions

Basal cardiac function (Table 1, Figures 1, 2 and 3)

In general, α-blocking agent treatments had no significant effect on heart rate or aortic flow. In contrast, treatment with the higher dose of phentolamine

Table 1 Effect of α-adrenoceptor antagonists on duration of ventricular tachycardia (VT) and ventricular fibrillation (VF) during ischaemia and reperfusion

Duration of VT-VF (in s min^{-1})	*Control* $n=10$	*Phentolamine* 7.1×10^{-6} M $n=7$	*Phentolamine* 7.1×10^{-5} M $n=6$	*Nicergoline* 3.1×10^{-6} M $n=7$	*Prazosin* 5.2×10^{-6} M $n=6$
Ischaemia	0	0	0	0	0
Reperfusion 1–3 min	44.1 ± 3.7[a]	14.8 ± 3.3[b]	0	4.9 ± 1.8[c]	41.4 ± 5.7[d]
Reperfusion 3–6 min	21.1 ± 5.3[e]	0	0	0	29.7 ± 6.5[f]
Reperfusion 6–9 min	19.3 ± 5.4[g]	0	0	0	17.1 ± 6.0[h]

Ischaemia = the last 3 min of coronary ligation.
Significance of difference between results: avsb: $P<0.001$; avsc: $P<0.001$; avsd: NS; avse: $P<0.01$; avsg: $P<0.001$; evsg: NS; bvsc: $P<0.05$; cvsd: $P<0.001$; dvsf: NS; dvsh: $P<0.05$; evsf: NS; gvsh: NS; fvsh: NS.

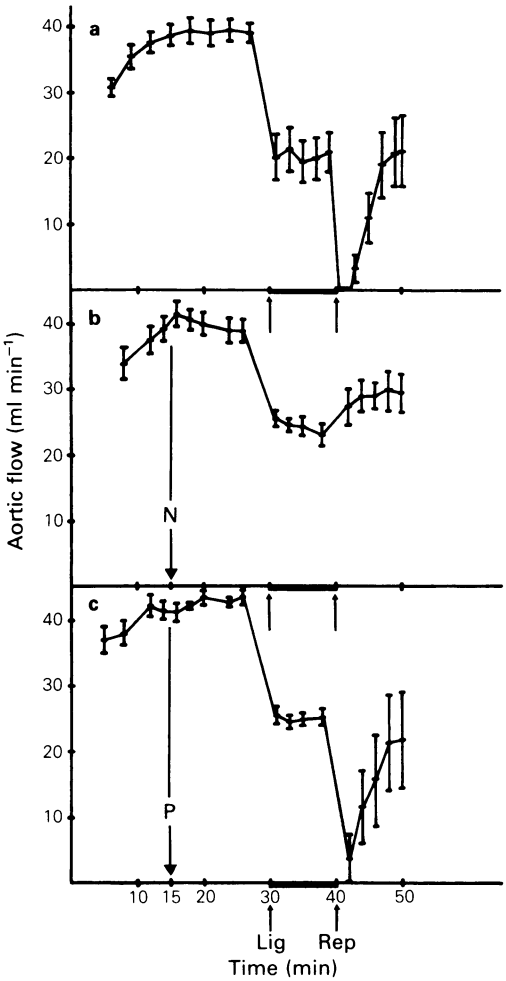

Figure 2 Effect of nicergoline (N) 3.1×10^{-6} M (b) and prazosin (P) 5.2×10^{-6} M (c) on aortic flow, in working rat heart; (a) controls. Means for 7 hearts, with s.e.mean shown by vertical lines. Lig: ligation; Rep: reperfusion.

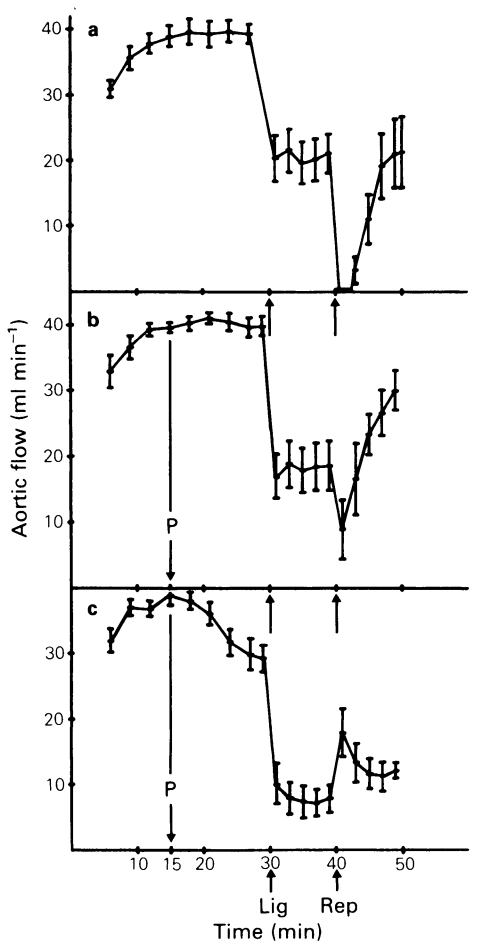

Figure 3 Effect of phentolamine (P) 7.1×10^{-6} M (b) and 7.1×10^{-5} M (c) on aortic flow in working rat heart; (a) controls. Means for 6 hearts; with s.e.mean shown by vertical lines. Lig: ligation; Rep: reperfusion.

Table 2 Effect of α-adrenoceptor antagonists on release of [^{3}H]-noradrenaline ([^{3}H]-NA) from isolated perfused working heart of rat during regional ischaemia and reperfusion

[^{3}H]-NA release % min^{-1} ($\times 10^{-3}$)	*Control* $n=10$	*Phentolamine* 7.1×10^{-6} M $n=7$		*Phentolamine* 7.1×10^{-5} M $n=6$		*Nicergoline* 3.1×10^{-6} M $n=7$		*Prazosin* 5.2×10^{-6} M $n=6$	
		P		*P*		*P*		*P*	
Ischaemia	29±1	NS	33±2	<0.001	59±5	<0.001	58±2	<0.001	148±14
Reperfusion 1–3 min	64±4	NS	67±2	<0.001	114±5	<0.001	103±3	<0.001	286±15
Reperfusion 3–6 min	46±2	<0.01	59±2	<0.001	105±5	<0.001	104±3	<0.001	216±14
Reperfusion 6–9 min	46±2	<0.01	58±2	<0.001	102±5	<0.001	103±3	<0.001	277±21

Ischaemia = the last 3 min of coronary ligation. All reperfusion values, $P<0.001$ vs the corresponding ischaemic period.

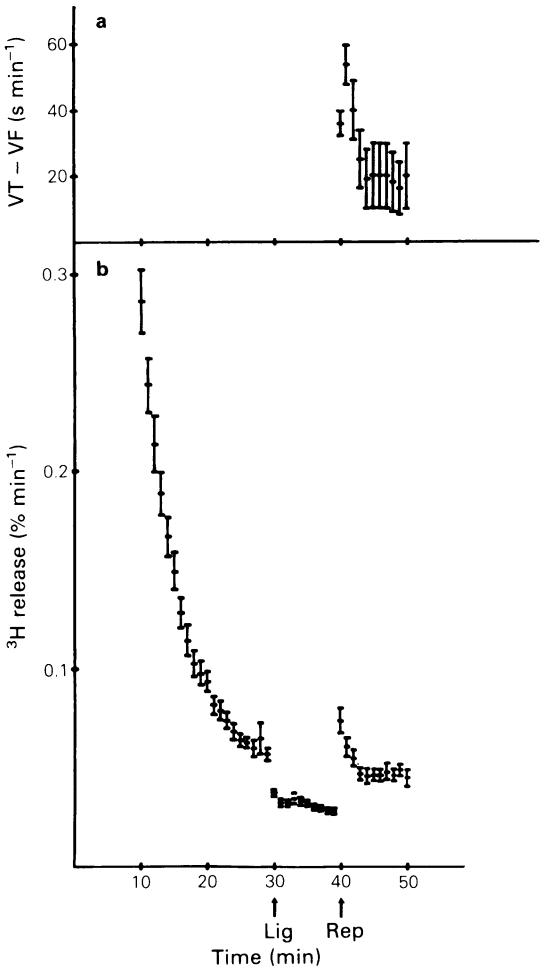

Figure 4 Effect of coronary artery ligation (Lig) and reperfusion (Rep) on reperfusion arrhythmias (VT–VF in seconds per minute) (a) and on release of [^{3}H]-noradrenaline ([^{3}H]-NA) (b) from working rat heart. Means for 10 hearts; s.e.mean shown by vertical lines.

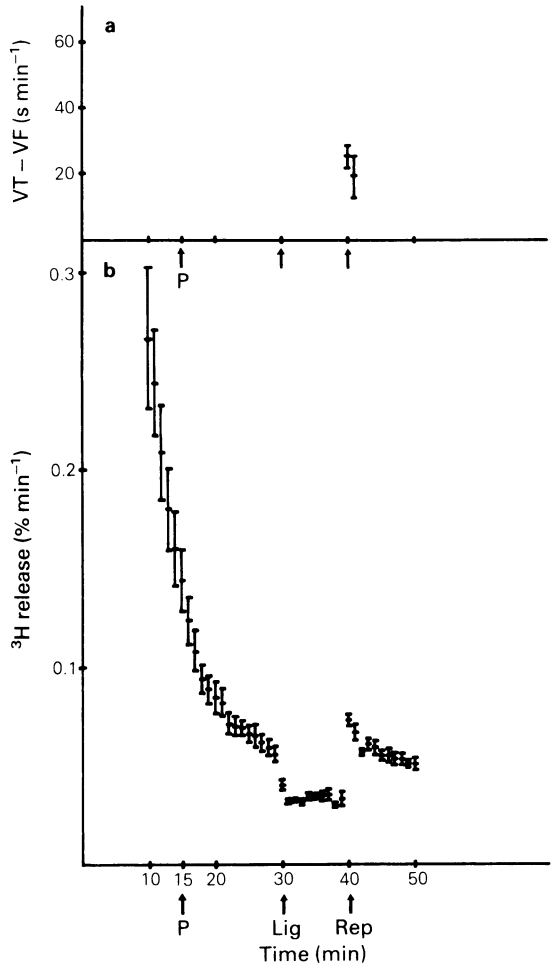

Figure 5 Effect of phentolamine (P) 7.1×10^{-6} M on reperfusion arrhythmias (a) and pattern of release of [^{3}H]-noradrenaline ([^{3}H]-NA) (b) from working rat heart. Means for 7 hearts; s.e.mean shown by vertical lines.

(7.1×10^{-5} M) reduced coronary flow significantly. The mean coronary flow decreased from 16.4 ± 0.8 ml min^{-1} (average heart weight 1.1 g) 3 min before the addition of phentolamine to 12.0 ± 0.9 ml min^{-1} 10 min after the addition of the α-blocking agent ($P<0.05$). This dose of phentolamine (7.1×10^{-5} M) decreased aortic flow and cardiac output in the preligation period. In the other series (phentolamine: 7.1×10^{-6} M; nicergoline 3.1×10^{-6} M or prazosin 5.2×10^{-6} M) basal cardiac function was not significantly altered after perfusion of the α-blocking drugs.

Reperfusion ventricular arrhythmias (Figure 1 and Table 1)

Nicergoline and phentolamine decreased the incidence of reperfusion ventricular arrhythmias in a concentration-related fashion whereas prazosin was not effective at 10^{-5} M. Prazosin (10^{-4} M) was antiarrhythmic but caused a very marked bradycardia. The agents that prevent reperfusion ventricular arrhythmias maintained cardiac output in the reperfusion period, thus avoiding the period of zero aortic flow in the early reperfusion period.

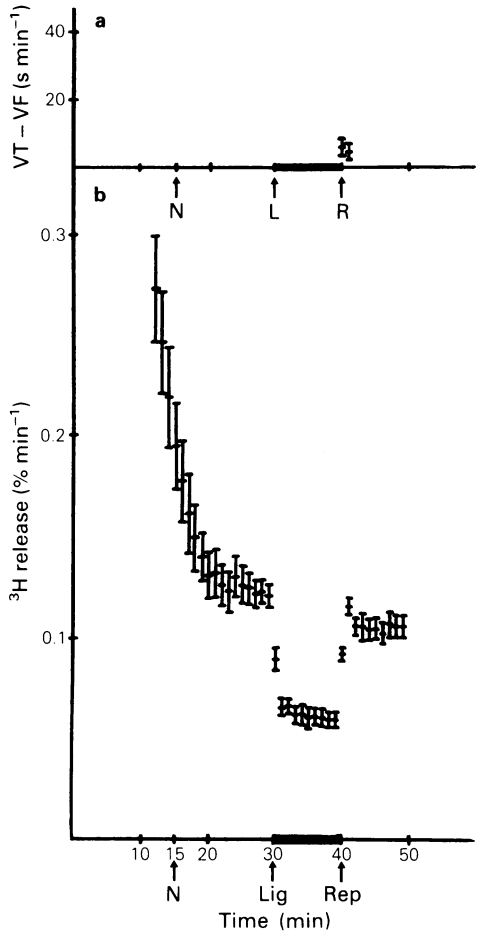

Figure 6 Effect of nicergoline (N) 3.1×10^{-6} M on reperfusion arrhythmias (a) and pattern of release of [^{3}H]-noradrenaline ([^{3}H]-NA) (b) from working rat heart. Means for 7 hearts; s.e.mean shown by vertical lines.

Effect of ischaemia, reperfusion and α-blocking agents on release of [^{3}H]-NA (Table 2)

The release profiles of radioactivity during the preischaemic period in the coronary effluent followed a multi-exponential pattern. During the ischaemic period, the spontaneous liberation of radioactivity remained relatively constant. Reperfusion was accompanied by a sudden release of radioactivity which was particularly significant during the first 3 min of reperfusion. It reached $64 \pm 4\%$ ($\times 10^{-3}$) for the first 3 min of reperfusion and $46 \pm 2\%$ (10^{-3}) for the next 3 min ($P < 0.05$ compared to the value during the last 3 min of occlusion: $29 \pm 1\%$ (10^{-3})). The increases in radioactivity efflux following reperfusion were associated with equivalent increases in [^{3}H]-NA. In all perfusion periods (preischaemic, ischaemic and reperfusion) [^{3}H]-NA accounted for about 60% of total radioactivity.

Phentolamine (7.1×10^{-6} M) did not alter the pattern of ^{3}H release (Figure 5). The high concentration of phentolamine (7.1×10^{-5} M) was both antiarrhythmic and depressed the myocardium; it increased the release of [^{3}H]-NA in preligation, ischaemic and reperfusion periods. Nicergoline (3.1×10^{-6} M) prevented reperfusion ventricular arrhythmias and increased the release of [^{3}H]-NA throughout all periods (Figure 6). Prazosin (5.1×10^{-6} M caused a very marked increase in release of [^{3}H]-NA but was not antiarrhythmic; the increase of release of [^{3}H]-NA was noted during ligation, reperfusion and also upon addition in the preligation period (Figure 7).

The effect of α-blocking drugs on rate of release of [^{3}H]-NA is indicated in Table 3. Phentolamine (7.1×10^{-5} M) and nicergoline (3.1×10^{-6} M) increased the percentage of radioactivity liberated by the heart and decreased the percentage of [^{3}H]-NA retained in perfused hearts. In contrast, prazosin (5.2×10^{-6} M) increased the percentage of radioactivity retained in perfused hearts and decreased the percentage of radioactivity liberated by hearts.

Table 3 Effect of α-adrenoceptor antagonists on rate of release [^{3}H]-noradrenaline ([^{3}H]-NA) from Langendorff perfused rat heart

Series	*No. of hearts*	*% of radioactivity liberated by heart*	*% of [^{3}H]-NA retained in perfused heart at the end of experiment*
Control	8	85.4 ± 0.7	9.8 ± 0.4
Phentolamine 7.1×10^{-6} M	6	88.5 ± 0.8*	8.9 ± 0.9
Phentolamine 7.1×10^{-5} M	6	96.5 ± 0.3**	2.4 ± 0.2**
Nicergoline 3.1×10^{-6} M	7	87.6 ± 0.4*	8.2 ± 0.5*
Prazosin 5.2×10^{-6} M	8	81.1 ± 0.3**	14.4 ± 0.3**

*$P < 0.05$ vs control hearts; **$P < 0.001$ vs control hearts.

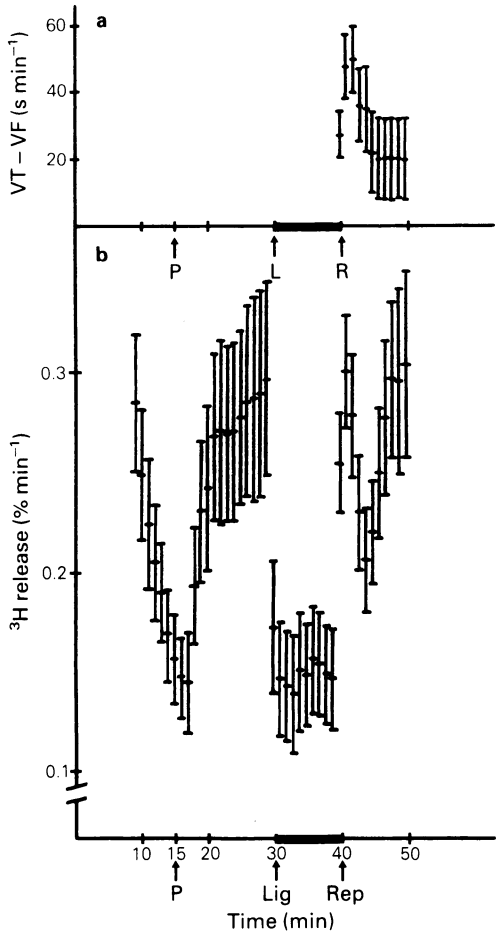

Figure 7 Effect of prazosin (P) 5.2×10^{-6} M on reperfusion arrhythmias (a) and pattern of release of [^{3}H]-noradrenaline ([^{3}H]-NA) (b) from working rat heart. Means for 6 hearts; s.e.mean shown by vertical lines.

Discussion

Ventricular fibrillation is a major cause of death in coronary artery disease (Goldstein *et al.*, 1972). Furthermore, most survivors of primary ventricular fibrillation exhibit no evidence of myocardial infarction. This suggests that mechanisms other than coronary occlusion or myocardial infarction must operate to produce sudden death (Schaffer & Cobb, 1975). In 1935, Tennant & Wiggers, reported that ventricular fibrillation could occur when coronary blood flow was rapidly restored to a ligated coronary artery in the dog. The relevance of these reperfusion arrhythmias to clinical syndromes including sudden death in human ischaemic disease has been suggested (Wiener *et al.*, 1976). Despite reperfusion arrhythmias being the subject of intense experimental study, the mechanisms implicated in the genesis of ventricular arrhythmias during reperfusion remain incompletely understood. There is general agreement that chemical and electrical gradients caused by washout of metabolites and electrolytes accumulated in the ischaemic zone, are responsible for the reperfusion arrhythmias (Suravicz, 1971). The release of catecholamines may contribute to both the α- and β-adrenoceptor effects implicated in ventricular fibrillation. Other evidence has strongly suggested a role for an increased cytoplasmic calcium accumulation in the genesis of ischaemic dysrhythmias (Opie & Thandroyen, 1983). However, how α-adrenoceptor stimulation could raise cytosolic calcium is not well understood. (Clusin *et al.*, 1982).

Our data show convincingly that phentolamine and nicergoline inhibited reperfusion arrhythmias. These agents are thought to act on both the postsynaptic α_1 and presynaptic α_2-receptors. (Phillips, 1980; Huchet *et al.*, 1981).

The potential antiarrhythmic properties of phentolamine were initially reported by Leindorfer (1952) who noted that its intravenous administration prevented arrhythmias due to nicotine and adrenaline. Experimental arrhythmias due to aconitine, inhalation of chloroform and digitalis are also prevented by phentolamine (for literature review, see Benfey, 1982). Penkoske *et al.* (1978) reported that phentolamine pretreatment had a significant effect on protecting the heart in the early phase of coronary occlusion from ventricular fibrillation and was effective in suppressing reperfusion arrhythmias. The study of Stewart *et al.* (1980) confirmed previous observations on the antiarrhythmic effect of phentolamine against ventricular reperfusion fibrillation. In clinical studies the effectiveness of phentolamine in suppressing ventricular premature beats and supraventricular premature beats has also been reported (Gould *et al.*, 1975).

In cats anaesthetized with chloralose, α-receptor blockade with either phentolamine or prazosin significantly reduced the number of premature ventricular complexes during coronary reperfusion, abolished early ventricular fibrillation and prevented the increase of idioventricular rate seen with coronary reperfusion (Sheridan *et al.*, 1980). Hence this ischaemic cat myocardium preparation offers direct evidence for the role of α-receptors in the genesis of dysrhythmia during ischaemia and reperfusion. In contrast to our results, Sheridan *et al.* (1980) showed that α-blockade by prazosin was effective in the prevention of arrhythmias. A possible explanation for the difference is that we studied the effect of coronary ligation for 10 min while they studied it for 30 min; possibly the duration of ischaemia may regu-

late the degree of α-receptor stimulation. It has been recently demonstrated that α_1-adrenoceptors increase nearly two fold in ischaemic tissue within 30 min with no apparent alteration in receptor affinity; the increase begins after 15 min of ischaemia (Corr *et al.*, 1981) and these changes correlate with the enhanced electrophysiological response. In contrast, in their preparation, β-receptor blockade with (±)-propranolol did not attenuate ventricular fibrillation after coronary reperfusion. In rat isolated heart preparation, we have shown (Rochette *et al.*, 1984) that the potentially β-antagonist agents that eliminated reperfusion arrhythmias were a 'high-dose' of acebutolol or a 'low' dose of (+)-propranolol; atenolol did not prevent reperfusion arrhythmias even in β-antagonist doses. It is possible that the 'membrane stabilizing' properties of some β-blocking agents are of importance in a variety of experimental circumstances, as in reperfusion arrhythmias. Thus the protective effect of α-antagonist agents may be due to a nonspecific action not involving α-adrenoceptors. So Northover (1983) demonstrated on tissue isolated from rat heart that α-adrenoceptor antagonists (phentolamine, prazosin and yohimbine) blocked the fast sodium channels in a manner similar to that displayed by lignocaine or quinidine. However, in our model prazosin, a selective α_1-adrenoceptor antagonist, was not effective in the prevention of reperfusion arrhythmias. The absence of an antiarrhythmic effect of prazosin in our present experiments is difficult to explain. It may be proposed that, in the concentrations used, the antiarrhythmic actions of prazosin are disguised by other properties. Thus Greenslade *et al.* (1979) provided biochemical evidence that prazosin inhibited phosphodiesterase; this effect can be responsible for a change in intracellular levels of cyclic AMP. Opie & Lubbe (1979) suggested that cyclic AMP may be one of the important factors in the production of ischaemic arrhythmias. Thus, in isolated perfused rat heart, when theophylline was added to inhibit phosphodiesterase a marked decrease in the fibrillation threshold was noted (Lubbe *et al.*, 1978).

Our results indicate that both phentolamine and nicergoline diminished the reuptake of [^{3}H]-NA and increased [^{3}H]-NA release. In contrast, prazosin caused a marked increase in release of [^{3}H]-NA and increased the uptake of [^{3}H]-NA. These results are surprising but one explanation may be that in our model the spontaneous [^{3}H]-NA release is studied in the presence of a high cencentration of prazosin with non specific effects. Therefore, there was no relation between the increased release of [^{3}H]-NA and the antiarrhythmic activity of these agents. Furthermore, prazosin caused a very marked increase of release of [^{3}H]-NA and did not prevent reperfusion arrhythmias. Our results do not prove that myocardial NA does not play a role in the genesis or the evolution of ventricular arrhythmias; the response of cardiac tissue to NA may be influenced by the metabolic state of the myocardium and the functional integrity of membranes. Therefore, it has been argued that reserpinization before reperfusion reduced but did not eliminate reperfusion ventricular fibrillation (Thandroyen *et al.*, 1983). Recent information indicates that alterations of membrane phosphatidylinositol in ischaemic tissues are important in the initiation of ventricular dysrhythmia and may influence the relative number of adrenoceptors (Corr *et al.*, 1981). It has been suggested that α_1-adrenoceptors are not linked to adenylate-cyclase but may involve phosphatidylinositol turnover and calcium (Michell & Kirk, 1981).

In summary, we show that α-blocking agents in relatively high doses prevent reperfusion arrhythmias. A 'membrane-stabilizing' effect seems the most appropriate explanation for these effects, since Rosen *et al.* (1971) showed that phentolamine produces electrophysiological changes in cardiac Purkinje fibres similar to those noted with class I antiarrhythmic drugs that possess membrane-stabilizing activity. But in our experiments the antiarrhythmic effect is not obtained with prazosin. In contrast, prazosin in low concentration is effective in cat blood-perfused preparations (Sheridan *et al.*, 1980). To reconcile such differences it is suggested that regional ischaemia exceeding 10 min is required for the α-mediated effect to occur. The present results also show that the effect of α-adrenoceptor blocking drugs on ventricular arrhythmias does not depend upon direct myocardial depression, because the beneficial effect was independent of haemodynamic alterations. α-Adrenoceptor blocking drugs mediate electrophysiological or metabolic changes which are not likely to be the result of α-adrenoceptor blockade but are more probably the result of a direct effect on the myocardial cell membrane.

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