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ADRENOCEPTOR-MEDIATED CARDIAC AND VASCULAR RESPONSES IN GENETICALLY GROWTH HORMONE-DEFICIENT RATS

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Abstract—This study has measured cardiovascular parameters, pharmacological responses to α- and β-adrenoceptor agonists, and cardiac β-adrenoceptor characteristics in growth hormone (GH)-deficient (dwarf) Lewis rats, normal Lewis rats and dwarf rats treated with GH (2 mg/kg/day for 28 days). Dwarf rats showed a decreased mean blood pressure and heart rate but an increased ventricular weight relative to body weight when compared with age-matched normal Lewis rats. Positive chronotropic responses *in vivo* to the non-selective β-adrenoceptor agonist, isoprenaline, were unchanged in dwarf rats. The selective β_1-adrenoceptor agonist, noradrenaline, was less potent in isolated right atria from dwarf rats although maximal responses were unchanged. Basal force of contraction was greater in isolated cardiac muscles from dwarf rats than from normal rats. Maximal positive inotropic responses to both calcium chloride and noradrenaline were reduced in left atria but increased in left ventricular papillary muscles from dwarf rats. Responses to the α_1-adrenoceptor agonist, phenylephrine, were markedly increased in isolated cardiac tissues from dwarf rats. Maximal contractile responses of isolated thoracic aortic rings from dwarf rats to KCl (100 mM) and the α-adrenoceptor agonist, noradrenaline, were markedly reduced compared to responses in normal rats. Left ventricular β-adrenoceptor density measured by ^{125}I-cyanopindolol binding was significantly increased in dwarf rats. Administration of GH (2 mg/kg/day for 28 days) reversed the altered responses in dwarf rats. We conclude that GH: (a) is required for the development of normal contractile capability of cardiac and vascular tissues; (b) regulates both β-adrenoceptors and α- and β-adrenoceptor-mediated responses; (c) differentially regulates atrial and ventricular responsiveness.

Cardiovascular alterations associated with increased growth hormone (GH†) concentrations in human acromegalics include cardiomegaly [1], hypertension, coronary artery disease and arrhythmias [2, 3]. Animal models of GH hypersecretion following tumour implantation have shown increases in heart rate, cardiac output and contractility [4] and improvements in both contractile performance and economy [5]. These results were obtained in states of GH hypersecretion which may involve a set of GH actions unlike those in normal secretory states. Recently, a dwarf strain of Lewis rats with a genetic GH deficiency has been described [6]. This genetic lesion appears to be specific for GH, leaving other pituitary hormones unaffected. This strain of dwarf Lewis rats offers advantages over hypersecretion models or experimental pituitary ablation since the absence or presence (by replacement) of GH is selective and hence the state of cardiovascular function should reflect more precisely the physiological actions of GH.

The cardiovascular system is partly regulated by the sympathetic nervous system which releases noradrenaline to activate α- and β_1-adrenoceptors. Both adrenoceptor types mediate positive inotropic responses in isolated rat cardiac tissues [7]; in addition, β-adrenoceptor agonists increase rate of contraction (positive chronotropy) and α-adrenoceptor agonists contract isolated blood vessels. The hypertension and the increase in heart rate and contractility observed in GH hypersecretion clearly suggest the involvement of the sympathetic nervous system. Thus, the aim of this study was to measure both basal and adrenoceptor-mediated responses of isolated cardiac and vascular tissues from groups of Lewis rats with different GH profiles to determine the role of GH in cardiovascular function.

MATERIALS AND METHODS

A dwarf GH-deficient strain of Lewis rats [6] and normal Lewis rats were used in this study. Male rats were obtained at 10–12 weeks of age from the Central Animal Breeding House (normal Lewis) or the Department of Physiology and Pharmacology (dwarf Lewis rats), The University of Queensland. The experimental design consisted of groups of dwarf rats treated for 28 days with daily subcutaneous injections of 2 mg GH/kg/day (recombinant bovine GH; Monsanto, Chesterfield Village, MO, U.S.A.), groups of dwarf rats injected with saline alone and groups of normal Lewis rats as controls.

Measurement of blood pressure and chronotropic responses to isoprenaline. In vivo responses were measured in rats anaesthetized with ketamine (50 mg/kg) and xylazine (10 mg/kg). Blood pressure was measured via a carotid artery catheter connected to a pressure transducer and a Grass amplifier and recorder; heart rate was monitored continuously by

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† Abbreviations: GH, growth hormone; ICYP, ^{125}I-cyanopindolol.

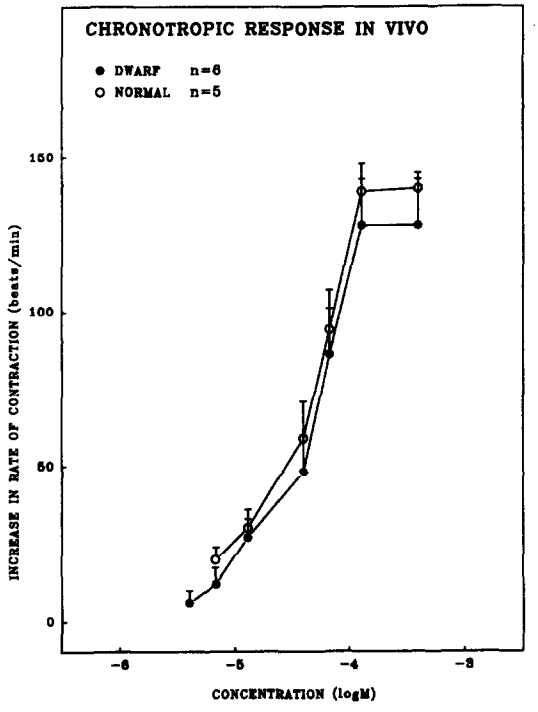

Fig. 1. Isoprenaline dose–response curves on heart rate *in vivo* in anaesthetized normal (open circles) and dwarf (closed circles) Lewis rats.

surface ECG leads connected to a Grass amplifier and recorder. Isoprenaline solutions were freshly prepared in normal saline for injection as bolus doses via a jugular vein catheter. Maximal chronotropic responses were measured within 60 sec; heart rate returned to normal within 5 min when the next dose was given.

Isolated cardiac and thoracic aortic preparations. The heart was rapidly removed after death by chloroform and the left and right atria, and left ventricular papillary muscles were prepared for measurement of changes in force of contraction during cumulative concentration–response curves to noradrenaline or phenylephrine, followed after washout by calcium chloride [7]. In experiments with phenylephrine, β-adrenoceptors were blocked by incubation with metoprolol (10 μM) for 30 min before and during the experiment. Thoracic aortic rings (approximately 4 mm in length) were suspended with a resting tension of 10 mN, and contracted with isotonic KCl (100 mM). The presence of endothelium was demonstrated by relaxation in response to acetylcholine (10 μM). After washout, a cumulative concentration–response (contraction) curve was determined for either noradrenaline or phenylephrine. Results are given as the maximal increase in force of contraction (in mN, left atria and left ventricular papillary muscles; in % of the maximal contraction to KCl 100 mM, thoracic aortic rings), or rate of contraction (in beats/min, right-atria), and the negative log EC_{50} as determined from individual concentration–response curves. Thoracic aorta were perfused with 10% buffered neutral formalin, embedded in wax, and 20 μm sections cut and stained with haemotoxylin and eosin. Image analysis (Wild-Leitz MD30+ image analysis system) of stained transverse sections of thoracic aortic rings was used to calculate lumen area and wall area.

Radioligand binding studies. Radioligand binding studies were performed to characterize β-adrenoceptors in left ventricular homogenates [8]. Left ventricle, homogenized in buffer A (10 mM Tris–HCl, 1 mM EDTA, pH 7.4), was left to stand for 10 min before addition of an equal volume of 1 mM KCl, pH 7.4, and centrifugation at 100,000 *g* for 45 min. The pellet was resuspended in buffer B (50 mM Tris–HCl, 10 mM $MgCl_2$, pH 7.4) and centrifuged at 100,000 *g* for 45 min. The pellet was resuspended as a 1:99 (w/v) dilution in buffer B.

Table 1. Cardiovascular parameters of normal, dwarf and GH-treated Lewis rats

	Normal	Dwarf	Dwarf + GH
Body weight (g)	305 ± 13 (13)	216 ± 6* (19)	271 ± 10* (10)
Mean blood pressure (mmHg)	163 ± 8 (6)	132 ± 7* (7)	—
Heart rate *in vivo* (beats/min)	240 ± 6 (6)	217 ± 4* (7)	—
Heart wet weights			
(LV + S) (mg)	634 ± 26	552 ± 21*	634 ± 20
(mg/kg)	2.1 ± 0.04	2.6 ± 0.1*	2.4 ± 0.1*
RV (mg)	167 ± 8	137 ± 5*	171 ± 4
(mg/kg)	0.55 ± 0.01	0.64 ± 0.02*	0.64 ± 0.02*
(LV + S)/RV	3.8 ± 0.1	4.1 ± 0.1*	3.7 ± 0.15
Thoracic aortic rings			
Wall area (mm^2)	0.30 ± 0.01	0.29 ± 0.01	0.31 ± 0.01
Lumen area (mm^2)	1.2 ± 0.02	0.82 ± 0.02*	0.89 ± 0.03*
Wall/lumen ratio	0.25 ± 0.004	0.35 ± 0.01*	0.35 ± 0.01*

* $P < 0.05$ compared to normal Lewis rats.
LV, left ventricle; S, septum; RV, right ventricle.

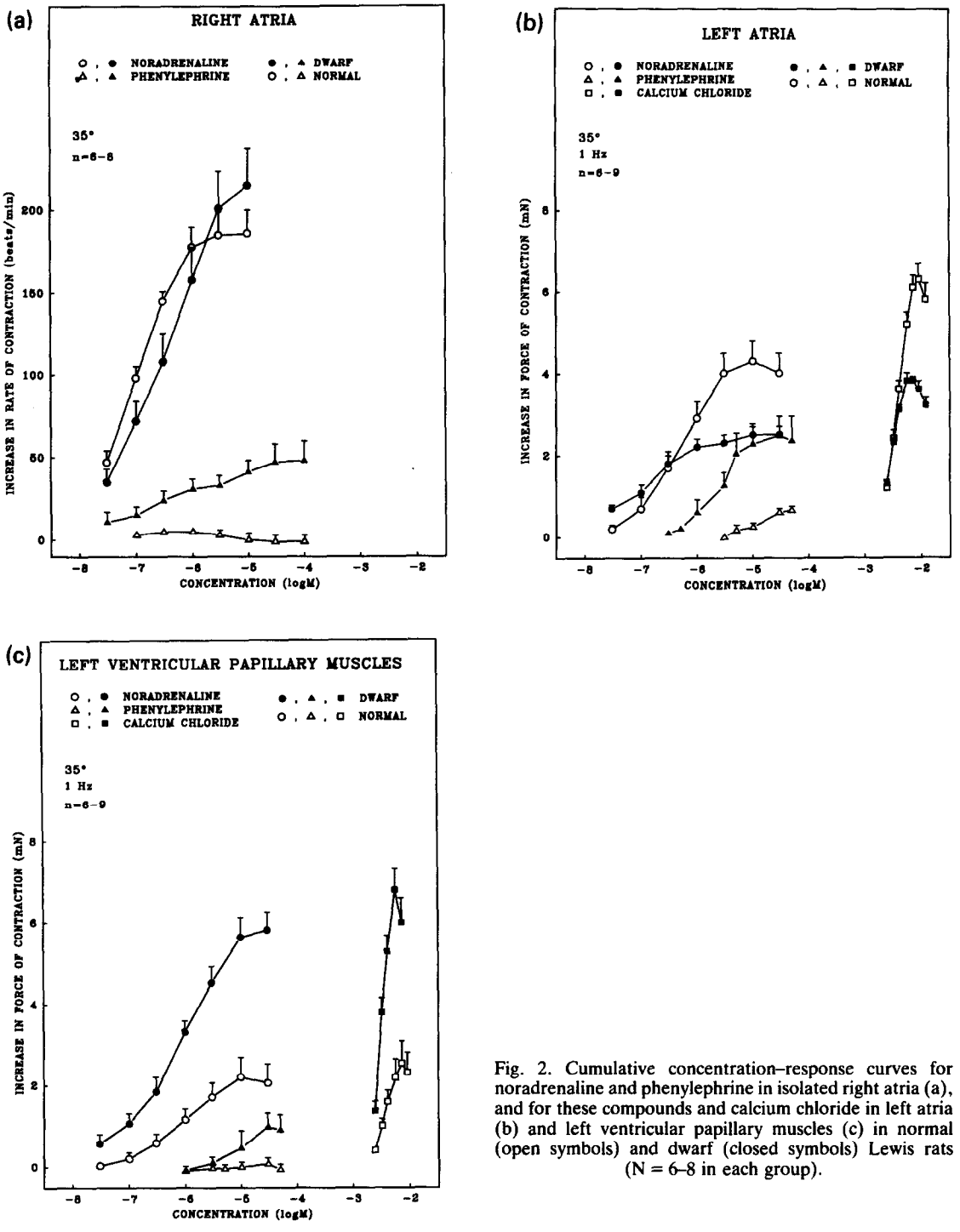

Fig. 2. Cumulative concentration–response curves for noradrenaline and phenylephrine in isolated right atria (a), and for these compounds and calcium chloride in left atria (b) and left ventricular papillary muscles (c) in normal (open symbols) and dwarf (closed symbols) Lewis rats (N = 6–8 in each group).

Protein content was measured in these homogenates by a dye-binding method [9] and found to be 68.5 ± 5.2 (normal Lewis, N = 8), 40.4 ± 3.6 (dwarf, N = 8) and 39.6 ± 0.8 (dwarf + GH, N = 10) mg protein/g tissue. Receptor density and affinity were determined by radioreceptor assays using ^{125}I-cyanopindolol (ICYP) as a non-selective β-adrenoceptor radioligand which was prepared and purified by HPLC [8]. Non-specific binding was defined as binding in the presence of propranolol (1 μM). The relative proportions of β_1- and β_2-adrenoceptors were determined by measuring ICYP binding in the presence of increasing concentrations from 10^{-9} to 10^{-4} M of the β_2-adrenoceptor-selective antagonist, ICI 118,551. Binding in individual experiments was analysed by the iterative curve-fitting program, LIGAND [10], using the program adapted for microcomputers by G. A. McPherson and published

by BIOSOFT (Cambridge, U.K.). The receptor density was expressed as fmol/mg protein.

Statistics. All results were expressed as group means ± SEM. Comparisons of group means were made by Student's *t*-test or Newman–Keuls multiple comparison test. $P < 0.05$ was considered significant.

RESULTS

Cardiovascular parameters

Comparison of age-matched normal and dwarf Lewis rats (Table 1) shows that GH deficiency was associated with decreases in body and heart chamber weights, blood pressure and basal heart rate, although heart weight relative to body weight was moderately greater in the dwarf rats. GH treatment reversed these effects of GH deficiency. The wall area of thoracic aortic rings was similar in all three groups of Lewis rats but the lumen area was reduced by about 30% in dwarf and GH-treated groups.

Positive chronotropic responses

Positive chronotropic responses were measured both in anaesthetized rats and in isolated rat right atria. Basal heart rate *in vivo* was lower in dwarf rats (Table 1). Responses *in vivo* to the β-adrenoceptor agonist, isoprenaline, were unchanged by growth hormone deficiency (Fig. 1; normal rats: $-\log ED_{50}$ 3.78 ± 0.04, maximal increase 139 ± 9 beats/min, N = 5; dwarf rats: $-\log ED_{50}$ 3.73 ± 0.08, maximal increase 128 ± 17 beats/min, N = 6).

The basal rate of contraction of isolated right atria was lower in dwarf rats (187 ± 6 beats/min, N = 13) than in normal Lewis rats (211 ± 5 beats/min, N = 13). Positive chronotropic responses to the β_1-adrenoceptor-selective agonist, noradrenaline, and the α_1-adrenoceptor-selective agonist, phenylephrine, are shown in Fig. 2a. Noradrenaline was less potent in dwarf rat right atria ($-\log EC_{50}$: normals 7.1 ± 0.1, dwarfs 6.5 ± 0.1) although maximal responses were not different. Phenylephrine produced small, inconsistent positive chronotropic responses in right atria from normal Lewis rats but significant responses in atria from dwarf rats.

Positive inotropic responses

Isolated cardiac tissues from dwarf rats showed an increased basal force of contraction (left atria: dwarf, 5.2 ± 0.3 mN, N = 18; normal, 3.3 ± 0.4 mN, N = 14; left ventricular papillary muscles: dwarf, 4.2 ± 0.4 mN, N = 14; normal, 1.6 ± 0.3 mN, N = 15). Positive inotropic responses to noradrenaline, phenylephrine and calcium chloride were determined in left atria (Fig. 2b) and left ventricular papillary muscles (Fig. 2c). Maximal increases in force were markedly different for the two tissues; the maximal response to noradrenaline was much greater in left atria of normal Lewis rats (Fig. 2b), while the converse was observed in ventricular tissue (Fig. 2c). Similarly, the maximal response to calcium chloride was greater in the atria of normal, and in the ventricles of dwarf, Lewis rats. The maximal response to phenylephrine was larger in dwarf rats for both left atria and left ventricles (Fig. 2b and c).

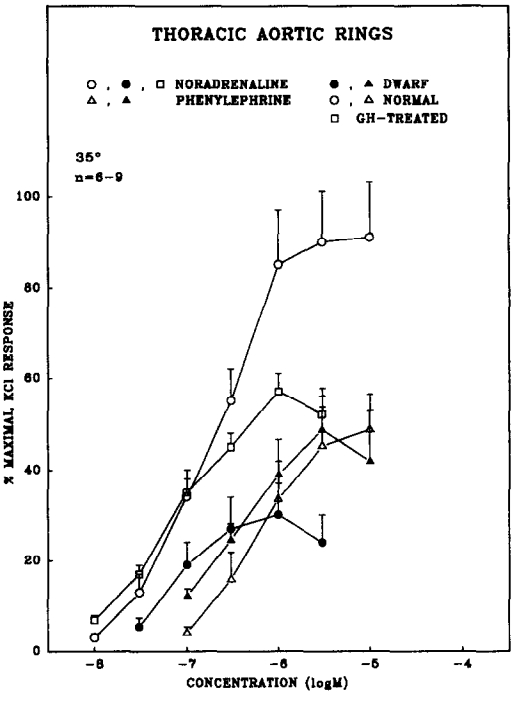

Fig. 3. Cumulative concentration–response curves for noradrenaline and phenylephrine in thoracic aortic rings from dwarf (closed circle and triangle), GH-treated dwarf (open square) and normal (open circle and triangle) Lewis rats (N = 6 in each group).

Contractility of thoracic aorta

Maximal contraction to KCl (100 mM) was markedly less in thoracic aortic rings from dwarf rats (8.2 ± 0.4 mN, N = 20) than in tissues from normal rats (16.8 ± 1.1 mN, N = 18). The α-adrenoceptor agonists, noradrenaline and phenylephrine, contracted thoracic aortic rings from both normal and dwarf rats (Fig. 3). Both agonists were more potent in dwarf rats ($-\log EC_{50}$: noradrenaline, dwarf 7.02 ± 0.11; normal 6.73 ± 0.06; phenylephrine, dwarf 6.56 ± 0.10; normal 6.15 ± 0.12). Relative to the maximal responses to KCl, noradrenaline responses were markedly decreased while phenylephrine responses were unchanged in dwarf rat thoracic aortic rings.

Effect of GH treatment on contractility

GH treatment of dwarf Lewis rats for 28 days led to a reduced basal force of contraction (left atria, 4.4 ± 0.6 mN, N = 7; left ventricular papillary muscles, 2.3 ± 0.5 mN, N = 8), in addition to the effects on general cardiovascular parameters already mentioned in relation to Table 1 (*vide supra*). GH treatment of dwarf rats decreased the inotropic responses of noradrenaline and calcium chloride towards those seen in normal Lewis rats (Figs 4 and 2c). Papillary muscles from GH-treated dwarf rats showed a marked tendency for ectopic beats at low noradrenaline concentrations (Fig. 4). The right

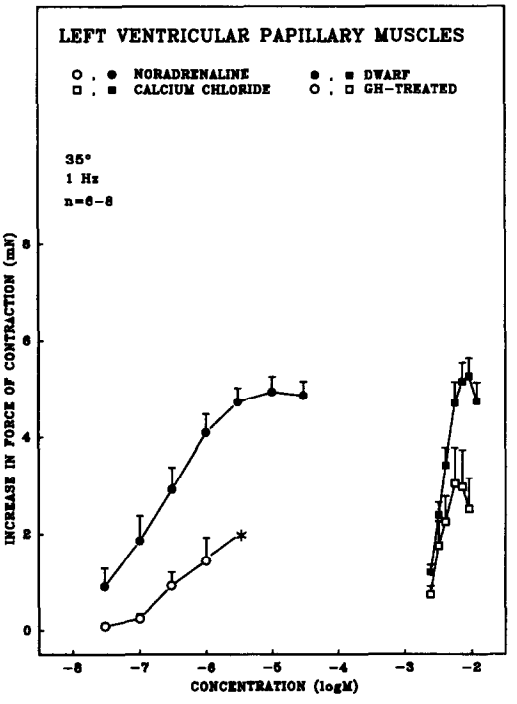

Fig. 4. Cumulative concentration–response curves for noradrenaline (circles) and calcium chloride (squares) in left ventricular papillary muscles from dwarf (closed symbols) and GH-treated dwarf (open symbols) Lewis rats (N = 6–8 in each group). The asterisk indicates that muscles showed ectopic beats at this concentration.

atria from these rats showed the same maximal chronotropic response to noradrenaline (207 ± 20 beats/min, N = 6) and potency ($-\log EC_{50}$ 7.0 ± 0.1) as normal Lewis rats (data not shown in Fig. 2a). GH treatment did not increase thoracic aortic ring responses to KCl (100 mM) (8.7 ± 1.0 mN, N = 8) nor was noradrenaline potency changed ($-\log EC_{50}$ 7.12 ± 0.05) compared with GH-deficient rats. The maximal response to noradrenaline was increased from 30 ± 6.8% of KCl (100 mM) in dwarf rats to 57.2 ± 4.3% after GH treatment.

Ventricular β-adrenoceptors

β-Adrenoceptors were measured in left ventricular homogenates by radioreceptor assays with the non-selective β-adrenoceptor radioligand ICYP and the β_2-adrenoceptor-selective compound ICI-118,551 as the competing ligand to distinguish β_1- and β_2-adrenoceptors. The results are shown in Fig. 5. Both β_1- and β_2-adrenoceptors were present, with β_1-adrenoceptors predominant and at a significantly higher density in dwarf (168 ± 20 fmol/mg protein) and GH-treated rats (136 ± 10 fmol/mg) than in normal Lewis rats (74 ± 8 fmol/mg). The density of β_2-adrenoceptors was also higher in dwarf (51 ± 4 fmol/mg) than normal Lewis rats (36 ± 5 fmol/mg). However, GH treatment did not significantly change the β_2-adrenoceptor density of dwarf rats. The affinity of the β_2-adrenoceptor-

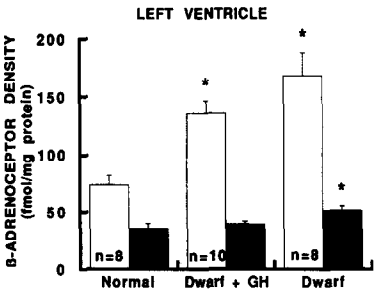

Fig. 5. Density of β_1-adrenoceptors (open) and β_2-adrenoceptors (hatched) in left ventricles from normal, dwarf and GH-treated dwarf Lewis rats.

selective ligand ICI 118,551 for β_1-adrenoceptors (normal Lewis, K_D 420 nM) and β_2-adrenoceptors (normal Lewis, K_D 4 nM) was similar for all groups of rats.

DISCUSSION

The physiological role of GH in the cardiovascular system is unclear despite many studies in humans [1, 2, 3, 11] and animals [5, 12, 13]. In humans, acromegaly (GH hypersecretion) is associated with marked cardiovascular abnormalities but these patients also show a high frequency of other cardiovascular risk factors such as cardiomegaly, hypertension, diabetes mellitus and atherosclerosis [3, 14]. Animal models of GH hypersecretion by implanted tumours [4, 13] show similar cardiovascular abnormalities to acromegalic patients. Further, decreased GH levels, as in adults with hypopituitarism, are associated with an increased mortality due to vascular disorders [15] but these patients rarely show a specific defect in GH production.

The present study used the genetically GH-deficient Lewis rat to elucidate the cardiac and vascular effects of GH. We have shown that while the absolute weights of the right and left ventricles were lower in dwarf rats than in normal rats, the ratio of ventricular weight to body weight was higher. The lumen area of the thoracic aorta was also lower in dwarf rats. Treatment with GH for 28 days induced changes in body weight, cardiac and vascular parameters towards those of the normal Lewis rat. Complete restoration to normal was not achieved, indicating that our GH treatment was shorter or at a lower dose than required for a complete reversal of GH deficiency. In addition, our method of GH administration does not mimic the normal pulsatile secretion of GH [16] which may be necessary for a complete reversal of GH deficiency.

Our results show that basal cardiac contractility and adrenoceptor-mediated responses are affected by GH. Thus, basal force of contraction in isolated atrial and ventricular tissue was greater in GH-deficient rats, indicating that GH suppresses the contractility of the unstimulated heart. However, the inotropic response to noradrenaline was markedly

different in atria and ventricles in that it was reduced in the atria and increased in the ventricles of dwarf rats (Fig. 2b and c). This differential effect of GH on atrial and ventricular inotropic responses to noradrenaline was also observed in the force generated by calcium chloride, indicating that the intrinsic contractile capability of cardiac tissue is responsive to GH. The chronotropic response to noradrenaline was, like the atrial inotropic response, reduced in dwarf rats (Fig. 2a). In spite of these chronotropic and inotropic differences between dwarf and normal rats, the *in vivo* response to isoprenaline was similar in dwarf and normal rats (Fig. 1), suggesting that, considering the overall haemodynamics, the decreased chronotropy in dwarf rats is effectively offset by the increased ventricular inotropy. However, these observations and the fact that GH treatment of dwarf rats markedly decreased ventricular contractility and induced a high incidence of ectopic beats (Fig. 4) have important implications under conditions of high GH secretion since cardiac function, ventricular contractility in particular, deteriorates. Thus, the high incidence of cardiac morbidity in acromegalics [2, 3] may be due both to direct cardiac effects and the consequences of haemodynamic disturbances.

Left ventricular β-adrenoceptor densities (Fig. 5) changed parallel to the left ventricular inotropic response to noradrenaline (Figs 2c and 4). The functional significance of these β-adrenoceptor changes is unclear, since the similar changes in both noradrenaline and calcium chloride responses indicates that the ability of the muscle to produce force has changed rather than a selective change in β-adrenoceptor-mediated responses. There may be a possible benefit of an increased receptor reserve to maintain cardiac responsiveness to sympathetic stimulation. Atrial β-adrenoceptor density was not measured in these rats. However, the parallel changes in receptor density and contractility observed in the ventricles suggest a lower receptor density in the atria of dwarf rats, corresponding to the lower contractility. This inference should be confirmed experimentally since it raises the interesting possibility of differential control of β-adrenoceptors by GH shown as an upregulation in atria and downregulation in ventricles.

Activation of α-adrenoceptors in isolated rat cardiac muscles increased force and rate of contraction [7]. The α-adrenoceptor agonist, phenylephrine, produced markedly greater responses in both atrial and ventricular tissues from GH-deficient rats (Fig. 2). Disease-induced changes in α-adrenoceptor-mediated responses have only rarely been reported; for example, responses were increased in non-infarcted hypertrophied muscles from rats with chronic myocardial infarction [17]. Our results are thus significant and represent the first report of a hormonal regulation of an α-adrenoceptor-mediated response which, based on the magnitude of the effect, could be physiologically relevant in cardiovascular control. One possible reason for an increased response is an increased α-adrenoceptor density. However, parallel changes in α-adrenoceptor density and inotropic responsiveness may not occur; for example, phenylephrine infusion [18] and spontaneously hypertensive rats [19] showed decreased cardiac α-adrenoceptor density but unchanged cardiac muscle responses to phenylephrine. Other reasons include increased second messenger responses or changes in myosin isoform proportions [5]. We have not performed these measurements so that our results do not allow differentiation between these options.

The maximal responses of vascular smooth muscle by KCl and the non-selective α-adrenoceptor agonist, noradrenaline, were directly proportional to GH levels, unlike the cardiac responses; thus, GH may increase contractility in this tissue. However, responses to the α_1-adrenoceptor-selective partial agonist, phenylephrine, were unchanged, indicating that this receptor subtype is not involved. GH treatment partially restored the responsiveness to noradrenaline but not to KCl. Thus, GH seems to play a complex role in both receptor-independent and α-adrenoceptor-mediated contraction of vascular smooth muscle in the rat.

In conclusion, we have shown that GH has important effects on cardiac and vascular contractility by: (a) changing the intrinsic, receptor-independent capacity of muscle to contract, (b) regulating the α- and β-adrenoceptor-mediated responses and (c) regulating the density of β-adrenoceptors and possibly of α-adrenoceptors.

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