Ventricular fibrillation is reduced in hypothyroid rats with enhanced myocardial α -adrenoceptor responsiveness

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1 The severity of ventricular arrhythmias induced by coronary artery occlusion and reperfusion has been examined in control rats and animals made hypothyroid by pretreatment with 6-propylthiouracil (PTU). The maximal driving frequency and sensitivity of isolated left atria and papillary muscles to isoprenaline and to phenylephrine in the presence of propranolol, were also examined in tissues from control and hypothyroid animals.

2 Pretreatment with PTU resulted in a potentiation of responses to the α -adrenoceptor agonist phenylephrine in both left atria and papillary muscles, while responses to isoprenaline were depressed in left atria but unaltered in papillary muscles from hypothyroid animals.

3 In rats subject to coronary artery occlusion, PTU pretreatment reduced the incidence of ventricular fibrillation during acute myocardial ischaemia and abolished reperfusion-induced ventricular fibrillation. Mortality during myocardial ischaemia and reperfusion was also abolished. Diastolic blood pressure was similar in hypothyroid and control animals, but there was a small reduction in systolic blood pressure and a marked decrease in heart rate in PTU pretreated animals.

4 These results demonstrate that PTU-induced hypothyroidism represents a condition where cardiac α -adrenoceptor-mediated responses are enhanced but the severity of ischaemia- and reperfusion-induced arrhythmias is reduced.

Introduction

It has been suggested that the activation of α -adrenoceptors in the myocardium is a primary mediator of the ventricular arrhythmias which occur during myocardial ischaemia and reperfusion (Sheridan *et al.*, 1980). This hypothesis is based on the fact that in the anaesthetized cat, the α -adrenoceptor antagonists phentolamine and prazosin, were effective in preventing ventricular arrhythmias during myocardial ischaemia and reperfusion (Sheridan *et al.*, 1980).

In recent years the contribution of α -adrenoceptor stimulation to the genesis of ventricular arrhythmias has received much attention, but the evidence obtained is conflicting. Although α -adrenoceptor antagonists have been shown to prevent reperfusion-induced ventricular arrhythmias in the cat (Sheridan *et al.*, 1980), dog (Benfey *et al.*, 1984) guinea-pig (Sheridan & Culling, 1985) and rat (Williams *et al.*, 1987), it has been suggested that the antiarrhythmic

properties of these compounds are due to additional membrane stabilizing effects (Dukes & Vaughan Williams, 1984; Bralet *et al.*, 1985; Daugherty *et al.*, 1986). The precise role of α -adrenoceptor stimulation in myocardial ischaemia and reperfusion is therefore unclear, particularly since α -adrenoceptor agonists have been shown to prolong the effective refractory period and promote spontaneous defibrillation in the rat (Sharma *et al.*, 1983).

Recently, this laboratory (Chess-Williams & Critchley, 1987a) and others (Ishac *et al.*, 1983) have demonstrated a potentiation of cardiac α -adrenoceptor-mediated responses in rats made hypothyroid with 6-propylthiouracil. The question that arises, is whether the increase in α -adrenoceptor responsiveness in these animals is associated with an increase in the incidence of ventricular arrhythmias during myocardial ischaemia and reperfusion. In the present study, this possibility has been investigated by examining the effects of 6-propylthiouracil treatment on cardiac α - and β -adrenoceptor-mediated

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responses and on the incidence and severity of ischaemia- and reperfusion-induced arrhythmias in anaesthetized rats.

Methods

Experiments were performed on male Wistar rats which had been bred in the departmental animal unit. Rats were housed in groups of 6 to 10, in a room maintained at 20°C on a 12 h light/dark cycle. Food (Labsure CRM diet) and water were available *ad libitum*. The treatment group of rats received 6-propylthiouracil (PTU) at a concentration of 0.4 mg ml⁻¹ in drinking water. After 8 to 10 weeks of PTU treatment rats were then subject to either *in vitro* or *in vivo* experiments along with age-matched controls.

In vitro experiments

Animals were killed by a blow to the head and exsanguinated. Left atria and left ventricular papillary muscles were rapidly removed and set up in a Krebs-bicarbonate solution (composition in mM: NaCl 118.4, KCl 4.7, NaHCO₃ 25.0, glucose 11.7, MgSO₄ 1.2, KH₂PO₄ 1.2, CaCl₂ 1.9) gassed with 5% CO₂ in O₂ at 37°C. Tissues were suspended under 0.8 g tension and paced at 1 Hz by square-wave pulses (5 ms duration; twice threshold voltage) delivered, via bipolar electrodes, from Grass S48 stimulators. Isometric developed tension was recorded via Lectromed UFI (57 g sensitivity range) force transducers, on a Lectromed MX2 polygraph.

Tissues were equilibrated for 30 min with several changes of bathing medium. In each tissue, maximal driving frequency (MDF) was determined at twice threshold voltage, by gradually increasing the pacing frequency until the tissue was unable to respond to each stimulus. After washing, a cumulative concentration-response curve to isoprenaline was obtained, followed after washout, by one to phenylephrine. Metanephrine (10 µM) and desipramine (1 µM) were added to the tissue bath 15 min before obtaining agonist responses; propranolol (1 µM) was added before constructing concentration-response curves to phenylephrine.

In vivo experiments

Rats were anaesthetized with sodium pentobarbitone 60 mg kg⁻¹ i.p. and prepared for coronary artery occlusion as described previously (Coker & Ellis, 1987). Arterial blood pressure was measured from the left carotid artery and recorded along with a Lead I ECG. After performing a left thoracotomy the rats were ventilated with room air at a rate of 54 strokes min⁻¹, a stroke volume of 1.0 to 1.5 ml

100 g⁻¹, and a positive end expiratory pressure of 0.5 to 1.0 cmH₂O. An incision was made in the pericardium and the heart was exteriorised briefly while a fine silk ligature was placed around the left coronary artery close to its origin. If arrhythmias occurred within 10 min of this procedure the experiment was terminated. After the stabilization period the coronary artery was occluded and the arrhythmias that occurred during the first 25 min of myocardial ischaemia were quantified in accordance with the Lambeth Conventions (Walker *et al.*, 1988). In survivors, the total number of ventricular premature beats (VPBs) was counted and divided into those occurring as singles, bigeminy or salvos and those occurring as ventricular tachycardia (VT, defined as 4 or more consecutive VPBs). The incidence and duration of VT, and ventricular fibrillation (VF) were also recorded along with the mortality.

Separate groups of rats were used to study reperfusion-induced arrhythmias. For these experiments both ends of the ligature were threaded through a small polythene button which was placed in contact with the heart. Coronary artery occlusion was achieved by applying tension and clamping the ligature against the button with a small pair of rubber-sheathed Dieffenbach forceps. After 5 min of myocardial ischaemia the forceps were removed, thus releasing the tension and allowing reperfusion. The incidence of VT, VF and mortality was noted.

Prior to coronary artery occlusion an arterial blood sample (0.1 ml) was taken and PO₂, PCO₂ and pH were measured with a Corning 158 blood gas/pH analyser. If necessary, the stroke volume of the ventilation pump was adjusted to maintain PCO₂ within appropriate limits. The anaesthetized rats were maintained at a temperature of 37 to 38°C by means of a heated table.

Drugs

All drugs for *in vitro* experiments were obtained commercially from Sigma, and were made up fresh in Krebs-bicarbonate solution. All reagents were of Analar grade. PTU was also obtained from Sigma.

Statistical analysis

Increases in developed tension to isoprenaline and phenylephrine were plotted as a percentage of the maximum increase for each drug. Individual EC₅₀ values were determined and geometric mean EC₅₀ values with 95% confidence limits calculated. Student's unpaired *t* test was performed on logarithmic EC₅₀ values to test for differences between control and PTU-pretreated rats. To compare maximum responses to phenylephrine in tissues from control and PTU-treated rats, the increases in devel-

oped tension to phenylephrine were plotted as a percentage of the maximum increase in developed tension induced by isoprenaline. This reduces the variability observed when responses are plotted simply as developed tension. Student's unpaired *t* test was then applied for a statistical analysis of the maximum phenylephrine responses in control and treated tissues. Differences in haemodynamics during *in vivo* experiments were also compared with an unpaired *t* test but a Mann-Whitney U test was used to compare ischaemia-induced VPBs since these data may not be distributed normally. A probability of $P < 0.05$ was considered to be significant. The incidence of events was compared with Fisher's exact test.

Results

In vitro experiments

Left atria: The resting tension of 0.58 ± 0.05 g developed by left atria from control animals was not significantly different from the 0.46 ± 0.14 g developed by atria from hypothyroid animals. However, the maximum driving frequency (MDF) for atria from PTU-pretreated rats (11.7 ± 0.7 Hz) was significantly lower ($P < 0.05$) than that obtained for control tissues (15.3 ± 0.9 Hz). The responses of these tissues to isoprenaline were also depressed with the EC_{50} values being significantly greater than in control tissues. The maximum developed tension to isoprenaline, however, was similar in control and hypothyroid animals (Table 1). In contrast, responses to phenylephrine obtained in the presence of propranolol, were enhanced in left atria from hypothyroid animals. Phenylephrine EC_{50} values were reduced in these animals and the maximum responses to phenylephrine relative to isoprenaline were significantly greater than in control tissues (Figure 1a; Table 1).

Figure 1 Mean ($n \geq 4$) concentration-response curves to isoprenaline (▽, ▼) and phenylephrine (△, ▲; in the presence of $1 \mu\text{M}$ propranolol) in (a) left atria and (b) papillary muscles from control (open symbols) and propylthiouracil (PTU)-pretreated (solid symbols) animals. Increases in developed tension are plotted as a percentage of the isoprenaline maximum.

Papillary muscles: As with left atria, the resting tensions developed by isolated papillary muscles were similar for control (0.63 ± 0.14 g) and treated tissues (0.53 ± 0.16 g). PTU-pretreatment reduced the maximum driving frequency of papillary muscles from 13.2 ± 0.7 Hz to 10.7 ± 0.5 Hz ($P < 0.05$). Responses of these tissues to phenylephrine were also enhanced, the EC_{50} values being reduced and the maximum response relative to isoprenaline being increased in papillary muscles from hypothyroid animals (Figure 1b; Table 1). However, in contrast

Table 1 Geometric mean EC_{50} values ($n \geq 4$) and maximum responses to isoprenaline and phenylephrine in isolated cardiac tissues from control and hypothyroid animals

	Control		Hypothyroid	
	Left atria	Papillary muscle	Left atria	Papillary muscle
Isoprenaline				
EC_{50} (nM)	1.9 (0.9–4.0)	43.9 (20.2–95.5)	51.0 (16.8–155.3)**	36.0 (5.7–228.7)
MDT (g)	1.00 ± 0.12	1.12 ± 0.25	0.76 ± 0.19	0.84 ± 0.14
Phenylephrine				
EC_{50} (μM)	12.6 (7.0–22.5)	21.6 (9.9–47.3)	6.4 (3.6–11.2)	3.5 (1.3–9.5)*
MDT (g)	0.57 ± 0.06	0.61 ± 0.07	0.67 ± 0.08	0.72 ± 0.16
MISO (%)	38.0 ± 7.3	27.0 ± 4.6	$82.2 \pm 8.1^{**}$	$70.9 \pm 9.6^{**}$

Maximum responses are expressed as the maximum developed tension (MDT) or the maximum increase in developed tension to phenylephrine as a percentage of the maximum increase in developed tension to isoprenaline (MISO).

* $P < 0.01$; ** $P < 0.001$ compared with corresponding control, unpaired *t* test.

to that seen in left atria, papillary muscle responses to isoprenaline were not altered by PTU-pretreatment. Neither the EC_{50} nor the maximum tension developed to isoprenaline were significantly different in hypothyroid animals compared with controls (Figure 1b; Table 1).

In vivo experiments

Pretreatment of rats with PTU for 8 to 10 weeks reduced their weight gain. The weight of the control rats was 290 ± 9 g whereas the PTU-treated rats weighed 244 ± 9 g ($P < 0.05$). After anaesthesia and preparation for coronary artery occlusion, differences in heart rate and arterial blood pressure were observed between the two groups. Heart rate was 436 ± 12 beats min^{-1} in the controls ($n = 18$) compared with 256 ± 6 beats min^{-1} in the PTU group ($n = 20$), $P < 0.001$. Systolic but not diastolic blood pressure was also significantly ($P < 0.05$) reduced in the PTU-treated rats; $107 \pm 4/86 \pm 3$ mmHg compared with $126 \pm 6/91 \pm 6$ mmHg in controls. Arterial blood gas values before coronary artery occlusion were similar in both groups. The overall values were PO_2 87 ± 5 mmHg; P_{CO_2} 30 ± 1 mmHg; pH 7.38 ± 0.02 .

The severity of arrhythmias induced by acute myocardial ischaemia was reduced in the rats which had been pretreated with PTU. Although the incidence of VT was similar, the incidence of VF was reduced (but did not reach statistical significance at the commonly accepted 5% level) and none of the PTU-treated rats died as a result of sustained VF in contrast to the 50% mortality in the control group (Figure 2). The total number of VPBs that occurred in survivors tended to be greater in the PTU-treated rats but this was not statistically significant,

Figure 2 Incidence of ventricular tachycardia (VT), ventricular fibrillation (VF) and mortality during the first 25 min of myocardial ischaemia in control rats ($n = 10$, hatched columns) and propylthiouracil (PTU)-treated rats ($n = 11$; solid columns). VF, $P = 0.11$; Mortality, $P = 0.025$; Fisher's exact test.

Figure 3 Incidence of ventricular tachycardia (VT), ventricular fibrillation (VF) and mortality induced by reperfusion after 5 min of myocardial ischaemia in control rats ($n = 8$, hatched columns) and propylthiouracil (PTU)-treated rats ($n = 9$, solid columns). VF, $P = 0.005$; Mortality, $P = 0.059$; Fisher's exact test.

Table 2 The number of ventricular premature beats that occurred in rats which survived 25 min of permanent myocardial ischaemia

	n	Ventricular premature beats		
		Total	as VT	Others
Control	5	746 $\pm$ 283	560 $\pm$ 245	186 $\pm$ 65
Propylthiouracil	11	1521 $\pm$ 407	862 $\pm$ 377	659 $\pm$ 76*

* $P < 0.05$ compared with control, Mann-Whitney U-test.

although it should be noted that comparison had to be made between $n = 5$ in one group and $n = 11$ in the other because of the higher mortality in the controls. When these VPBs were divided into those occurring as VT and those occurring as singles, bigeminy or salvos (others) it can be seen that there was a significant increase in the less severe 'other' VPBs in the hypothyroid rats (Table 2).

The antiarrhythmic effect of PTU-induced hypothyroidism was more marked in the rats subject to reperfusion after 5 min of ischaemia. Although the reduction in the incidence of VT was not significant, none of the PTU-treated rats fibrillated. In contrast, the majority of the control rats succumbed to VF following reperfusion and in 50% of the group this was fatal (Figure 3).

Discussion

Propylthiouracil has been used widely to induce a hypothyroid state in experimental animals (Ciaraldi & Marinetti, 1977; Ishac *et al.*, 1983). In the present study PTU was administered in the drinking water

and we have shown previously that this method of administration results in changes in left atrial responsiveness identical to those found after thyroidectomy (Kunos, 1977; Chess-Williams & Critchley, 1987b). The marked fall in resting heart rate in the anaesthetized animals was also indicative of a hypothyroid state.

In rats subject to coronary artery occlusion, pretreatment with PTU resulted in a reduction in the incidence of ventricular fibrillation and mortality during ischaemia and reperfusion. This protective effect, occurred despite pretreatment being accompanied by an enhancement of cardiac α -adrenoceptor responsiveness. A similar increase in responsiveness to α -adrenoceptor agonists has been found in the ischaemic cat heart (Sheridan *et al.*, 1980) and since α -adrenoceptor antagonists exerted an anti-arrhythmic effect in this species, it was proposed that α -adrenoceptor activation may contribute to the genesis of ventricular arrhythmias during ischaemia and reperfusion (Sheridan *et al.*, 1980). A protective effect of α -adrenoceptor blockade against reperfusion-induced arrhythmias has also been reported in the guinea-pig (Sheridan & Culling, 1985) and rat (Williams *et al.*, 1987). These previous studies suggest, therefore, that arrhythmogenesis may be expected to be greater in conditions where α -adrenoceptor responses are enhanced.

Since the cardiac adrenergic changes which occur in hypothyroid animals resemble those which occur during ischaemia, the present study examined the severity of ischaemia- and reperfusion-induced arrhythmias in hypothyroid rats. Not only are cardiac α -mediated responses enhanced in both conditions but the mechanism responsible appears to be similar with an increase in α -adrenoceptor number during ischaemia (Corr *et al.*, 1981; Allely & Brown, 1988) and hypothyroidism (Ciaraldi & Martinetti, 1977; Fox *et al.*, 1985). Of more physiological relevance is the finding that cardiac responses to noradrenaline may be similarly affected in the two disease states. Responses to noradrenaline or sympathetic nerve stimulation are mediated via β -adrenoceptors in the normal heart but during ischaemia (Sheridan *et al.*, 1980) and in hypothyroidism (Chess-Williams & Critchley, 1987b), α -adrenoceptors may be involved in the cardiac response. Thus the changes in the adrenergic system which occur in hypothyroidism resemble those which occur in myocardial ischaemia.

If α -adrenoceptor stimulation is involved in the genesis of ventricular arrhythmias, an increase in the severity of arrhythmias might therefore be predicted in hypothyroid animals. However, the opposite was found, with the incidence of ventricular fibrillation and mortality during ischaemia and reperfusion being reduced. This contrasts with the results of Wil-

liams *et al.* (1987) where no significant protective effect of PTU pretreatment could be demonstrated in rats subject to reperfusion-induced arrhythmias. However the method of PTU administration was different in the two studies. Williams *et al.* (1987) administered the drug as a single daily injection for 1 week which, considering its short half life (4 h) in the rat (Sitar & Thornhill 1972), may have failed to induce a hypothyroid state. This would explain the lack of a significant fall in heart rate found by these authors. In the present study, PTU was administered in the drinking water to ensure a constant dose of drug throughout the pretreatment period and resulted in a highly significant bradycardia in the treated animals. This fall in heart rate may have influenced the severity of arrhythmias seen in hypothyroid animals since it has been reported that heart rate correlates positively with the occurrence of ventricular tachycardia and fibrillation during ischaemia (Bolli *et al.*, 1986) and also the severity of arrhythmias induced by reperfusion (Coker & Parratt, 1985). Alternatively, the increase in α -adrenoceptor responsiveness itself may have exerted a protective effect, since α -adrenoceptor agonists have been shown to prolong the effective refractory period (Sharma *et al.*, 1983; Dukes & Vaughan Williams, 1984) and reduce ventricular automaticity (Rosen *et al.*, 1984), effects which would be expected to be anti-arrhythmic. Indeed, Sharma *et al.* (1983) have found that α -adrenoceptor stimulation can promote spontaneous defibrillation in the rat and Williams *et al.* (1987) have shown that noradrenaline infusion can reduce reperfusion-induced ventricular fibrillation. These results appear to conflict with the reported protective role for α -adrenoceptor antagonists during ischaemia and reperfusion. However, in the rabbit (Dukes & Vaughan Williams, 1984) and the rat (Daugherty *et al.*, 1986; Bralet *et al.*, 1985) the protective effects of α -adrenoceptor blockers have been explained by the additional membrane stabilizing properties these compounds possess and may not be related to α_1 -adrenoceptor antagonism. This conclusion is further supported by the demonstration that ischaemic conditions may enhance the local anaesthetic properties of these drugs (Vaughan Williams, 1978).

When considering the present results, it is important to note that the maximum frequency at which isolated left atria and papillary muscles could be paced was reduced in tissues from hypothyroid animals. This indicates a prolongation of the effective refractory period in the hypothyroid heart and agrees with the reported prolongation of the repolarization phase of the action potential in atria from hypothyroid rabbits (Freedberg *et al.*, 1970). Such an increase in effective refractory period would tend to reduce the severity of ventricular arrhythmias. It is

possible that the combined effects of reduced heart rate and increased effective refractory period may have overcome any proarrhythmic effect exerted by the elevated α -adrenoceptor responsiveness. Thus the role of cardiac α -adrenoceptors in the genesis of

malignant arrhythmias remains uncertain, although we have been able to demonstrate a situation where α -adrenoceptor responsiveness is increased and the severity of ischaemia- and reperfusion-induced arrhythmias is reduced.

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