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# Reduction by β-adrenoceptor blockade of hypoxia-induced right heart hypertrophy in the rat

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1 The study was undertaken to assess the role of β-adrenoceptors in the induction of compensatory cardiac hypertrophy in an *in vivo* model.

2 In the rat, exposure to severe hypoxia (6% inspired oxygen for 8 h day) caused a 51% increase in right heart weight and a 75% increase in haematocrit.

3 The hypoxia-induced right ventricular hypertrophic response was reduced by 65% by oral treatment with a high dose of the non-selective β-adrenoceptor antagonist, propranolol (80 mg $kg^{-1}$ body weight); the drug treatment caused only a minor reduction (6%) in secondary polycythaemia.

4 With a less severe degree of hypoxia (7% inspired oxygen) there was only minimal secondary polycythaemia (+15%), and a lesser degree of compensatory right ventricular hypertrophy in untreated rats (+33%).

5 Treatment with the $\beta_1$-adrenoceptor antagonist, atenolol, in a dose of 80 mg $kg^{-1}$ body weight abolished right ventricular hypertrophy in response to 7% inspired oxygen, without affecting haematocrit and caused a small reduction in the ratio of heart weight to body weight in normoxic rats.

6 The results show that the effect of propranolol on hypoxic right ventricular hypertrophy is not secondary to any effect on secondary polycythaemia as has previously been suggested and that a marked reduction of compensatory cardiac hypertrophy can be obtained by a $\beta_1$-selective adrenoceptor antagonist. Thus these findings support the view that noradrenaline released from cardiac sympathetic nerve terminals exerts a trophic effect on myocardial cells and demonstrates that *in vivo*, this trophic effect can be reduced by $\beta_1$-adrenoceptor blockade.

**Keywords:** Hypoxia; cardiac hypertrophy; noradrenaline; propranolol; atenolol; right ventricular hypertrophy; β-adrenoceptors; β-adrenoceptor antagonists

## Introduction

There is evidence that noradrenaline released from cardiac sympathetic nerve terminals acts on myocardial β-adrenoceptors to induce cardiac growth in many of the experimental models used to study compensatory cardiac hypertrophy (Östman-Smith, 1979; 1981; Yamori *et al.*, 1980; Zierhut & Zimmer, 1989). It has been suggested that right ventricular hypertrophy occurring in response to hypoxia may be an exception (Dennis & Vaughan-Williams, 1982; Vaughan-Williams & Dukes, 1983). However, parenteral non-selective β-adrenoceptor blockade has been shown to reduce right ventricular hypertrophy in response to simulated high altitude, although it has been suggested that at least part of the reduction in right ventricular hypertrophy could be due to a reduction in the degree of polycythaemia by a $\beta_2$-adrenoceptor blocking action (Ostadal *et al.*, 1978; Voekel *et al.*, 1980). There has been debate whether catecholamines exert trophic actions on myocardium through $\alpha_1$-, or $\beta_2$-adrenoceptors (Simpson & McGrath, 1983; Simpson, 1985; Larson *et al.*, 1985), but recent *in vitro* work has largely focussed on the role of $\alpha_1$-adrenoceptors in the induction of protein synthesis (Morgan & Baker, 1991; van Bilsen & Chien, 1993; Fedida *et al.*, 1993). However, several *in vivo* studies show $\alpha_1$-adrenoceptor blockade to be ineffective, or only partially effective, in preventing compensatory cardiac hypertrophy (Zierhut & Zimmer, 1989; Nishimura *et al.*, 1993). The present study was undertaken to study the effect of oral high dose $\beta_1$-selective and non-selective β-adrenoceptor blockade on right ventricular hypertrophy, occurring in response to normobaric hypoxia.

## Methods

Since female rats, in contrast to male rats, cease longitudinal growth after sexual maturity is reached, mature female DA rats (an inbred, small-sized, agouti-pigmented rat strain supplied by the Biomedical Services breeding unit at the John Radcliffe Hospital) were used to minimize the influence of age-related growth. The animals, weighing around 200 g, were exposed to hypoxia in a 90 × 90 × 90 cm box with varying degrees of hypoxia created by a constant flow of nitrogen mixed with compressed room air. Carbon dioxide was removed by soda lime trays and overheating was prevented by cool water circulating through a copper coil heat exchanger. Oxygen concentration within the box was monitored with an oximeter. In pilot studies with continuous ECG monitoring, it was established that an inspired oxygen of 5% was associated with cardiac arrhythmias and bradycardia. Therefore it was decided to use the lowest oxygen concentration not associated with arrhythmias, namely 6%, for the first study. In an effort to reduce the stimulus for polycythaemia the sessions of hypoxia were restricted to 8 hours/day. The rats had 5 hypoxia sessions/week and in both studies a total of 18 sessions of hypoxia were given.

When the second study was started the object of the experiment was not a direct comparison of the efficacy of propranolol and atenolol as the dose had not been matched for degree of $\beta_1$-adrenoceptor blockade. This is because propranolol and atenolol doses were dictated by diet mixes available from ICI. Pilot studies with 24 h ECG monitoring showed that none of the available diet concentrations of propranolol and atenolol were equipotent in *in vivo* reductions of heart rate. The atenolol diet with maximal $\beta_1$-adrenoceptor blocking effect was chosen, and it was also decided to use a slightly less severe degree of hypoxia in the study using atenolol, namely 7% inspired oxygen. This was because the degree of hypoxia in the first study produced significant weight loss in one hypoxic group and also severe polycythaemia; it was hoped to limit these effects by reducing the severity of hypoxia slightly.

In the first study, rats were divided in four groups, normoxic rats on control diet, normoxic rats on propranolol diet, hypoxic rats on control diet and hypoxic rats on propranolol diet.

In the second study similarly there were normoxic and hypoxic controls, and normoxic and hypoxic atenolol-treated rats. Propranolol was mixed in the diet at a 0.1% concentration, corresponding to a daily intake of approximately 80 mg $kg^{-1}$ body weight. Atenolol was also given in a 0.1% concentration in the diet giving a dose of approximately 80 mg $kg^{-1}$ body weight. The drug-containing diets were started one week before exposure to hypoxia was begun, and all control groups were at the same time changed from the standard animal house diet to the control diet used by ICI as a vehicle for the drug. Pilot experiments with 24 h ECG recording were carried out during normoxia, using subcutaneous ECG electrodes inserted under a brief ether anaesthesia. The ECG of unrestrained rats moving freely in a specially designed cage was recorded on a Medilog 1 tape recorder (Oxford Instruments), and computer analysis of the hourly mean, minimum and maximum heart rates recorded established that the β-adrenoceptor blocking effects of both propranolol and atenolol were present throughout the 24 h period. The analysis showed that treatment with either propranolol or atenolol significantly reduced mean heart rate during sleep by about 10% (controls: 325±5; propranolol 296±7, $P<0.02$; atenolol 296±9, $P<0.04$). During periods of activity mean and maximal heart rates were reduced by 18% and 21% respectively by atenolol, and by 12% for both these measurements by propranolol treatment (controls: mean heart rate 381±19, max heart rate 456±16; propranolol: mean heart rate 336±3, $P<0.04$, max heart rate 400±5, $P<0.02$; atenolol: mean heart rate 312±2, $P<0.03$, max 360±1, $P<0.004$).

Rats were killed by cervical dislocation, weighed and chest and abdomen opened and blood from the descending aorta sampled for haematocrit measurements. The hearts were excised and dissected into free wall right ventricle, interventricular septum and free wall left ventricle and these portions were weighed separately. The atrial weight was included in total heart weight. In the first study the right ventricle, and the rest of the heart, were dried to constant weight at 80°C after the wet weight had been established, for estimation of % dry matter.

Drugs used were propranolol 80 mg $kg^{-1}$, atenolol 80 mg $kg^{-1}$. Both drug-containing rat diets were kindly supplied by ICI.

Statistical comparisons were made by paired and unpaired *t* tests and two-way analysis of variance for unbalanced designs.

## Results

### *Propranolol study*

The findings in the study using hypoxia with 6% oxygen are summarized in the Table 1. Paired *t* test showed a highly significant weight loss in the propranolol-treated group subjected to hypoxia ($P<0.001$) compared with pre-hypoxia exposure weight; there was also a suggested trend towards weight loss in the hypoxic group on control diet but this did not reach statistical significance. Furthermore a marked degree of polycythaemia was seen in the hypoxic groups, with a 75% increase in haematocrit in the rats on control diet; however, there was no statistically significant difference in *t* test between the degree of polycythaemia in rats on control or propranolol diet. Two-way analysis of variance (Two-way ANOVA) show that propranolol on its own does not affect haematocrit ($P=0.85$), but suggests that it probably does interact with the polycythaemic response to hypoxia ($P=0.028$).

In the rats on control diet there was marked right ventricular hypertrophy in the hypoxic group, with a 51% increase in right ventricular weight, and a 59% increase in right ventricular/body weight ratio (RV ratio), both highly significant ($P<0.001$). The propranolol-treated rats showed a much reduced hypertrophic response to hypoxia with increase in right ventricular weight of only 18% and increase of 33% in RV ratio; both these values are significantly smaller than those seen in control rats ($P<0.001$ for both). Two-way ANOVA shows that the propranolol treatment significantly interacts with the effect of hypoxia on both right ventricular weight ($P=0.0007$), and RV ratio ($P=0.0095$). There was no left ventricular hypertrophy in either hypoxic group, and propranolol treatment on its own produced no changes in body weight or heart weight in the normoxic non-growing rats. The hypertrophied right ventricles showed no difference in dry matter content between hypoxic or normoxic groups, or after propranolol treatment.

### *Atenolol study*

The findings in the study using hypoxia with 7% oxygen are summarized in Table 2. The lesser degree of hypoxia used did not induce any significant weight loss, and caused only a slight degree of polycythaemia (+15% in rats on control diet). This increase was not significant on intergroup *t* test. However, two-way ANOVA suggests that the small increase in haematocrit seen in both hypoxia-exposed groups taken together was significant ($P=0.0001$). Atenolol did not influence the haematocrit, or the effect of hypoxia on haematocrit significantly ($P=0.17$ for both). The hypoxia employed still caused a substantial degree of right ventricular hypertrophy in rats on control diet with a 33% increase in right ventricular weight, and a 36% increase in RV ratio, both significant at $P<0.001$ level. Atenolol treatment did not alter body weight in normoxic rats, but it did cause a small reduction in heart weight, significant only when expressed as heart ratio ($P<0.001$). This

**Table 1** Effect of propranolol on hypoxic right ventricular hypertrophy

| | *Normoxic controls* ($n=10$) | *Normoxic propranolol treatment* ($n=11$) | *Hypoxic controls* ($n=10$) | *Hypoxic propranolol treatment* ($n=11$) |
|---|---|---|---|---|
| Body weight (g) | 200±22 | 191±22 | 192±26 | 169±13 |
| Haematocrit (%) | 40±3 | 43±4 | 70±3*** | 66±5*** |
| RV weight (mg) | 90±13 | 84±8 | 136±19*** | 99±13[a]* |
| LV weight (mg) | 249±41 | 258±36 | 258±30 | 229±29 |
| Heart weight (mg) | 517±67 | 505±61 | 569±8 | 488±47[b] |
| RV ratio (g 100 $g^{-1}$ body wt.) | 0.045±0.004 | 0.044±0.003 | 0.072±0.011*** | 0.059±0.008[b]* |
| Heart ratio (g 100 $g^{-1}$ body wt.) | 0.259±0.010 | 0.264±0.010 | 0.298±0.015 | 0.288±0.015 |
| RV % dry weight | 23±2 | 24±2 | 22±2 | 21±2 |
| % dry weight (heart) | 24±1 | 24±1 | 23±1 | 22±1 |

Values are mean±s.d. RV, right ventricle; LV, left ventricle.
* Denotes different from normoxic groups on same diet $P<0.05$.
*** Denotes different from normoxic group on same diet $P<0.001$.
[a] Denotes different from hypoxic controls $P<0.001$.
[b] Denotes different from hypoxic controls $P<0.01$.

**Table 2** Effect of atenolol on hypoxic right ventricular hypertrophy

| | *Normoxic controls* ($n=12$) | *Normoxic atenolol* ($n=12$) | *Hypoxic controls* ($n=12$) | *Hypoxic atenolol* ($n=12$) |
|---|---|---|---|---|
| Body weight (g) | 185±7 | 186±10 | 183±9 | 179±11 |
| Haematocrit (%) | 40±3 | 40±2 | 46±4 | 43±5 |
| RV weight (mg) | 78±11 | 76±19 | 104±15*** | 67±20[a] |
| LV weight (mg) | 264±20 | 245±35 | 257±34 | 267±20 |
| Heart weight (mg) | 484±31 | 443±45 | 509±51 | 422±75 |
| RV ratio (g 100 $g^{-1}$ body wt.) | 0.042±0.005 | 0.041±0.009 | 0.057±0.010*** | 0.037±0.010[a] |
| LV ratio (g 100 $g^{-1}$ body wt.) | 0.143±0.009 | 0.132±0.015 | 0.146±0.016 | 0.149±0.020 |
| Heart ratio (g 100 $g^{-1}$ body wt.) | 0.263±0.013 | 0.239±0.016*** | 0.280±0.032 | 0.235±0.036[b;c] |

Values are mean±s.d. RV, right ventricle; LV, left ventricle.
*** Denotes different from normoxic control group $P<0.001$.
[a] Denotes different from hypoxic control group $P<0.001$.
[b] Denotes different from hypoxic controls $P<0.01$.
[c] Denotes different from normoxic controls $P<0.05$.

effect is confirmed by two-way ANOVA ($P<0.0001$), as is the absence of any interaction with the effect of hypoxia. Furthermore atenolol completely abolished compensatory right ventricular hypertrophy in response to this degree of hypoxic stress: there was no increase in right ventricular weight or RV ratio when compared to normoxic rats on either control or atenolol diet. Two-way ANOVA confirms that atenolol significantly interacts with the effect of hypoxia on both right ventricular weight ($P=0.0005$) and RV ratio ($P=0.0006$).

## Discussion

### *General observations*

The second study using the less severe degree of intermittent hypoxia proved that it is possible to devise regimes of hypoxia exposure that produce only minimal increases in haematocrit, and thereby the aetiological chain inducing right ventricular hypertrophy can be studied without confusion resulting from therapeutic interventions having large effects on the degree of polycythaemia produced as in some previous studies of hypobaric hypoxia (Ostadal *et al.*, 1978; Voelkel *et al.*, 1980).

### *Right ventricular hypertrophy*

Ostadal *et al.* (1978) attributed at least some, and Voelker *et al.* (1980) all, of the attenuation of hypoxia-induced right ventricular hypertrophy caused by non-selective β-adrenoceptor blocking drugs to inhibition of haematopoiesis by $\beta_2$-adrenoceptor blockade. This has been disproved by the present findings, as in the study with severe hypoxia and polycythaemia, propranolol caused a large reduction in right ventricular hypertrophy with only a minor reduction in polycythaemia. Furthermore, in the second study with milder hypoxia and very minimal polycythaemia, significant right ventricular hypertrophy was still seen in the control group but was totally abolished by the $\beta_1$-adrenoceptor antagonist, atenolol. In the rat, atenolol is 45 times more potent as a $\beta_1$-antagonist than a $\beta_2$-antagonist when given intravenously in a dose of 1 mmol $kg^{-1}$ (Piercy, 1988). Although atenolol is not totally devoid of $\beta_2$-adrenoceptor blocking properties in high doses, it remains at least ten times more potent as a $\beta_1$- than as a $\beta_2$-adrenoceptor antagonist after chronic oral treatment in the rat in dose ranges of 50–80 mg $kg^{-1}$ (ICI, personal communication). The fact that propranolol did affect the degree of polycythaemia while atenolol did not ($\beta_2$-adrenoceptor effect), and at the same time atenolol had a proportionally greater effectiveness in reducing right ventricular hypertrophy, suggests that the latter response is mediated predominantly via $\beta_1$-adrenoceptors *in vivo*.

In the intact rat, propranolol does not influence the rise in right ventricular pressure caused by hypoxia (Zierhut & Zimmer, 1989). Interestingly, Voelkel *et al.* (1980) found that (+)-propranolol was as effective as (±)-propranolol in somewhat decreasing (but not abolishing) pressor responses to hypoxia in the perfused lung, but that it had no effect on the right ventricular hypertrophy occurring in response to hypoxia, and therefore concluded that the right ventricular hypertrophy was not directly related to the degree of pulmonary hypertension. (+)-Propranolol has only about one 50th of the β-adrenoceptor blocking activity of (−)-propranolol (Bowman & Rand, 1980), and this is a likely explanation for its failure to reduce right ventricular hypertrophy. It has been shown that exposure to hypoxia (6% inspired oxygen) causes an increase in overall cardiac sympathetic nervous activity, although the right and left ventricles were not studied separately (Goldman & Harrison, 1970). During hypoxia it is mainly right heart work that is increased because of hypoxia-induced pulmonary hypertension. The hypothesis that would account for all of the above reported findings is that the right heart stress caused by hypoxia causes increased release of noradrenaline from the sympathetic nerves innervating the right ventricle in order to increase its contractile performance. The noradrenaline released would then exert a trophic response on the myocardial cell as has been found in exercise-induced cardiac hypertrophy (Östman-Smith, 1976) and has been suggested to occur in many other experimental models as well (Östman-Smith, 1981). That sympathetic nerves do exert a trophic effect in right ventricular hypertrophy secondary to pulmonary hypertension is supported by the finding that Tucker *et al.* (1983) were able to reduce markedly right ventricular hypertrophy occurring in response to monocrotaline injection using chemical sympathectomy with 6-hydroxydopamine.

The concept of noradrenaline having trophic actions on the heart has been supported by findings in a biochemical model (Claycomb, 1976), and by the observation of trophic effects of noradrenaline and isoprenaline on neonatal rat myocyte cells in culture (Simpson *et al.*, 1982; Bishopric & Kedes, 1991). Simpson originally suggested that this trophic effect is mediated via $\alpha_1$-adrenoceptors, again based on tissue culture studies (Simpson & McGrath, 1983; Simpson, 1985); however, the effect was not clearcut, since methoxamine was only a slightly more potent agonist in their system than isoprenaline. Some subsequent tissue culture studies on cardiomyocytes have confirmed that in some *in vitro* systems $\alpha_1$-adrenoceptor agonists are more potent than β-adrenoceptor agonists in inducing hypertrophy (Simpson *et al.*, 1991; Schlüter & Piper, 1992). The discrepancy between *in vivo* work and tissue culture findings may partly stem from the immaturity of the neonatal myocyte used for tissue culture and from the hormonal environment of the myocyte; e.g. Simpson's group used a serum-free medium without thyroxine or steroids. β-Adrenoceptor numbers are increased, and α-adrenoceptor numbers probably decreased, by thyroxine treatment, and adrenalectomy causes a decrease in the ability of β-adrenoceptors to form a high-affinity state (Wikberg & Lefkowitz, 1984). Bishopric & Kedes (1991) found that in low density cultures, noradrenaline in-

duction of α-actin gene expression and hypertrophy was mediated via $\alpha_1$-adrenoceptors, whereas in high-density cultures with cell contact and myocardial bridging, the noradrenaline induction of the α-actin gene, and induction of hypertrophy and contractility, were all mediated via β-adrenoceptors. These observations underline the dangers of extrapolating *in vitro* studies on isolated cells to the *in vivo* situation where the cardiac myocyte is in a complex hormonal environment and subject to autonomic nerve stimulation. Certainly the fact that cardiac hypertrophy in response to isoprenaline is not reduced by prior chemical sympathectomy (Östman-Smith, 1979) excludes the suggestion that the hypertrophy seen after isoprenaline is due to α-adrenoceptor stimulation caused by a reflex-increase in cardiac sympathetic nervous activity as argued by Simpson & McGrath (1983). It has been suggested that circulating adrenaline could be the 'myocardial hypertrophy hormone' acting on $\beta_2$-adrenoceptors (Womble *et al.*, 1980; Larson *et al.*, 1985). Why a circulating hormone in some instances should cause right ventricular hypertrophy and in others left ventricular hypertrophy, has not been explained by proponents of this hypothesis. This suggestion is also incompatible with the finding that there was no exercise-induced cardiac hypertrophy in sympathectomized rats, in spite of the fact that their adrenal adrenaline excretion was higher than that seen in the rats with intact sympathetic nerves that did show compensatory cardiac hypertrophy (Östman-Smith, 1976). Furthermore, the finding in the current study that $\beta_1$-adrenoceptor blockade totally abolished the right ventricular hypertrophy induced by moderate hypoxia is not consistent with a general trophic role for adrenaline, and against the notion that the trophic effects of noradrenaline might be mediated via its weak $\beta_2$-adrenoceptor agonist properties.

The findings in this study are in contrast to those of Dennis & Vaughan-Williams (1982) who failed to reduce right ventricular hypertrophy in rabbits exposed to 22 h/day of normobaric hypoxia with propranolol and atenolol treatment. This discrepancy is likely to be dose-related, as these authors administered only 5 mg $kg^{-1}$ propranolol, and 3–6 mg $kg^{-1}$ atenolol 12 hourly, although previous results had suggested that the degree of adrenoceptor blockade with this propranolol dose was modest at peak effect, and had virtually gone after 7 h (Raine & Vaughan-Williams, 1980). Thus these rabbits clearly did not have a sufficient degree of β-adrenoceptor blockade to block the effect of intense sympathetic nerve activity.

Thus, there is now considerable agreement that non-selective β-adrenoceptor blockade reduces hypoxia-induced right ventricular hypertrophy (Moret & Duchosal, 1976; Ostadal *et al.*, 1978; Voelkel *et al.*, 1980) and the present study shows that this action is independent of any effect on blood viscosity due to polycythaemia.

The present study also provides evidence that a large dose of a selective $\beta_1$-adrenoceptor blocking drug can reduce right ventricular hypertrophy in response to hypoxia. As only a minute proportion of ventricular β-adrenoceptors are of the $\beta_2$-subclass (Wikberg & Lefkowitz, 1984) it would seem most likely that trophic actions of noradrenaline are mediated via $\beta_1$-adrenoceptors and this notion is supported by the effect of atenolol on right ventricular hypertrophy.

## Conclusions

Compensatory right ventricular hypertrophy induced by hypoxia can be markedly reduced by treatment with both a non-selective β-adrenoceptor antagonist, and a $\beta_1$-selective adrenoceptor antagonist, and the effect is unrelated to whether secondary polycythaemia is present or not. This study suggests that *in vivo* the trophic effects from increased sympathetic nervous activity on the heart are exerted predominantly via $\beta_1$-adrenoceptors.

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