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Reduction by oral propranolol treatment of left ventricular hypertrophy secondary to pressure-overload in the rat

I. Östman-Smith

Departments of Cardiovascular Medicine and Paediatrics, John Radcliffe Hospital, Headington, Oxford OX3 9DU

1 Studies on cardiac myocyte cell cultures have postulated a role for α_1-adrenoceptors and mechanical stretch in the induction of cellular changes thought to be important in compensatory cardiac hypertrophy. However, *in vivo* work suggests that β-adrenoceptors are important and the present study was designed to analyse the effect of propranolol on the cardiac hypertrophy caused by a pressure-overload in a way that takes account of the effects of propranolol on the work load itself.

2 The compensatory cardiac hypertrophy that develops in response to experimental coarctation of the aorta was studied in the rat. Pressure gradients and total cardiac work load (expressed as rate × pressure product) were assessed, and the relationship between increasing cardiac work load and the resulting left ventricular hypertrophy was established in a control group and compared with left ventricular hypertrophy in a group treated with a high dose of oral propranolol (80 mg kg^{-1} body weight).

3 In the rats with mean pressure gradients over the coarctation in the range of 15-31 mmHg, the animals on control diet showed a 38% increase in left ventricular weight/body weight ratio (LV ratio) and a 30% increase in heart weight/body weight ratio (heart ratio), whereas rats given high dose oral propranolol-treatment showed increases of only 13% and 9%, respectively.

4 In a second series of rats with a wider range of pressure gradients, the regression lines of LV ratio versus mean pressure gradient, and of LV ratio versus cardiac work, were different in the two groups with a slope that was only half as steep in the propranolol-treated rats as in the controls. Thus, for the same increment in cardiac work load, the degree of compensatory cardiac hypertrophy in propranolol-treated rats was half that observed in controls.

5 The reduction in compensatory cardiac hypertrophy was not associated with an increase in incidence of congestive heart failure and the propranolol-treated rats were able to sustain equally high (or higher) degrees of pressure over-load as controls did.

6 It is concluded that propranolol treatment approximately halves the compensatory cardiac hypertrophy occurring in response to a left ventricular pressure over-load by a mechanism indepenent of its effect on cardiac work load. This finding provides further support for the view that noradrenaline released from sympathetic nerve terminals in the heart exerts a trophic effect on cardiac myocytes, and that the sympathetic nervous system may be the final common pathway in many forms of compensatory cardiac hypertrophy. In contrast to *in vitro* models, this effect appears to be largely mediated via β-adrenoceptors in the intact animal

Keywords: Cardiac hypertrophy; noradrenaline; coarctation; hypertension; β-adrenoceptor antagonist; β-adrenoceptor; propranolol

Introduction

In pathological cardiac hypertrophy the myocardial muscle cell can hypertrophy to such an extent that myocardial performance deteriorates (Spann *et al.*, 1967; Cooper, 1987; Tsutsui *et al.*, 1993). Thus it would be of benefit to clinical medicine to devise a treatment that could reduce the development of cardiac hypertrophy in situations where the pressure overload itself cannot be relieved, as long as myocardial function is not compromised by the treatment. In rats, compensatory cardiac hypertrophy occurring in response to chronic exercise can be completely abolished by chemical sympathectomy (Östman-Smith, 1976), whereas hypertrophy occurring in response to isoprenaline treatment is unaffected by sympathectomy (Östman-Smith, 1979). These findings led to the hypothesis that noradrenaline released from cardiac sympathetic nerves, and acting on myocardial β-adrenoceptors, constitutes the final common pathway for the induction of cardiac cell growth in many physiological and pathological conditions leading to compensatory cardiac hypertrophy (reviewed by Östman-Smith, 1981). *In vitro* studies confirm that noradrenaline can induce cardiac myocyte growth (Simpson *et al.*, 1982; 1991; Bishopric & Kedes, 1991).

In some studies β-adrenoreceptor blocking drugs have been reported to reduce cardiac hypertrophy, e.g. in experimental renal hypertension (Fernandes *et al.*, 1976), in spontaneously hypertensive rats (Richer *et al.*, 1980; Lundin *et al.*, 1984), and in systemic hypertension in man (Sau *et al.*, 1982; Corea *et al.*, 1984; Vyssoulis *et al.*, 1992). However, these studies either did not accurately quantify the effect of the drug on the cardiac work load (Fernandes, 1976), or else it was clear that cardiac work load had been substantially reduced (Richer *et al.*, 1980; Sau *et al.*, 1982; Corea *et al.*, 1984; Lundin *et al.*, 1984; Vyssoulis *et al.*, 1992). Thus the question remains open whether the action of the drug was specifically on the hypertrophic process, or simply secondary to altered cardiac work load. This study was designed with the aim of determining whether β-adrenoceptor blockade could reduce compensatory cardiac hypertrophy in response to pressure overload, which is the strongest pathophysiological stimulus to adaptive hypertrophy of the myocyte, through an action that was independent of its effect on cardiac work load. To aid in this analysis a novel way of expressing degree of cardiac hypertrophy as a regression equation of increments in cardiac work versus the resulting proportional increase in cardiac hypertrophy was utilized.

Methods

Male Sprague-Dawley rats (180) were used, each initially weighing 170-190 g. One group received oral propranolol in the diet in a concentration of 0.1% w/w which, with the

measured dietary intake, corresponded to a dose of approximately 80 mg kg^{-1} body weight per day. The other group received a control diet which, apart from the propranolol, was identical (but different from their previous feed). After one week on the new diets the rats were operated on under chloral hydrate anaesthesia (0.8 ml 100 g^{-1} body weight of a 5% w/v solution i.p., dissolved in physiological saline). The abdominal aorta was constricted by use of a 2-0 silk ligature between the coeliac artery and the superior mesenteric artery and, by tying the ligature around metal probes, constrictions with diameters of 0.76 mm, 0.82 mm, 0.90 mm, and 1.02 mm were created in different animals. Control rats were sham-operated using the same dissection but without tying the ligature. Two weeks after surgery a 24 h electrocardiogram (ECG) was recorded by thin subcutaneous electrodes inserted under ether anaesthesia. ECG was recorded on a Medilog 1 tape recorder (Oxford Medical Instruments); recording started 2 h after recovering from the ether anaesthesia. The rats were unrestrained, moving freely in a specifically designed cage. In a few rats two successive 24 h periods were recorded, and there was good agreement between the heart rate patterns on both recordings. The 24 h ECG was analyzed by computer to determine hourly minimum, maximum and mean heart rates, and heart rate variability was displayed on a 24 h print-out.

Three weeks after the experimental coarctations the rats were studied. In a first series of experiments initially the femoral artery pressure, and then the simultaneous carotid and femoral artery pressure, was measured under chloral anaesthesia (as above). During these conditions blood pressures were lower than during normal consciousness, and in a second series of rats the pressures at the same locations were recorded under light ether anaesthesia. In pilot studies this was shown to give the same blood pressure during anaesthesia as that found as the eventual steady state in an unrestricted rat after recovery from the ether (measured by indwelling tail artery catheter). In measuring simultaneous carotid and femoral artery pressure it was found that whereas the size of the systolic gradient varied considerably in the same rat with alterations of heart rate and blood pressure level, the mean arterial pressure gradient between the two loci remained remarkably constant, and the degree of pressure overload is therefore expressed as mean arterial pressure gradient, and as the carotid artery systolic blood pressure during ether anaesthesia.

After the pressure measurements the heart was excised, blotted dry and weighed, after dissection into 'left ventricle' including the interventricular septum, and the rest of the heart. Subsequently the hearts were dried at 80°C to constant weight.

Using the systolic blood pressure before the coarctation and the average 24 h mean heart rate, the rate × pressure product was calculated as an indication of cardiac work.

Statistical analysis was carried out using Student's *t* test, and regression lines were plotted by computer by the method of least squares. Two-way analysis of variance for unbalanced design (Two-way ANOVA) was carried out with a commercial statistics software programme (Statgraphics).

Drugs

Propranolol hydrochloride was generously supplied by ICI Pharmaceuticals, as a component (0.1% w/w) of a standard rat diet.

Results

Effect of propranolol treatment per se *(see Table 1)*

The normal rate of gain in body weight in male rats was slightly reduced in the propranolol-treated sham-operated rats although the food intake, which was measured, was the same in both groups. The reduced weight gain may be due to reduced adipose tissue as the absolute heart weights (and kidney and liver weights) remained the same in both groups. Because

Table 1 The effect of propranolol on coarctation-induced left ventricular hypertrophy

	Control + sham op $n=11$	*P-diet + sham op* $n=13$	*Control + coarct* $n=10$	*P-diet + coarct* $n=7$	*t-test C-sh v P-sh*	*t test C-sh v C-coarct*	*t test* C-coarct *v P-coarct*	*Two-way ANOVA* coarct	*Two-way ANOVA* interaction P-diet *v coarctation*
Body wt (g)	333 ± 5	318 ± 6	331 ± 3	320 ± 6	$P<0.001$	NS	$0.05<P<0.1$	NS	NS
Heart wt (g)	0.924 ± 0.028	0.987 ± 0.026	1.189 ± 0.017	1.089 ± 0.034	NS	$P<0.001$	$P<0.02$	$P<0.00001$	$P=0.02$
Heart ratio (g 100 g^{-1} body wt.)	0.277 ± 0.005	0.311 ± 0.005	0.359 ± 0.003	0.334 ± 0.006	$P<0.001$	$P<0.001$	$P<0.02$	$P<0.00001$	$P=0.0002$
% increase in ht ratio			29.5 ± 1.3	8.5 ± 2.2			$P<0.001$		
Dry ht weight (% of wet)	26.7 ± 0.4	25.6 ± 0.6	25.0 ± 0.6	24.9 ± 0.7	NS	NS	NS		
LV weight (g)	0.655 ± 0.018	0.700 ± 0.021	0.880 ± 0.016	0.802 ± 0.033	NS	$P<0.001$	$P<0.02$	$P<0.00001$	$P=0.012$
LV ratio (g 100 g^{-1} body wt.)	0.193 ± 0.003	0.219 ± 0.004	0.266 ± 0.004	0.249 ± 0.006	$P<0.001$	$P<0.001$	$P<0.05$	$P<0.00001$	$P=0.0002$
% increase in LV ratio			37.6 ± 2.0	13.2 ± 3.1			$P<0.001$		
Dry LV wt (% of wet)	26.4 ± 0.6	24.9 ± 0.5	24.3 ± 0.3	24.5 ± 0.8	NS	NS	NS		
Pressure gradient (mean, mmHg)			22 ± 1	22 ± 2			NS		
Mean 24 h ht rate	420 ± 17	346 ± 8	355 ± 7	345 ± 5	$P<0.001$	$P<0.001$	NS		

Values are given as mean ± s.e.mean. At the beginning of the experiment the average body weight of rats in all the groups was the same. Animals were fed the control and propranolol-containing diet for four weeks prior to death. Abbreviations: *n* = number of observations; Two-way ANOVA = two-way analysis of variance; sh and sham op = sham-operation; P-diet and P- = propranolol diet; coarct = experimental coarctation; C- = control diet; wt = weight; ht = heart; LV = left ventricular; NS = not statistically significant. The % increase in heart and LV ratio is calculated as percentage increase compared with the mean value of the sham-operated group on the same diet.

of the lower body weights however, both heart ratio (g heart weight/100 g body weight) and left ventricular ratio (g left ventricle weight/100 g body weight) were higher in the propranolol-treated rats than in rats on control diet. There was no significant change in the percentage of the heart weight that was constituted by dry matter.

Efficacy of β-adrenoceptor blockade

Propranolol treatment reduced the average 24 h heart rate by 18% (Table 1), and the heart rate variability was less (maximum heart rate controls: 535±17, propranolol; 421±11; −21%, $P<0.001$). Analysis of the graphic printouts of 24 h heart rate profiles showed no evidence of the propranolol effect wearing off during the 24 h period. In a pilot study the maximal heart rate response to i.v. bolus doses of isoprenaline required a 10^3 times larger dose in the rats on propranolol diet (0.9 mg kg^{-1} versus 0.9 μg kg^{-1}), and the ED_{50} dose was also 10^3 times greater. Nevertheless the propranolol-treated rats responded to the stress of handling by a moderate increase (30%) in heart rate, which was not due to vagal withdrawal as it persisted after atropine treatment (up to 240 μg i.v.). The heart rate increase after handling was reduced to 15%, but never abolished, after further intravenous doses of propranolol (up to 15 mg kg^{-1}, i.v.). These findings suggest that β-adrenoceptor blockade in rats on the propranolol-containing diet was virtually complete for circulating catecholamines, but still only partial as regards the higher concentrations of noradrenaline occurring between the sympathetic nerve endings and the cardiac muscle cell.

Effect of experimental coarctation

There was a considerable mortality from congestive heart failure and from acute abdominal haemorrhage secondary to aortic rupture in the first few days after surgery. This was highest in the group with a 0.76 mm narrowing, where all rats that survived had aneurysms bypassing the ligature. Aneurysms also occurred in rats with less severe degrees of coarctation, and the results from these rats were discarded. The overall incidence of congestive heart failure was the same in propranolol-treated rats as in rats on control diet (21%), but the incidence of acute haemorrhage appeared lower in propranolol-treated rats (22%) than in control rats (31%).

As well as measuring absolute and relative heart weights, cardiac hypertrophy was expressed as % increase in heart ratio, and % increase in LV ratio. These values were calculated for each rat with a coarctation by dividing the observed heart or LV ratio respectively with the mean value for sham-operated rats on the same diet. This measurement enables closer examination of the relationship between differing degrees of pressure and work overload and the resulting cardiac hypertrophy.

In the first series of experiments, where the gradients were measured during chloral hydrate anaesthesia, the rats which had mean arterial pressure gradients between 15–31 mmHg were grouped together in order to be able to compare degrees of compensatory cardiac hypertrophy as mean values of absolute heart weights in two groups of rats with equivalent degrees of pressure overload. The control diet group showed marked compensatory cardiac hypertrophy with a 29% increase in heart weight, and a 34% increase in LV weight compared with sham-operated animals, correlating very well with the 30% increase in heart ratio ($P<0.001$) and the 38% increase in LV ratio ($P<0.001$). (Table 1).

In the second series of experiments, in rats with coarctations of a wider range of severity, the pressure gradients were studied under ether anaesthesia, and the resultant increase in heart ratio and left ventricular ratio was plotted against the mean arterial pressure gradient across the coarctation, in the manner of a linear 'dose-response curve'. It was found that, over the range of pressure gradients encountered, the compensatory cardiac hypertrophy of rats on a control diet increased linearly with the pressure gradient, both when expressed as % increase in heart ratio (Figure 1), and when expressed as % increase in LV ratio (Figure 2), with a highly significant variance ratio and correlation coefficients of 0.95 in both instances.

Effect of propranolol treatment on left ventricular hypertrophy

Propranolol treatment markedly reduced the cardiac hypertrophy occurring in response to a pressure gradient of 15–31 mmHg, with a non-significant increase of only 10% and 15% in heart and LV weight over the values in sham-operated rats. Only the 13% increase in LV ratio is significant when compared to the values in sham-operated animals ($P<0.01$) (see Table 1). When compared with the control diet coarctation group, the heart and LV weights were significantly lower in the propranolol-treated group ($P<0.02$). Because propra-

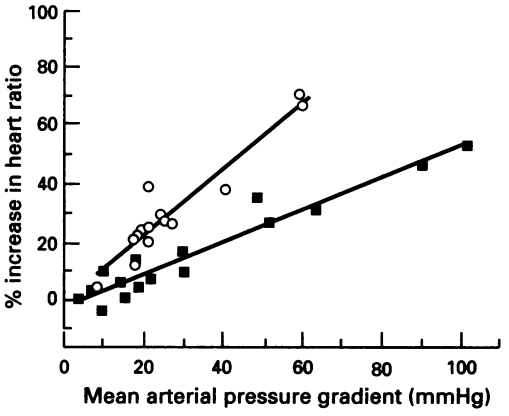

Figure 1 Relationship between heart weight and cardiac pressure overload in rats with experimental coarctation of the aorta. The graph shows the mean arterial pressure gradient (between carotid and femoral artery mean pressures) plotted against the percentage increase in heart ratio (g heart weight/100 g body weight) of each rat as compared with the mean heart ratio for sham-operated rats on the same diet: (○) rats on control diet; (■) rats on propranolol diet (80 mg kg^{-1} body weight day^{-1}). The slopes of the regression lines of the two groups are significantly different ($P<0.001$); for numerical values see text.

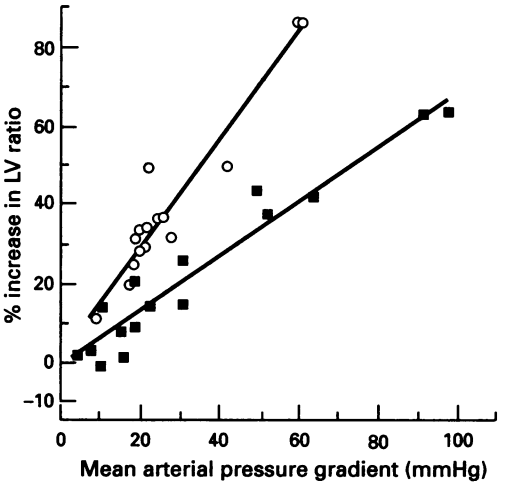

Figure 2 Relationship between left ventricular weight and cardiac pressure overload in rats with experimental coarctation of the aorta. The graph shows the mean arterial pressure gradient (between carotid and femoral artery pressures) plotted against the percentage increase in LV ratio (g left ventricular weight/100 g body weight) of each rat compared with the mean of the LV ratios for sham-operated rats on the same diet: (○) rats on control diet; (■) rats on propranolol diet. The slopes of the regression lines of the two groups are significantly different ($P<0.001$); for numerical values see text.

nolol treatment by itself causes an increase in heart and LV ratio due to reduced weight gain (see above), the difference in hypertrophic response between the two coarctation groups is most accurately expressed by comparing the percentage increases in heart and LV ratio over the values of the respective sham-operated controls. This comparison shows a highly significant reduction in hypertrophic response in the propranolol-treated rats (Table 1). Two-way analysis of variance (Two-way ANOVA) also confirms that propranolol significantly interacts with the increases in heart weight, heart ratio, LV weight and LV ratio caused by experimental coarctation ($P<0.00001$ for all interactions). Thus, in spite of the mean pressure gradients being the same in both groups the propranolol treatment caused a 65% reduction in the degree of compensatory left ventricular hypertrophy. This reduction was not associated with any significant change in the proportion of the heart weight constituted by dry matter (see Table 1).

In the second series with the wider range of pressure gradients the hearts of propranolol-treated rats, like the control rats, showed a linear increase in degrees of compensatory hypertrophy in response to increasing severity of pressure load, with correlation coefficients of 0.96 and 0.95 respectively. However, when the slopes of the regression lines of propranolol-treated rats are compared with those of control rats, it can be seen that they are less steep in propranolol-treated rats (see Figures 1 and 2). The differences in slope are highly significant both for the regression of heart ratio versus mean pressure gradient (control: 1.12 ± 0.10 (s.e.), propranolol: 0.56 ± 0.04; $P<0.001$), and with the regression of LV ratio versus mean pressure gradient (control: 1.34 ± 0.12, propranolol 0.67 ± 0.06; $P<0.001$). Thus in both instances the slope is exactly halved in the propranolol-treated rats (see Figures 1 and 2).

Plotting LV ratio versus carotid systolic blood pressure produces the same separation in two different linear regressions of the two groups, with a halving of the slope in the propranolol-treated group (slopes different $P<0.002$; not illustrated.

Effect of propranolol treatment on cardiac work

Although there was some reduction in cardiac work in propranolol-treated rats on account of a reduction in heart rate, the degree of this reduction was surprisingly small. Thus, when the 24 h heart rates of rats with mild to moderate degree of coarctation were compared, there was only a 3% lower average heart rate in propranolol-treated rats compared with rats on control diet (see Table 1, difference not statistically significant). The main explanation (see Discussion) for this surprisingly small difference is that the control rats with coarctation had significantly lower mean heart rates (355 cf. 420 per min) than sham-operated rats on control diet ($P<0.001$), while there was no difference between the propranolol-treated rats with coarctation or sham-operation (see values in Table 1).

In Figure 3 the cardiac work, expressed as the rate × pressure product, is plotted against the increase in left ventricular ratio. It can be seen that when the cardiac work load is expressed this way the slope of the regression line for the control rats (2.28 ± 0.16) is still far steeper, and significantly different from, the slope of the regression line for the propranolol-treated rats (1.08 ± 0.14; $P<0.001$).

General observations

When the mean 24 h heart rates were plotted against increases in heart or left ventricular ratio in rats with coarctation it was evident that there was no correlation within either of the two treatment groups between mean 24 h heart rate and the degree of compensatory hypertrophy. It is noteworthy that, although the degree of compensatory left ventricular hypertrophy was markedly reduced in propranolol-treated rats, they were able to sustain systolic blood pressures of up to 245 mmHg without any clinical evidence of heart failure. Furthermore, three propranolol-treated rats survived with mean arterial pressure gradients >62 mmHg, whereas none of the rats on control diet did. Thus, the reduction in compensatory cardiac hypertrophy was not disadvantageous in terms of symptoms or survival.

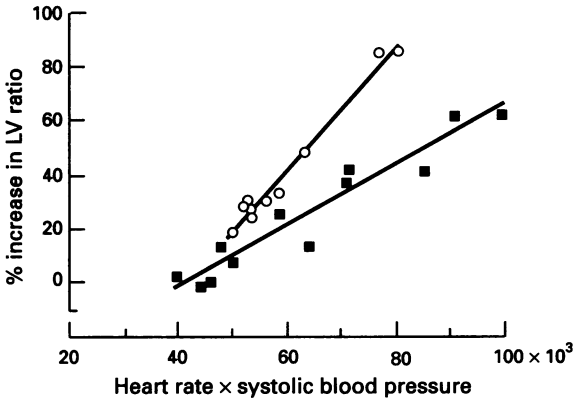

Figure 3 Relationship between left ventricular hypertrophy and cardiac work in rats with experimental coarctation of the aorta. The graph shows the cardiac work load in rats (expressed as the product of systolic carotid artery pressure and 24 h average heart rate) plotted against the percentage increase in LV ratio (g left ventricular weight/100 g body weight) of each rat compared with the mean of the LV ratios for sham-operated rats on the same diet: (○) rats on control diet; (■) rats on propranolol diet. The slopes of the regression lines of the two groups are significantly different ($P<0.001$); for numerical values see text.

Discussion

General observations

The finding that rats with an experimental coarctation had a significantly slower heart rate than sham-operated rats, and that this difference was abolished in the propranolol-treated groups suggest that there is still considerable baroreflex activity in these rats causing a relative bradycardia by reduced sympathetic drive to the sino-atrial node. This does not in any way invalidate the notion that there is at the same time increased nervous activity in the sympathetic nerves to the left ventricle as there is very localized projection of distal sympathetic nerve branches (Randall *et al.*, 1968; 1972; Randall, 1984), and since the majority of the nerves innervating the right atrium and right ventricle arise from the right-sided sympathetic trunk, whereas those innervating left atrium and left ventricle arise from the left-sided trunk (Calaresu *et al.*, 1975; Kralios *et al.*, 1975; Randall, 1984). It has in fact been established that overall cardiac sympathetic nervous activity is increased in experimental coarctation (Fischer *et al.*, 1965; Woo *et al.*, 1991).

Cardiac hypertrophy

The purpose of these experiments was to determine whether propranolol influenced the compensatory cardiac hypertrophy occurring in rats exposed to a left ventricular pressure overload by a mechanism independent of its effect on cardiac work. The results show that the hypertrophic response can be reduced by up to 65% by high dose oral propranolol treatment. As the slopes of the regression lines were significantly different, it can be concluded that for each increment in pressure overload, or total cardiac work expressed as a rate pressure product, the compensatory hypertrophic response in the propranolol-treated rats is only about half of that in the control rats. Thus it is clear that propranolol modifies the development of cardiac

hypertrophy by a mechanism distinct from any effect of propranolol on the systolic stress or the total work load of the heart.

These results provide further support for the hypothesis that noradrenaline released from cardiac sympathetic nerves and acting on myocardial β-adrenoceptors is a major final common pathway in the induction of cardiac hypertrophy (Östman-Smith, 1976; 1979; 1981; Tarazi *et al.*, 1982; Sen & Tarazi, 1983). This view is also supported by the finding that α-methyldopa in a dose that did not prevent hypertension nevertheless prevented the occurrence of compensatory cardiac hypertrophy in spontaneously hypertensive rats (Tomanek *et al.*, 1979) and in human hypertension (Fouad *et al.*, 1982). Propranolol treatment was found to reduce the development of cardiac hypertrophy in renal hypertensive rats even though they remained hypertensive (Fernandes *et al.*, 1976); however, these authors did not measure cardiac work load, nor did they have drug-treated control animals. Conversely, vasodilator therapy that normalizes the blood pressure and at the same time increases cardiac sympathetic nervous activity, is not associated with regression, but often with progression, of cardiac hypertrophy in the spontaneously hypertensive rat (Sen & Tarazi, 1983; Tsoporis *et al.*, 1988).

Thus, as demonstrated in the present study and the works referred to above, the mechanical stress of systolic overload can be experimentally dissociated from the process of compensatory cardiac hypertrophy *in vivo*. Accordingly, the systolic wall stress in the heart cannot be the only direct mediator of compensatory hypertrophy. *In vitro* studies on cultured cardiac myocytes have shown that mechanical stretch can induce protein synthesis and the expression of oncogenes, and increase cell surface area (Mann *et al.*, 1989; Komuro *et al.*, 1990; Komuro & Yazaki, 1993). In spite of that, studies in the well-oxygenated working heart preparation show that alterations of working pressure from 30 mmHg to 160 mmHg (Schreiber *et al.*, 1967), or insertion of a ventricular vent to offload the left ventricle in the Langendorff-preparation (Morgan *et al.*, 1984), did not cause any alteration in protein synthesis; (see Östman-Smith, 1981, for detailed discussion). Furthermore, Zierhut & Zimmer (1989) found that the cardiac hypertrophy and increase in RNA/DNA ratio seen *in vivo* in rats following constant intravenous noradrenaline infusion was not influenced when concurrent verapamil treatment was used to reduce considerably mean aortic pressure, left ventricular dP/dt_{max} and heart rate; this finding provides a further example of experimental dissociation between the degree of pressure overload and the resulting cardiac hypertrophy. Thus the *in vivo* role of increased myocardial tension in the induction of cardiac hypertrophy is far from clear although Cooper *et al.* (1985) were able to demonstrate selective atrophy in off-loaded papillary muscle. The finding that chemical sympathectomy abolishes exercise-induced cardiac hypertrophy (Östman-Smith, 1976), and that atenolol prevents right ventricular hypertrophy in response to hypoxia (Östman-Smith, 1995, preceding paper), demonstrates that a moderate *in vivo* increase in myocardial mechanical stress is not a sufficient stimulus on its own to induce myocyte hypertrophy.

It has been suggested that circulating angiotensin could be the chief physiological trigger for cardiac hypertrophy (Khairallah & Kanabus, 1983; Aceto & Baker, 1990). How a circulating agent could induce compensatory cardiac hypertrophy in one cardiac chamber only, leaving the rest of the heart unaffected, as is the situation in many models of cardiac hypertrophy is difficult to explain. A causative rather than permissive role for the renin-angiotensin system is rendered unlikely by the finding of Fernandes *et al.* (1976) that there was no effect of propranolol treatment on blood renin levels in renal hypertensive rats at times when the cardiac hypertrophy was reduced. On the other hand, the finding that atenolol abolishes cardiac hypertrophy in response to noradrenaline infusion without normalizing blood pressure (Yamori *et al.*, 1980) re-inforces the view that myocardial β-adrenoceptors are a major common pathway in the *in vivo* induction of cardiac hypertrophy.

There is considerable controversy in the literature regarding the efficacy of propranolol in preventing compensatory cardiac hypertrophy in various experimental models. The different results can be accounted for by variations in doses employed and in mode of administration, and in the all too frequent absence of propranolol-treated control groups. As seen in this study propranolol treatment by itself causes an increase in heart ratio by a reduction in body weight without change in heart weight, which illustrates that no valid conclusions about failure to reduce cardiac hypertrophy can be drawn unless absolute heart weights are recorded and proper controls used. The dose effect is illustrated by the reduction of compensatory hypertrophy seen in this study by 80 mg kg^{-1} given in the diet as in this study, or 60–100 mg kg^{-1} in the drinking water as used to reduce cardiac hypertrophy by Richer *et al.* (1980) in spontaneously hypertensive rats and by Fernandes *et al.* (1976) in renal hypertensive rats. In contrast, Zimmer & Peffer (1986) failed to reduce the increase in cardiac protein synthesis induced by experimental coarctation of the aorta by 10 mg kg^{-1} given subcutaneously 12 hourly, and Dennis & Vaughan-Williams (1982) failed to reduce right ventricular hypertrophy in the rabbit in response to hypoxia by 5 mg kg^{-1} given subcutaneously 12 hourly. That the failure of propranolol to reduce hypertrophy in the latter experiment was due to too low a dose of the drug is suggested by the fact that the non-selective β-adrenoceptor blocker, trimepranol, was effective in reducing right ventricular hypertrophy due to hypobaric hypoxia (Ostadal *et al.*, 1978), and confirmed by the finding that propranolol 80 mg kg^{-1} given orally reduced the right ventricular hypertrophy induced by hypoxia by 65% (Östman-Smith, 1995).

What conclusions can be drawn from the fact that in both the coarctation model and the hypoxia model this dose of propranolol roughly halves the degree of compensatory cardiac hypertrophy caused by a left or right ventricular pressure overload, but does not abolish it? The possibilities are that the residual hypertrophy occurring was induced via a different molecular switch, e.g. via α-adrenoceptors or the direct effect of mechanical stretch, or that the degree of β-adrenoceptor blockade was incomplete. That incomplete β-adrenoceptor blockade might have been a factor is suggested by the fact that atenolol, in a dose that caused more profound β-adrenoceptor blockade than 80 mg kg^{-1} propranolol, was able to abolish completely the right ventricular hypertrophy in response to moderate hypoxia (Östman-Smith 1995). Because of the complexities of the mechanical, neural and endocrine signals involved in the induction of compensatory cardiac hypertrophy (see reviews by Morgan & Baker, 1991; van Bilsen & Chien, 1993) it is a process that is very difficult to study in *in vitro* systems, and this study shows that *in vivo* the roles of β-adrenoceptors in the induction of cardiac hypertrophy is much more important than had been assumed from *in vitro* tissue culture work.

Wider implications

The dose of propranolol used might seem very large in comparison with doses used in clinical medicine, but it must be remembered that small mammals such as the rat have a much higher sympathetic tone and a higher metabolic rate than large mammals. This is illustrated by the fact that even this dose did not completely block stress-induced changes in heart rate. That high dose oral propranolol may be beneficial in reducing pathological cardiac hypertrophy in man is suggested by the finding that propranolol in doses of 7–18 mg kg^{-1} was found to cause substantial regression of hypertrophy in symptomatic infants with hypertrophic cardiomyopathy (Östman-Smith, 1985; 1991).

Conclusions

High dose oral propranolol reduces compensatory left ventricular hypertrophy, occurring in response to experimental

coarctation of the aorta, by a mechanism related to its β-adrenoceptor blocking action and distinct from any effect of propranolol on cardiac work load. This finding provides further support for the hypothesis that noradrenaline released from cardiac sympathetic nerves is a major common pathway in the induction of compensatory cardiac hypertrophy.

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