Pergamon

Biochemical Pharmacology, Vol. 47, No. 2, pp. 281–288, 1994.

0006-2952/94 $6.00 + 0.00

ADRENOCEPTOR-MEDIATED CARDIAC AND VASCULAR RESPONSES IN HYPOTHYROID RATS

LINDSAY BROWN,* RICHARD NANKERVIS, DAVID KERR and CONRAD SERNIA
Department of Physiology and Pharmacology, The University of Queensland, 4072 Australia

(*Received* 20 *July* 1993; *accepted* 28 *September* 1993)

Abstract—This study has investigated adrenoceptor-mediated responses and β-adrenoceptors in neonatal-onset hypothyroidism in rats. Four groups of adult rats were studied: controls, neonatal-onset uncorrected hypothyroidism (continuous oral methimazole treatment) and after chronic triiodothyronine (T_3) replacement of these rats at either 25 or 100 μg/kg/day for 8 weeks beginning at 12 weeks of age. Hypothyroid rats were 61% smaller with an 18% decrease in heart rate; food and water intake were reduced to 43% and 52%, respectively; O_2 consumption was reduced to 20% and rectal temperature was 2.9° lower. T_3 administration increased body weight to 60–62% of controls; metabolic changes were reversed; but tachycardia and cardiac hypertrophy (60–120% increases) resulted. The positive inotropic responses to the selective α_1-adrenoceptor agonist, phenylephrine, in left ventricular papillary muscles were abolished; the β_1-adrenoceptor agonist, noradrenaline, was significantly less potent as an inotropic compound in isolated cardiac tissues from hypothyroid rats. The potency of phenylephrine to contract thoracic aortic rings was reduced in hypothyroid rats. These changes in α- and β-adrenoceptor mediated responses were reversed by T_3 administration. Both β_1- and β_2-adrenoceptor densities were increased in the hypothyroid left ventricle; T_3 administration further increased β_1-adrenoceptor density. We conclude that neonatal hypothyroidism produces pronounced physiological responses, changes in adrenoceptor-mediated responses and an increased ventricular β_1-adrenoceptor density. T_3 replacement reversed the changes in cardiac responses and metabolic parameters, except body weight, but produced cardiac symptoms of hyperthyroidism (tachycardia, hypertrophy as well as an increased β_1-adrenoceptor density).

The physiological effects of uncorrected hypothyroidism are marked; the cardiovascular changes include bradycardia, low cardiac index and an increased systemic vascular resistance [1] which resemble a suppressed sympathetic nervous system. The sympathetic neurotransmitter, noradrenaline, activates both α- and β_1-adrenoceptors; cardiac adrenoceptor density was reduced in perinatal [2] and adult-onset hypothyroidism [3]. Agonists at α- and β-adrenoceptors altered force of contraction of the heart in parallel with the receptor changes in adult-onset hypothyroidism [4, 5]. Replacement therapy with either of the thyroid hormones, thyroxine or triiodothyronine (T_3), usually reversed the effects of adult-onset hypothyroidism including cardiovascular changes [6, 7] but therapeutic success in neonatal hypothyroidism depends on early diagnosis and replacement.

The aim of the present study was to determine the reversibility of changes induced by neonatal-onset hypothyroidism in adrenoceptor-mediated cardiac and vascular responses and in cardiac β-adrenoceptors. Hypothyroidism was induced by chronic treatment with oral methimazole starting on gestation day 18; in some rats, T_3 was administered for 8 weeks beginning at 12 weeks of age. We have then defined the responses to the adrenoceptor agonists, phenylephrine and noradrenaline, in isolated cardiac and vascular tissues. Isolated tissues were used to avoid the complex cardiovascular regulatory systems *in vivo*. Ventricular β-adrenoceptors were characterized in each group of rats using radioligand binding studies with left ventricular membranes.

MATERIALS AND METHODS

Wistar rats were obtained from the Central Animal Breeding House of the University of Queensland. Methimazole (0.5 g/L drinking water) was given continuously to confirmed pregnant rats from gestational day 18 until weaning of offspring, and to the offspring. T_3 was given to two groups of about 12-week-old methimazole-treated rats by daily subcutaneous injections at a dose of either 25 or 100 μg/kg for 8 weeks; methimazole treatment was continued during T_3 administration. Food and water intake were measured daily. For measurement of blood pressure, rats were anaesthetized with ketamine (50 mg/kg) and xylazine (10 mg/kg) given intraperitoneally and a cannula placed in the carotid artery. Blood pressure was measured via this cannula connected to a Statham P23 pressure transducer and Grass recorder. Heart rate was measured via ECG lead II attached to a Grass tachygraph and recorder. Rats were killed 24 hr after the last T_3 dose; blood was taken from the abdominal aorta.

Isolated cardiac muscles. Under anaesthesia, the chest wall was opened and the heart rapidly removed. The left and right atria and left ventricular papillary muscles were removed and suspended in organ baths in Tyrode solution containing $CaCl_2$ (1.8 mM) at 35° [8, 9]. Cumulative concentration–response curves

* Corresponding author. Tel. (61) 7 365 3098; FAX (61) 7 365 1766.

were measured to phenylephrine (in the presence of metoprolol, 1×10^{-5} M added 30 min previously) or noradrenaline and, following washout, to calcium chloride. Right ventricular free wall and left ventricular weights were measured. At the end of the experiments, papillary muscle dimensions were measured by micrometer under the loading conditions of the experiment; all tissues were blotted and weighed.

Thoracic aortic rings. Thoracic aortic rings (approximately 4 mm in length) were suspended with a resting tension of 10 mN and contracted twice with isotonic KCl (100 mM). The presence of endothelium was demonstrated by relaxation in response to acetylcholine (1×10^{-5} M). After washout, a cumulative concentration–response (contraction) curve was determined for phenylephrine.

Radioligand binding studies. Studies were performed using ^{125}I-cyanopindolol as a non-selective β-adrenoceptor radioligand to characterize left ventricular β-adrenoceptors. Left ventricular homogenates were prepared by homogenization in buffer A (10 mM Tris–HCl, 1 mM EDTA, pH 7.4), addition of an equal volume of 1 mM KCl, standing for 10 min followed by centrifugation twice at 100,000 *g* for 45 min. The pellet was resuspended as a 1:99 (w/v) dilution in buffer B (50 mM Tris–HCl, 10 mM $MgCl_2$, pH 7.4) [10]. Membranes were incubated in duplicate with ^{125}I-cyanopindolol (approx. 20,000 dpm/tube, 5 fmol) in the presence of increasing concentrations (1×10^{-9} to 1×10^{-4} M as non-specific binding) of the β_2-adrenoceptor selective antagonist, ICI 118,551, in a final volume of 300 μL of a buffer containing Tris–HCl (50 mM) and $MgCl_2$ (1 mM), pH 7.4, for 2 hr at 37°. Binding was analysed by the iterative curve-fitting program, LIGAND, as in previous studies [10]. The protein content of these left ventricular homogenates was 25.4 ± 2.0 (methimazole-treated), 36.1 ± 4.6 (methimazole-treated with T_3, 25 μg/kg/day), 52.6 ± 1.2 (methimazole-treated with T_3, 100 μg/kg/day) and 50.3 ± 2.2 (controls) mg/g tissue.

Data analysis. All results are given as mean ± SEM of the maximal increase in force of contraction (in mN: left atria, papillary muscles, thoracic aortic rings) or rate of contraction (in beats/min: right atria) and the potency ($-\log EC_{50}$) determined from the concentration giving half-maximal effects in individual concentration–response curves. Statistical significance was analysed by Student's *t*-test. $P < 0.05$ was considered significant.

Materials. The following compounds were purchased from the Sigma Chemical Co. (St Louis, MO, U.S.A.): (−)-noradrenaline hydrochloride, (−)-phenylephrine hydrochloride, (±)-metoprolol (+)-tartrate, 3,3',5'-triiodo-DL-thyronine (T_3) and methimazole. Plasma T_3 and thyroxine concentrations were measured by radioimmunoassay (Abbott Diagnostics, Sydney, Australia). All compounds except T_3 were dissolved in distilled water shortly before the experiments; T_3 as the free acid was dissolved in 40% dimethyl sulphoxide in water.

RESULTS

Thyroid function

Rats that received continuous methimazole treatment from gestation day 18 until 12 weeks of age showed symptoms of pronounced hypothyroidism such as low plasma T_3 concentrations (0.22 ± 0.04 ng/mL; control, 0.80 ± 0.10 ng/mL), marked growth retardation, decreased food and water intake, decreased rectal temperature and O_2 consumption, bradycardia, hypotension and increased thyroid gland weights (Table 1). Administration of T_3 (25 μg/kg for 8 weeks) to methimazole-treated rats starting at 12 weeks of age did not equally affect all parameters. Plasma T_3 increased to 0.60 ± 0.04 ng/mL; the bradycardia and decreased rectal temperature were fully reversed while food intake, O_2 consumption and body weight were increased towards control values; relative heart and kidney weights were increased above control values. Administration of T_3 (100 μg/kg for 8 weeks) starting at 12 weeks of age produced some signs of hyperthyroidism such as resting tachycardia, hypertension and cardiac hypertrophy although absolute values of other parameters such as plasma T_3 concentrations (0.64 ± 0.05 ng/mL), food and water intake, rectal temperature and O_2 consumption were not different from control rats (Table 1). Thoracic aortic rings were significantly smaller in hypothyroid rats; T_3 treatment (100 μg/kg/day) did not normalize these values. The basal force of contraction was increased in left ventricular papillary muscles yet decreased in left atria from hypothyroid rats; T_3 replacement returned the ventricular values to control but increased the force in left atria above control values (Table 1).

Positive inotropic responses

The selective α_1-adrenoceptor agonist, phenylephrine (in the presence of metoprolol), was used to define α_1-adrenoceptor-mediated positive inotropic responses in isolated rat left atria and left ventricular papillary muscles (Fig. 1). Responses to calcium chloride were measured in the same muscles to define the maximal contractile responses of the tissues. Phenylephrine produced significant increases in force of contraction in both left atria and left ventricular papillary muscles from control rats. Chronic hypothyroidism did not change atrial responses of phenylephrine relative to calcium chloride responses but phenylephrine caused decreases in force of contraction in left ventricular papillary muscles at concentrations up to 1×10^{-4} M. Administration of T_3 (25 μg/kg/day for 8 weeks) did not alter left atrial responses; phenylephrine produced neither increased nor decreased force in papillary muscles. After T_3 (100 μg/kg/day for 8 weeks), left atria showed negative inotropic responses with phenylephrine; papillary muscle responses to phenylephrine were now similar to control rats although maximal calcium chloride responses were reduced.

Noradrenaline increased force in left ventricular papillary muscles from control, hypothyroid and T_3-replacement rats (Fig. 2). The potency of noradrenaline was markedly reduced in hypothyroid rat tissues; after T_3 replacement, responses to lower noradrenaline concentrations were similar to control tissues. After T_3 (100 μg/kg/day) treatment, papillary

Table 1. Physiological parameters of rats

	Methimazole-treated			
	Only* (N = 14)	+T_3† (25 μg/kg) (N = 14)	+T_3† (100 μg/kg) (N = 20)	Control (N = 15)
Body weight (g)	166 ± 9	255 ± 15	262 ± 12	421 ± 16
Food intake (g/day)	12 ± 0.2	19.5 ± 0.8	28.5 ± 0.9	28 ± 0.6
Water intake (mL/day)	23 ± 0.9	27.1 ± 2.0	42.4 ± 2.4	44 ± 1.4
Rectal temperature (°C)	34.9 ± 0.2	38.2 ± 0.2	37.8 ± 0.2	37.8 ± 0.1
O_2 consumption (mL/min)	2.5 ± 0.2	6.9 ± 0.2	11.5 ± 0.5	12.6 ± 1.0
Heart rate *in vivo* (beats/min)	206 ± 10	277 ± 10	402 ± 17	251 ± 5
Systolic blood pressure (mmHg)	74 ± 7 (N = 6)	157 ± 11 (N = 8)	148 ± 11 (N = 6)	122 ± 6 (N = 7)
Diastolic blood pressure (mmHg)	60 ± 5 (N = 6)	122 ± 6 (N = 8)	104 ± 10 (N = 6)	113 ± 3 (N = 7)
Organ weights (mg/g body weight)				
Left ventricle	1.70 ± 0.05 (NS)	2.33 ± 0.08	3.08 ± 0.16	1.71 ± 0.02
Right ventricle	0.49 ± 0.02 (NS)	0.63 ± 0.03	0.94 ± 0.06	0.42 ± 0.01
Left atria	0.030 ± 0.003 (NS)	0.040 ± 0.003	0.067 ± 0.003	0.024 ± 0.002
Right atria	0.16 ± 0.015 (NS)	0.20 ± 0.014	0.28 ± 0.019	0.14 ± 0.01
Thyroid glands	0.86 ± 0.07	0.10 ± 0.01	0.048 ± 0.005	0.017 ± 0.002
Kidneys	6.8 ± 0.2 (NS)	9.7 ± 0.2	13.1 ± 0.5	6.9 ± 0.1
Left ventricular papillary muscles				
Length (mm)	6.2 ± 0.3 (NS)	6.8 ± 0.3 (NS)	6.8 ± 0.3 (NS)	5.7 ± 0.4
Width (mm)	0.88 ± 0.07 (NS)	1.1 ± 0.05 (NS)	1.1 ± 0.06 (NS)	1.1 ± 0.09
Wet weight (mg)	5.8 ± 0.7 (NS)	8.5 ± 0.7	11.7 ± 1.1	5.1 ± 0.5
Basal force of contraction (mN)				
Left atria	1.7 ± 0.2	4.0 ± 0.4	3.6 ± 0.3	2.4 ± 0.4
Left ventricular papillary muscles	4.1 ± 0.3	2.7 ± 0.3	2.6 ± 0.5	2.4 ± 0.3
Thoracic aortic dimensions (mm^2) (N = 6)				
Lumen area	1.03 ± 0.06	—	1.04 ± 0.07 (NS)	1.57 ± 0.04
Wall area	0.36 ± 0.02	—	0.41 ± 0.03 (NS)	0.47 ± 0.02

* These values were compared with those of control rats.
† Values were compared with rats given methimazole only.
NS, non-significant differences.

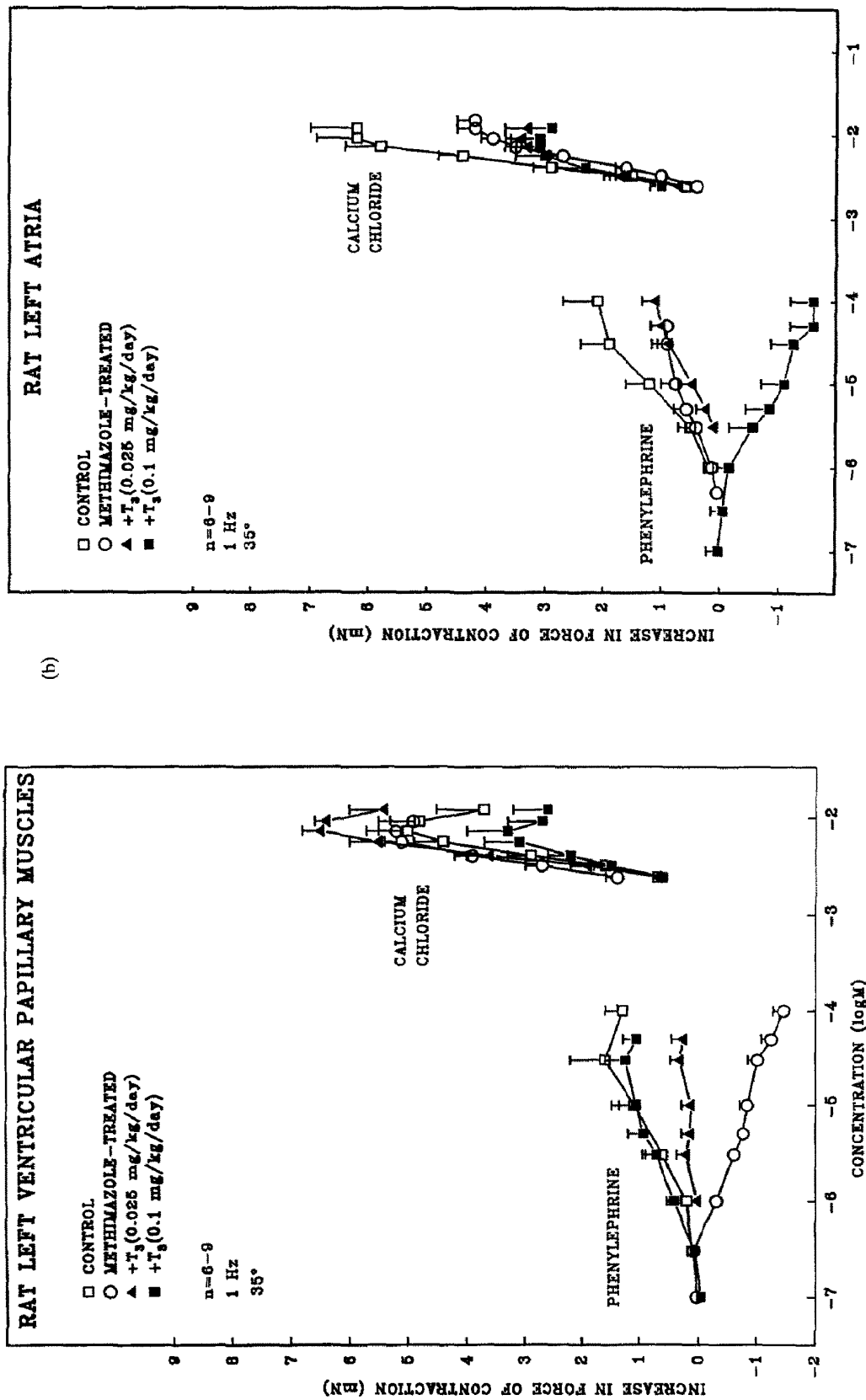

Fig. 1. Cumulative concentration–response curves for phenylephrine and calcium chloride in left ventricular papillary muscles (a) and in left atria (b) from control rats (□) or rats given methimazole alone (○) or with T_3 (25 μg/kg/day) (▲) or T_3 (100 μg/kg/day) (■). Phenylephrine potency and maximal response (in brackets) were: left ventricular papillary muscles: (□) 5.30 ± 0.11 (1.6 ± 0.6 mN); (■) 5.6 ± 0.2 (1.3 ± 0.4 mN); left atria: (○) 5.36 ± 0.13 (0.9 ± 0.3 mN); (▲) 4.97 ± 0.13 (1.1 ± 0.2 mN); (□) 5.16 ± 0.08 (2.1 ± 0.6 mN). Calcium chloride potency (maximal increase) was: left ventricular papillary muscles: (○) 2.48 ± 0.014 (5.5 ± 0.5 mN); (▲) 2.38 ± 0.03 (6.5 ± 0.3 mN); (■) 2.49 ± 0.01 (3.3 ± 0.7 mN); (□) 2.44 ± 0.02 (5.1 ± 0.8 mN); left atria: (○) 2.33 ± 0.03 (4.2 ± 0.3 mN); (▲) 2.46 ± 0.03 (3.4 ± 0.3 mN); (■) 2.50 ± 0.03 (3.2 ± 0.5 mN); (□) 2.36 ± 0.02 (6.4 ± 0.7 mN).

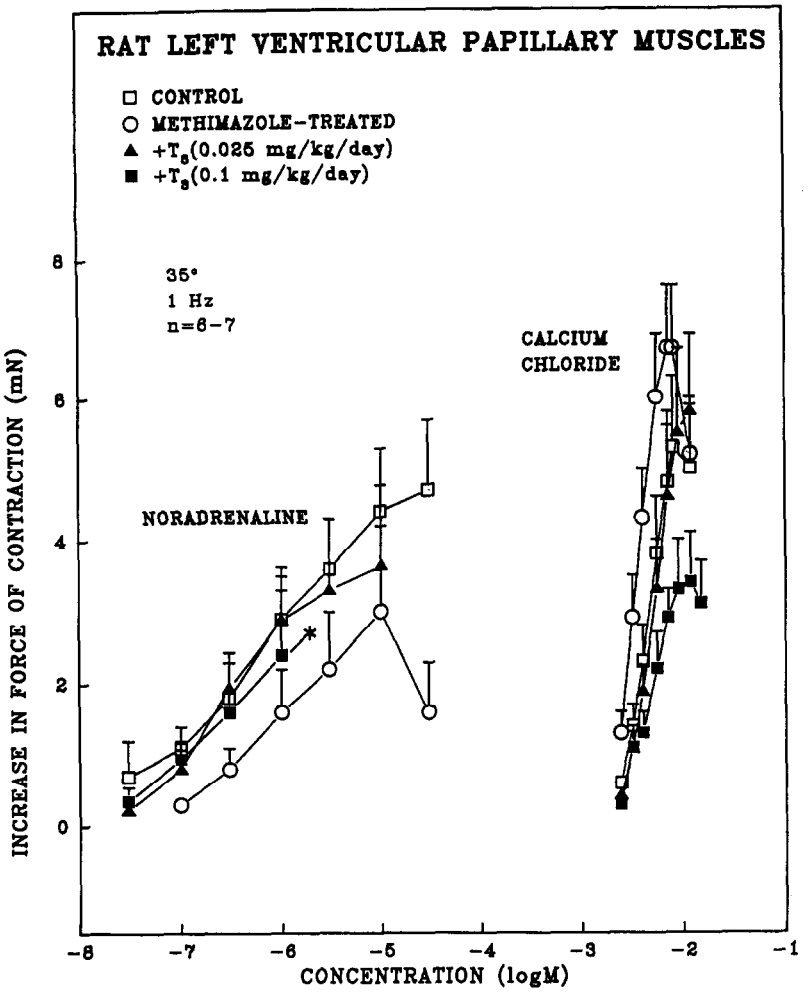

Fig. 2. Cumulative concentration–response curves for noradrenaline and calcium chloride in left ventricular papillary muscles from control rats (□) or rats given methimazole alone (○) or with T_3 (25 μg/kg/day) (▲) or T_3 (100 μg/kg/day) (■). Noradrenaline potency and maximal response (in brackets) were: (○) 5.79 ± 0.12 (3.0 ± 1.2 mN); (▲) 6.50 ± 0.13 (3.6 ± 1.1 mN); (■) 6.68 ± 0.10 (2.9 ± 0.6 mN); (□) 6.50 ± 0.13 (4.5 ± 1.0 mN). Calcium chloride potency (maximal increase) was: (○) 2.44 ± 0.02 (7.1 ± 1.1 mN); (▲) 2.28 ± 0.02 (5.8 ± 1.1 mN); (■) 2.32 ± 0.03 (3.3 ± 0.6 mN); (□) 2.45 ± 0.03 (5.1 ± 1.0 mN).

muscles developed arrhythmias at noradrenaline concentrations of 3×10^{-6} M and higher.

Positive chronotropic responses

Noradrenaline produced similar chronotropic responses in right atria from control and hypothyroid rats (Fig. 3). T_3 treatment at either 25 or 100 μg/kg/day increased noradrenaline potency without alteration of the maximal response to noradrenaline.

Vasoconstrictor responses

α-Adrenoceptor agonists such as phenylephrine contract isolated thoracic aortic rings. The potency of phenylephrine was reduced in hypothyroid thoracic aortic rings (controls, 7.03 ± 0.09; hypothyroid, 6.66 ± 0.03). T_3 treatment returned phenylephrine potency values to those of controls (100 μg/kg/day; 7.13 ± 0.05) (Fig. 4).

Cardiac β-adrenoceptors

After continuous administration of methimazole, left ventricular β_1-adrenoceptor density was 82.2 ± 8.9 fmol/mg protein (control rats, 60.5 ± 8.4 fmol/mg protein). β_1-Adrenoceptor density was unchanged after treatment with T_3 (25 μg/kg/day) (88.5 ± 9.3 fmol/mg protein) but increased after T_3 (100 μg/kg/day) treatment to 121 ± 22 fmol/mg protein. Left ventricular β_2-adrenoceptor density was markedly increased after methimazole treatment and T_3 replacement in these rats (control, 19.2 ± 3.1; methimazole-treated, 67.0 ± 8.9; + T_3 25 μg/kg/day, 82.4 ± 10.7; 100 μg/kg/day, 55.8 ± 5.4 fmol/mg protein).

DISCUSSION

Thyroid hormones play an essential role in normal

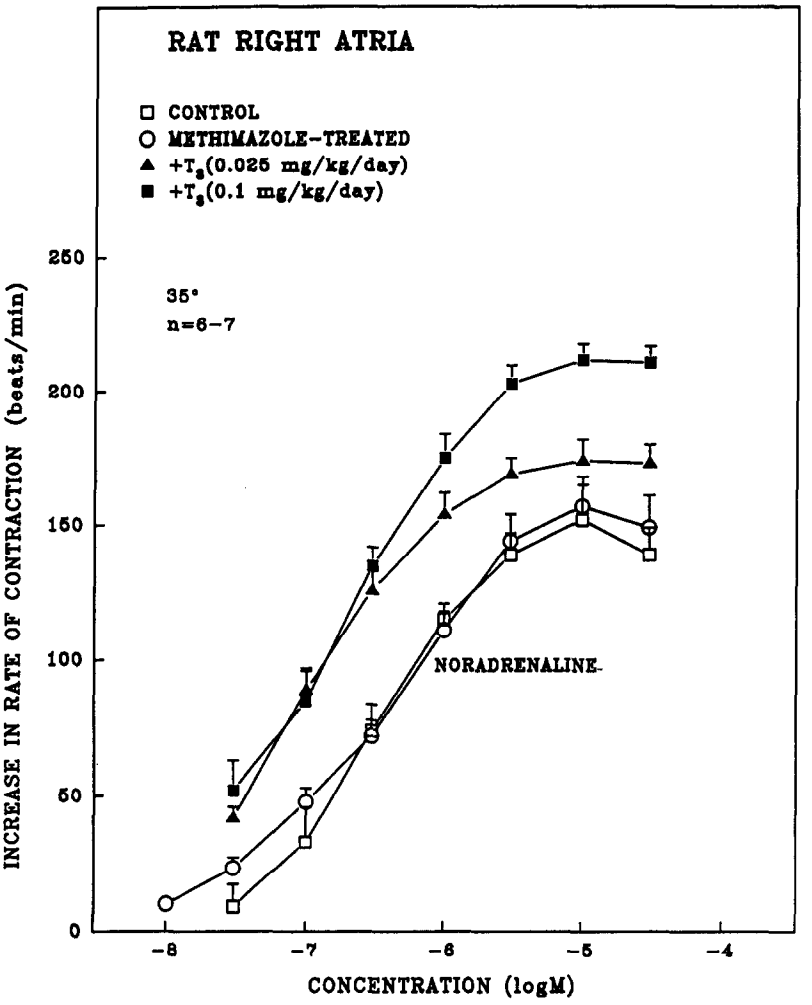

Fig. 3. Cumulative concentration–response curves for adrenaline in right atria from control rats (□) or rats given methimazole alone (○) or with T_3 (25 μg/kg/day) (▲) or T_3 (100 μg/kg/day) (■). Noradrenaline potency and maximal response (in brackets) were: (○) 6.45 ± 0.07 (157 ± 11 bpm); (▲) 6.91 ± 0.10 (174 ± 8 bpm); (■) 6.79 ± 0.09 (213 ± 6 bpm); (□) 6.51 ± 0.14 (160 ± 11 bpm).

development with marked changes, especially in cardiovascular parameters, in hypothyroid states [1, 11, 12]. Thyroid hormone replacement, particularly in adult-onset hypothyroidism, reversed the biochemical changes of hypothyroidism and led to clinical improvement of the cardiovascular symptoms [6, 7]. In the present study, the physiological changes in rats resulting from neonatal hypothyroidism were variably reversed by 8 weeks of T_3 replacement begun at 12 weeks of age. Body weight did not return to control values, unlike the metabolic parameters. However, T_3 replacement produced cardiac signs of hyperthyroidism such as tachycardia and ventricular hypertrophy. These cardiac changes may be related to T_3-induced changes in cardiac thyroid hormone receptors [13].

Positive inotropic responses to β-adrenoceptor agonists were decreased in left atria from hypothyroid rats; thyroid hormone replacement restored the responses [5]. Our study extends these results to the left ventricle by showing that β-adrenoceptor agonists were less potent as positive inotropic compounds in hypothyroid rats and that these changes were reversed by thyroid hormone replacement. Papillary muscles from hypothyroid rats treated with T_3 (100 μg/kg/day) showed an increased sensitivity to the arrhythmic effects of noradrenaline; this is a characteristic of hyperthyroid ventricular tissues [14].

Inotropic responses mediated by α-adrenoceptors in disease states have received less attention [15]. Phenylephrine was a more potent positive inotropic compound in left atria from adult-onset hypothyroid rats; thyroid hormone replacement reversed this increase [4, 5]. Our study showed similar left atrial responses to phenylephrine in normal and neonatal-onset hypothyroid rats; however, left ventricular responses to phenylephrine were absent in hypothyroid rats. Thyroid hormone replacement reversed this loss of responsiveness in the ventricle; in the

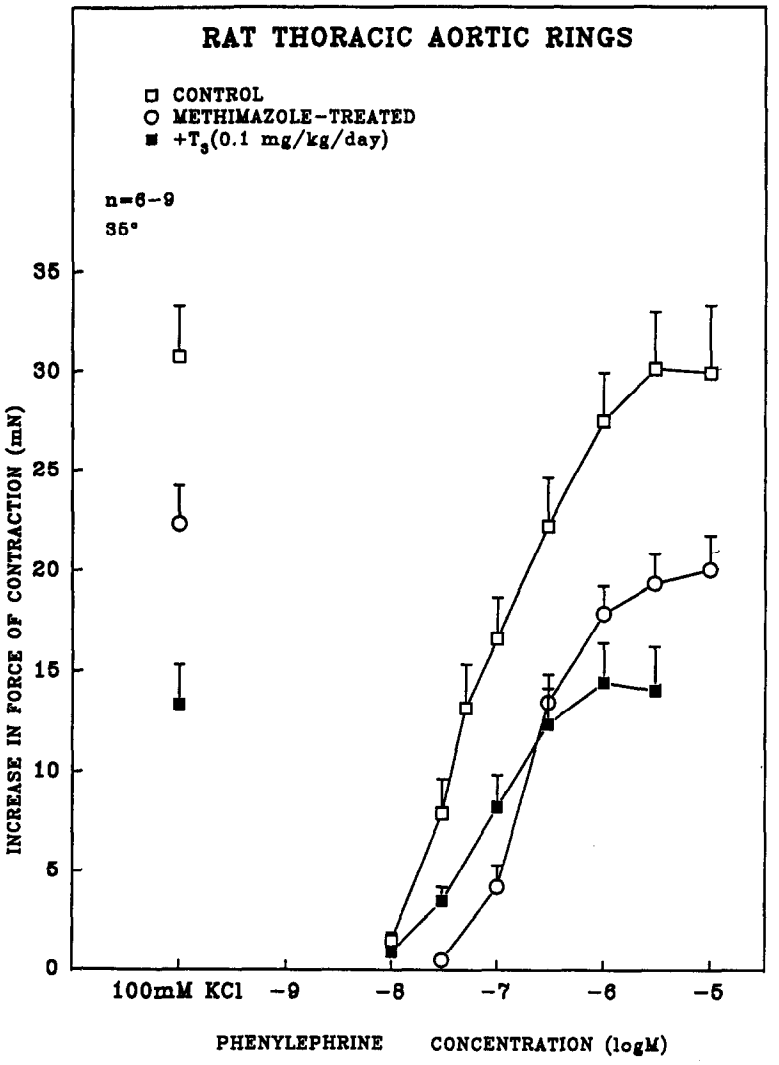

Fig. 4. Cumulative concentration–response curves for phenylephrine in thoracic aortic rings from control rats (□) or rats given methimazole alone (○) or with T_3 (100 μg/kg/day) (■).

left atria, T_3 replacement (100 μg/kg/day) led to a loss of responsiveness to phenylephrine. These differences between disease-induced alterations in atrial and ventricular responsiveness indicate that the left atria is inadequate to predict ventricular changes [8]. The reason for the different atrial and ventricular responses is not obvious. Contractile proteins are altered in hypothyroidism; for example, myosin heavy chain shifts from the α- to the β-isoform [13]. Atria contain a different myosin isoform to ventricles [16]; differential regulation by thyroid hormones may be involved in the physiological differences. Further, hypothyroid rats are also growth hormone-deficient [17]; however, genetically growth hormone-deficient rats showed increased inotropic responses to phenylephrine in left atria and ventricles [10] unlike the present results in hypothyroid left ventricles.

In contrast to the decreased inotropic responsiveness of the heart in hypothyroidism, positive chronotropic responses to noradrenaline were unchanged. T_3 replacement (25 μg/kg) produced the increase in noradrenaline potency characteristic of hyperthyroidism [14]. α-Adrenoceptor agonists were less potent vasoconstrictors in thoracic aorta from hypothyroid rats [18] as in the present study. Our results show that T_3 replacement restored responsiveness indicating a specific T_3-mediated defect.

Decreases in β-adrenoceptor density due to adult-onset hypothyroidism have been widely reported [3]; short perinatal hypothyroidism prevented the synthesis of β-adrenoceptors [2]. In contrast, our studies in adult, continuously hypothyroid rats show an increased β-adrenoceptor density, especially of the β_2-subtype, in the left ventricle, together with reduced inotropic responses. This implies deficient post-receptor mechanisms, for example a reduced

adenylate cyclase activity [19], to account for the decreased inotropic responses [19]. T_3 replacement at 100 μg/kg/day begun in adult life increased β_1-adrenoceptor density above hypothyroid values to values similar to those in hyperthyroid rat hearts [3]; responses returned to control values although the ventricle was more likely to become arrhythmic with noradrenaline.

The clinical importance of these results lies in the apparent reversibility of the function of cardiac adrenoceptors by thyroid hormone replacement. The caution is that cardiac signs of hyperthyroidism may occur during T_3 replacement leading to tachycardia, hypertrophy and possibly arrhythmias.

Acknowledgements—These studies were supported by the National Health and Medical Research Council and the National Heart Foundation of Australia.

REFERENCES

1. Klein I and Ojamaa K, Cardiovascular manifestations of endocrine disease. *J Clin Endocrinol Metab* **75**: 339–342, 1992.
2. Pracyk JB and Slotkin TA, Thyroid hormone regulates ontogeny of *beta* adrenergic receptors and adenylate cyclase in rat heart and kidney: effects of propylthiouracil-induced perinatal hypothyroidism. *J Pharmacol Exp Ther* **261**: 951–958, 1992.
3. Bilezikian JP and Loeb JN, The influence of hyperthyroidism and hypothyroidism on α- and β-adrenergic receptor systems and adrenergic responsiveness. *Endocr Rev* **4**: 378–388, 1983.
4. Nakashima N, Maeda K, Sekiya A and Hagino Y, Effect of hypothyroid status on myocardial responses to sympathomimetic drugs. *Jpn J Pharmacol* **21**: 819–825, 1971.
5. Kunos G, Thyroid hormone-dependent interconversion of myocardial α- and β-adrenoceptors in the rat. *Br J Pharmacol* **59**: 177–189, 1977.
6. Keating FR Jr, Parkin TW, Selby JB and Dickinson LS, Treatment of heart disease associated with myxedema. *Prog Cardiovasc Dis* **3**: 364–381, 1961.
7. Crowley WF Jr, Ridgway EC, Bough EW, Francis GS, Daniels GH, Kourides IA, Myers GS and Maloof F, Noninvasive evaluation of cardiac function in hypothyroidism. Response to gradual thyroxine replacement. *N Engl J Med* **296**: 1–6, 1977.
8. Brown L, Sernia C, Newling R and Fletcher P, Comparison of inotropic and chronotropic responses in rat isolated atria and ventricles. *Clin Exp Pharmacol Physiol* **18**: 753–760, 1991.
9. Brown L, Cragoe EJ Jr, Abel KC, Manley SW and Bourke JR, Amiloride analogues induce responses in isolated rat cardiovascular tissues by inhibition of Na^+/Ca^{2+} exchange. *Naunyn Schmiedebergs Arch Pharmacol* **344**: 220–224, 1991.
10. Brown L, Wyse B and Sernia C, Adrenoceptor-mediated cardiac and vascular responses in genetically growth hormone-deficient rats. *Biochem Pharmacol* **45**: 2223–2229, 1993.
11. Pic P and Bouquin JP, Thyrotropic hormone and thyroidal function in fetal rat. *J Dev Physiol* **7**: 207–214, 1985.
12. Kolár F, Seppet EK, Vetter R, Procházka J, Grünermel J, Zilmer K and Ostádal B, Thyroid control of contractile function and calcium handling in neonatal rat heart. *Pflügers Arch/Eur J Physiol* **421**: 26–31, 1992.
13. Balkman C, Ojamaa K and Klein I, Time course of the *in vivo* effects of thyroid hormone on cardiac gene expression. *Endocrinology* **130**: 2001–2006, 1992.
14. Fox AW, Juberg EN, May JM, Johnson RD, Abel PW and Minneman KP, Thyroid status and adrenergic receptor subtypes in the rat: comparison of receptor density and responsiveness. *J Pharmacol Exp Ther* **235**: 715–723, 1985.
15. Benfey BG, Function of myocardial α-adrenoceptors. *Life Sci* **46**: 743–757, 1990.
16. Morkin E, Regulation of myosin heavy chain genes in the heart. *Circulation* **87**: 1451–1460, 1993.
17. Hendrich CE and Porterfield SP, Serum growth hormone levels in hypothyroid and GH-treated thyroidectomized rats and their progenies. *Proc Soc Exp Biol Med* **201**: 296–302, 1992.
18. Gunasekera RA and Kuriyama H, The influence of thyroid states upon responses of the rat aorta to catecholamines. *Br J Pharmacol* **99**: 541–547, 1990.
19. Brodde O-E, Schümann H-J and Wagner J, Decreased responsiveness of the adenylate cyclase system on left atria from hypothyroid rats. *Mol Pharmacol* **17**: 180–186, 1980.