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Hypothyroidism changes adrenoceptor- and muscarinic receptor-mediated blood pressure responses

Takeshi Iwata[a], Hideo Honda[a,b,*], Hitomi Matsuda[a], Miwa Kondo[a], Jun Taniguchi[c], Takashi Miwa[c], Kenichi Kumasaka[a], Hiroko Moroe[a], Yoko Notoya[c]

[a]*Second Department of Physiology, School of Medicine, Showa University, Hatanodai 1-5-8, Shinagawa-ku, Tokyo 142-8555, Japan*
[b]*Department of Pharmacology, School of Pharmacy, Tokyo University of Pharmacy and Life Science, 1432-1, Horinouchi, Hachioji, Tokyo 193-0392, Japan*
[c]*Department of Internal Medicine, Tokyo Medical University, 6-7-1, Nishi-shinjuku, Shinjuku, Tokyo 160-0023, Japan*

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Abstract

Hypothyroidism was induced by the administration of 0.03% methimazole to drinking water for 1, 2 or 6 weeks to study whether there is a change in adrenoceptor- and muscarinic receptor-mediated blood pressure responses in hypothyroid rats. After 1, 2 and 6 weeks of treatment, the pressor response to norepinephrine was progressively suppressed, and after 6 weeks a significant suppression was observed as compared to control. The depressor response induced by isoprenaline, acetylcholine or sodium nitroprusside was not significantly different between control and hypothyroid rats at any time. The pressor response induced by N^G-nitro-L-arginine (L-NOARG), an inhibitor of nitric oxide (NO) synthase, was significantly reduced in hypothyroid rats after 1, 2 or 6 weeks of treatment, and the magnitude of the reduction was almost the same for three groups. These results indicated that hypothyroidism causes a time-dependent decrease in pressor responses mediated by α-adrenoceptors, but a time-independent decrease in those induced by L-NOARG, and suggest that a progressive decrease in α-adrenoceptor-mediated pressor responses occurs in hypothyroidism; however, the decrease in basal NO production and/or release in the peripheral vasculature already occurs in hypothyroid rats at an early stage of the disease.

Keywords: Hypothyroidism; Blood pressure; Adrenoceptor; Muscarinic receptor; Nitric oxide (NO)

1. Introduction

Hypothyroidism is characterized by arterial hypotension with reduced cardiac output and increased vascular resistance (Bradley et al., 1974). These symptoms are suggestive of the existence of a hypoadrenergic state (Polikar et al., 1993). It is accepted that there is a hypothyroid-induced desensitization of tissues to adrenergic stimuli (Coulombe et al., 1976; Polikar et al., 1990; Fagius et al., 1990), but there is an opposite theory. For instance, vascular smooth muscles have an increased sensitivity to vasoconstrictors in experimental models of hypothyroidism (Macmillan and Rand, 1962; Rosenqvist and Boreus, 1972).

Endothelial nitric oxide (NO) makes an important contribution to cardiovascular regulation through the release of vasoconstrictor and vasodilator factors (Furchigott, 1983; Palmer et al., 1987, 1988). The administration of specific inhibitors of NO synthesis to rats results in a substantial increase in blood pressure (Gardiner et al., 1990; Kiff et al., 1991; Rees et al., 1989) and this increase is reversed by the i.v. administration of L-arginine but not D-arginine (Whittle et al., 1989), suggesting that NO has an important role in controlling tone in the peripheral vasculature. A reduction in endogenous NO biosynthesis may be involved in the pathogenesis of some forms of hypertension (Moncada et

* Corresponding author. Department of Pharmacology, School of Pharmacy, Tokyo University of Pharmacy and Life Science, 1432-1, Horinouchi, Hachioji, Tokyo 193-0392, Japan. Tel./fax: +81 426 76 4529.
E-mail address: hhonda@ps.toyaku.ac.jp (H. Honda).

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al., 1991), and excessive formation of NO contributes to arterial hypotension of cirrhotic rats (Pizcueta et al., 1992). These studies have focused primarily on vascular response to acetylcholine, which are reported to be impaired in atherosclerosis (Guerra et al., 1989, Honda et al., 2001a, Honda et al., 2001b), diabetes (Oyama et al., 1986), and a variety of models of hypertension (Lockette et al., 1986; Konishi and Su, 1983; Winquist et al., 1984).

It is well known that the alterations in both cardiac and vascular functions through adrenoceptor, muscarinic receptor and NO systems play important roles in regulating systemic blood pressure. It has been suggested that pressor responses induced by norepinephrine (Vargas et al., 1991) and a NO synthase inhibitor, N^G-nitro-L-arginine methyl ester (Vargas et al., 1994), are suppressed by methimazole treatment for 5 and 6 weeks, respectively. In these studies, methimazole treatment for only one period (5 or 6 weeks) was used. To our knowledge, there is no report in which the blood pressure response was compared at different stages of hypothyroidism. Therefore, the aim of the present study was to compare the blood pressure responses mediated by adrenoceptor, muscarinic receptor and NO systems at different stages of hypothyroidism in rats. This was done first by making models of hypothyroidism of different disease duration, then comparing blood pressure responses to the vasoactive compounds.

2. Materials and methods

2.1. Animals and induction of acute hypothyroidism

This investigation conforms with the Guide for the Care and Use of Laboratory Animals, published by the U.S. National Institute of Health (NIH Publication No. 85-23, revised 1996). Seven-week-old male rats of Wistar strain were maintained in temperature (23±1 °C)-, humidity (55±5%)- and light (12 h light/day)-controlled quarters and were given rat chow and drinking water ad libitum. Hypothyroidism was induced by the addition of 0.03% methimazole to their drinking water over a period of 1, 2 or 6 weeks. Age-matched control rats were given plain water (Ampong et al., 2002).

2.2. Assessment of hypothyroid state

To confirm the establishment of hypothyroidism, body weight was recorded daily. Heart and thyroid weights were measured at the end of treatment period.

2.3. Measurements of arterial blood pressure and heart rate

In anaesthetized rats (with sodium pentobarbital 40 mg/kg i.p.), a polyethylene catheter containing heparin dissolved in isotonic saline was inserted into the carotid artery for measurement of blood pressure with a pressure transducer. An additional catheter was inserted into the femoral vein for injection of drugs. Heart rate was monitored via the systolic blood pressure pulse (Honda et al., 2003). The doses of norepinephrine and isoprenaline were injected at 0.3 and 3.0 μg/kg. Acetylcholine and sodium nitroprusside were injected at the doses of 0.3 or 3.0 μg/kg, and 1 or 10 μg/kg, respectively. L-NOARG was injected at doses of 0.3 and 3.0 mg/kg. These doses were found to be optimal from the dose–effect relationship for blood pressure change in preliminary studies. The minimum time between treatments was 10 min and the next treatment was not performed until the rat recovered from the change in blood pressure after each dose. Percentage change in blood pressure was defined as the change in blood pressure after the drug treatment divided by blood pressure before it. Percentage change in heart rate was also calculated in the same way.

2.4. Drugs and chemicals

Methimazole (Sigma, St. Louis, MO, USA) was dissolved in distilled water. Norepinephrine, isoprenaline, acetylcholine, sodium nitroprusside or L-NOARG (Sigma) was dissolved in isotonic saline and was administered at 1.0 ml/kg except L-NOARG (3.0 mg/kg) which was administered at 3.0 ml/kg.

2.5. Statistical analysis

The experimental values were expressed as the means± S.E.M. Statistical analysis of data was performed with a Student's *t*-test. Differences were considered significant for $P<0.05$.

3. Results

3.1. Effects of methimazole treatment on morphological and haemodynamic parameters

Table 1 summarizes the effect of methimazole treatment on the various parameters monitored. The body weight of all methimazole-treated rats was significantly lower than that of their age-matched controls. The mean arterial blood pressure was significantly decreased only in rats treated for 6 weeks. The heart rate was significantly decreased in methimazole-treated rats. Heart weight was also decreased but thyroid weight was increased in methimazole-treated rats.

3.2. Effects of norepinephrine and isoprenaline on blood pressure

Norepinephrine-induced hypertensive responses were transient, with the mean arterial pressure returning to basal levels within 1–2 min, but the duration of isoprenaline hypotensive responses was slightly longer (3–4 min) in both control and methimazole-treated rats. The pressor responses

Table 1
Morphological and haemodynamic variables

		BW (g)	MAP (mm Hg)	HR (beat/min)	HW (/100 g)	TW (/100 g)
One week	Control	309.3±7.4	111.8±4.4	327.8±15.5	300.5±9.2	7.2±0.3
	Hypothyroid	283.0±5.2[a]	101.3±7.4	241.7±14.3[a]	257.8±3.7[a]	14.1±1.0[a]
Two weeks	Control	319.1±7.1	113.9±7.6	335.7±10.0	298.8±4.7	8.1±0.5
	Hypothyroid	292.6±5.1[a]	106.4±7.1	238.4±10.9[a]	246.8±4.3[a]	18.4±0.6[a]
Six weeks	Control	398.0±11.8	105.7±3.2	286.8±14.3	285.5±4.7	6.5±0.4
	Hypothyroid	282.9±4.7[a]	97.5±2.6[b]	212.9±6.7[a]	226.9±3.8[a]	28.6±1.9[a]

Body weight (BW), mean arterial pressure (MAP) heart rate (HR), heat weight (HW), and thyroid weight (TW) in control and hypothyroid rats. Each value is mean±S.E.M. from six to seven rats.

[a] $P<0.01$ from control.

[b] $P<0.05$ from control.

induced by 3.0 μg/kg norepinephrine were 31.9±1.4%, 43.8±3.7% and 42.7±2.5% for 1, 2 and 6 weeks, respectively, in control rats, and 27.7±2.7%, 32.0±9.6% and 33.9±3.0% for 1, 2 and 6 weeks, respectively, in methimazole-treated rats. Methimazole treatment for 6 weeks significantly decreased norepinephrine-induced pressor responses, but had no significant influence on them after for 1 and 2 weeks (Fig. 1A). Tachycardia was observed in response to norepinephrine in both groups. There was no significant difference in the change in heart rate in response to norepinephrine between the groups at any time (1W: control 5.4±3.7% methimazole-treated 9.0±1.2%, 2W: control 8.2±4.1% methimazole-treated 1.3±3.3%, 6W: control 10.4±1.8% methimazole-treated 5.3±4.9%).

The suppressive response induced by 3.0 μg/kg isoprenaline was −52.9±2.7%, −54.6±3.7% and −57.3%±3.6% for 1, 2 and 6 weeks, respectively, in control rats, and −48.7±5.1%, −59.1±4.6% and −57.9±5.4% for 1, 2 and 6 weeks, respectively, in methimazole-treated rats. No significant difference in isoprenaline-induced suppressive responses was seen between the groups at any time (Fig. 1B). Tachycardia was observed in response to isoprenaline and there was also no significant difference between the groups at any time (1W: control 26.8±3.8% methimazole-treated 34.8±3.1%, 2W: control 29.0±3.7% methimazole-treated 33.3±5.6%, 6W: control 30.5±7.2% methimazole-treated 37.8±5.0%). Norepinephrine- and isoprenaline-induced responses were significantly inhibited by 90 μg/kg phentolamine and 90 μg/kg propranolol, respectively (data not shown).

3.3. Effects of acetylcholine and sodium nitroprusside on blood pressure

Hypotensive responses to acetylcholine were transient, with the mean arterial pressure returning to control levels within 1–2 min, but the duration of the suppressive effects of sodium nitroprusside was slightly longer (3–4 min) in

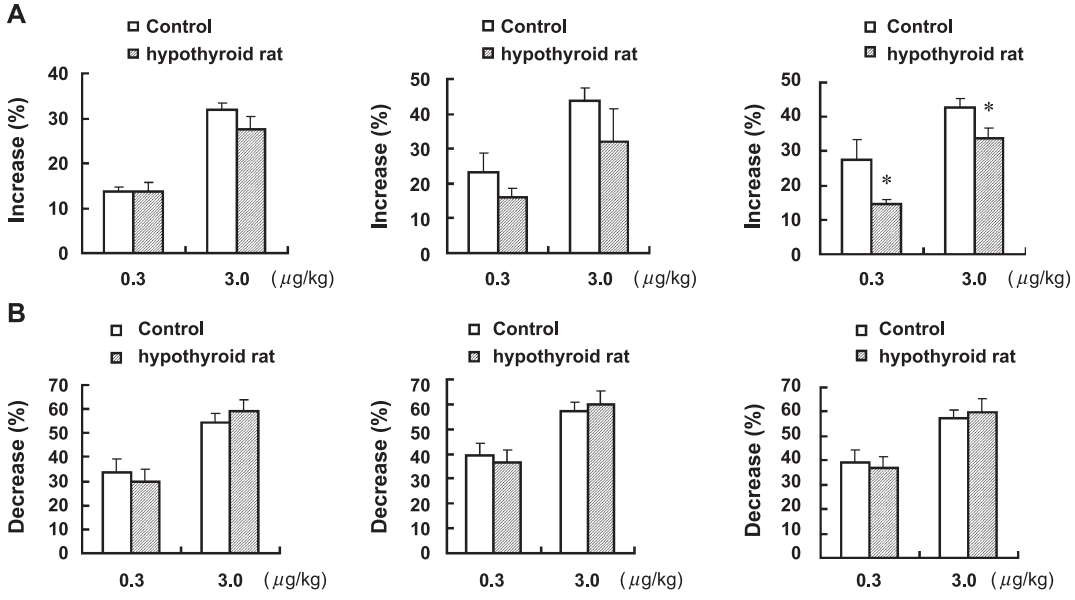

Fig. 1. Effects of norepinephrine (0.3, 3 μg/kg) (A) and isoprenaline (0.3, 3 μg/kg) (B) on mean arterial pressure in control and hypothyroid rats. Values are means±S.E.M. from six or seven rats. *$P<0.05$ from control rats.

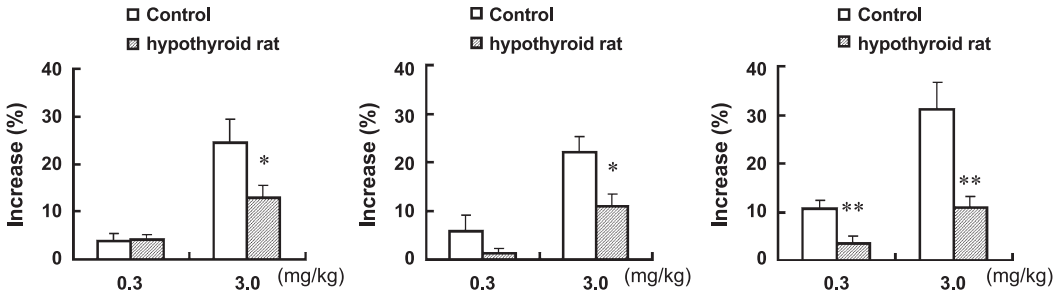

Fig. 2. Effects of N^G-nitro-L-arginine (0.3, 3 mg/kg) on mean arterial pressure in control and hypothyroid rats. Values are means±S.E.M. from six or seven rats. *P<0.05, **P<0.01 from control rats.

both control and methimazole-treated rats. The suppressive responses induced by 3.0 μg/kg acetylcholine were −48.6±3.5%, −59.4±2.4% and −56.7±4.7% for 1, 2 and 6 weeks, respectively, in control rats, and −49.3±4.5%, −61.3±4.6% and −61.9±6.3% for 1, 2 and 6 weeks, respectively, in methimazole-treated rats. There was no difference between the groups at any time. Transient reflex tachycardia was produced in response to acetylcholine and no significant difference was seen between the groups at any time (1W: control 7.2±1.6% methimazole-treated 6.4±0.6%, 2W: control 5.6±0.9% methimazole-treated 6.7±1.4%, 6W: control 5.8±3.0% methimazole-treated 5.2±0.8%). Acetylcholine-induced responses were significantly inhibited by 10 μg/kg atropine (data not shown).

The suppressive responses induced by 10 μg/kg sodium nitroprusside were −46.3±2.5%, −47.4±5.0% and −60.4±6.5% for 1, 2 and 6 weeks, respectively, in control rats, and −37.7±4.8%, −46.6±6.1% and −46.8±4.7% for 1, 2 and 6 weeks, respectively, in methimazole-treated rats. No significant difference was seen between the groups at any time. Transient reflex tachycardia was produced in response to sodium nitroprusside and there was also no significant difference between the groups at any time (1W: control 8.8±2.2% methimazole-treated 6.4±2.4%, 2W: control 7.1±2.0% methimazole-treated 5.6±1.6%, 6W: control 7.1±8.3% methimazole-treated 8.3±1.1%).

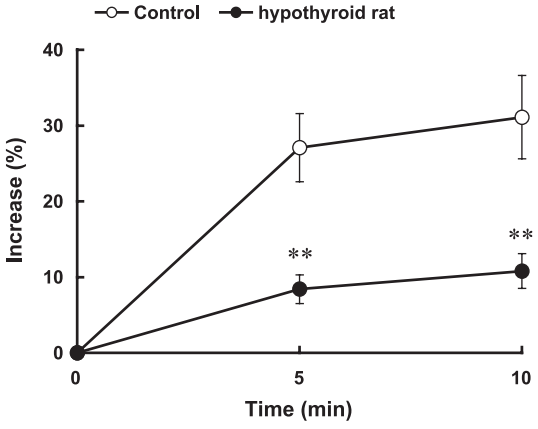

Fig. 3. Effects of N^G-nitro-L-arginine (3 mg/kg) on mean arterial pressure in control (○) and hypothyroid rats (●). Hypothyroidism was induced by methimazole treatment for 6 weeks. Values are means±S.E.M. from six rats. **P<0.01 from control rats.

3.4. Effects of L-NOARG on blood pressure

To clarify whether NO is involved in the alteration in blood pressure responses in hypothyroidism, the pressor responses to L-NOARG were investigated at different stages of hypothyroidism in rats. The onset of L-NOARG-induced hypertension developed more slowly, with the maximal change in mean arterial pressure occurring between 5 and 10 min after injection in both control and methimazole-treated rats. The increased responses induced by 3.0 mg/kg L-NOARG were 24.6±4.8%, 21.9±5.0% and 31.1±5.5% at 1, 2 and 6 weeks, respectively, in control rats and 12.9±2.5, 10.9±2.5 and 11.0±2.2% for 1, 2 and 6 weeks, respectively, in methimazole-treated rats. Methimazole treatment at all times significantly decreased 3.0 mg/kg L-NOARG-induced hypertensive responses (Fig. 2). Moderate bradycardia was observed after injection of L-NOARG in both groups, and there was no difference between the groups at any time (1W: control 16.0±3.5% methimazole-treated 11.9±2.9%, 2W: control 8.9±4.2% methimazole-treated 12.7±4.8%, 6W: control 11.8±1.9% methimazole-treated 14.5±1.4%).

In both control and methimazole-treated rats (6 weeks), intravenous injection of L-NOARG produced a time-dependent increase in arterial blood pressure. Methimazole treatment for 6 weeks significantly decreased the blood pressure responses induced by 3 mg/kg of L-NOARG (Fig. 3).

4. Discussion

The effectiveness of adding 0.03% methimazole to drinking water for 1, 2 or 6 weeks was confirmed by the parameters monitored. Body weight, heart weight and heart rate were significantly decreased but thyroid weight was increased after 1 week of methimazole treatment. This concentration of methimazole has already been shown to result in stable and reproducible hypothyroidism (Sabio et al., 1994; Vargas et al., 1995; Ampong et al., 2002). These results suggest that 1 week of methimazole treatment is

sufficient to produce hypothyroidism in rats. In a preliminary study, we observed that both serum thyroxine and triiodothyronine levels were significantly decreased and reached critical levels after only 1 week of methimazole treatment, and serum thyroid stimulating hormone levels were already increased by 1 week of methimazole treatment.

After 1 or 2 weeks of methimazole treatment, the pressor response to norepinephrine tended to be lower than that in control rats, but after 6 weeks, a marked reduction was observed as compared to control. It is suggested that hypothyroidism has a time-dependent and progressive influence on blood pressure responses mediated by α_1-adrenoceptors. We have previously reported that norepinephrine-induced contraction is decreased in the aorta of rats treated with methimazole for 2 and 6 weeks (Ampong et al., 2002). The vascular responsiveness to norepinephrine and other α_1-adrenoceptor agonists is decreased in several preparations from hypothyroid animals (Rahmani et al., 1987; Sabio et al., 1994; Grieve et al., 1999; Moreno et al., 2003). Recently, it has been suggested that the enhanced production of NO by the endothelium plays a role in the hyporesponsiveness to α_1-adrenergic agonists (Grieve et al., 1999). In contrast, hypothyroidism may reduce the responsiveness to vasoconstrictors even in the absence of NO (Vargas et al., 1995). Quesada et al. (2002) reported that in hypothyroid rats, NO synthase (NOS) activity showed a heterogeneous pattern, with significant increases in both ventricles but significant reduction in the aorta, while in the vena cava, renal cortex and medulla the enzyme activity also tended to be higher, but a significance was not reached. In the present study, we investigated whether resting release/production of NO is involved in the pathogenesis of the alteration in blood pressure responses in hypothyroidism. This hypothesis was tested by administering L-NOARG, an inhibitor of NOS (Ishii et al., 1990; Honda et al., 1999; Honda et al., 2001a,b; Unemoto et al., 2003), to control and hypothyroid rats. The findings showed that the pressor response induced by L-NOARG through inhibition of NO production was significantly smaller in hypothyroid rats than in control rats, and it already occurred in hypothyroid rats at an early stage of the disease, namely after 1 week of methimazole treatment. The reduced pressor responsiveness to L-NOARG in hypothyroidism may be due to a decrease in resting NO production by the vascular endothelium. Therefore, these results suggest that the hyporesponsiveness to norepinephrine observed after methimazole treatment for 6 weeks cannot be attributed to the enhanced NO production in the endothelium. In the chronic phase of hypothyroidism, the sensitivity to a number of vasoconstrictors is reduced in rat aorta (Rahmani et al., 1987; Gunasekera and Kuriyama, 1990; Grieve et al., 1999; Ampong et al., 2002). The inhibitory effect of hypothyroidism on phenylephrine-induced contractions was restored by thyroxine replacement therapy (Grieve et al., 1999). Considering the present results and those in the literature, we suggest that the sensitivity to vasoconstrictors in hypothyroidism is time-dependent.

The depressor responses to both acetylcholine, a NO producer in the endothelium, and sodium nitroprusside, a NO donor, were not significantly different between control and hypothyroid rats at any time. The dissociation between the responses to L-NOARG and acetylcholine in hypothyroid rats suggests that there is a difference in basal NO synthesis between hypothyroid and control rats, whereas the response to endothelium stimulation by acetylcholine is maintained, as previously reported in rat aorta (Ampong et al., 2002). Studies with an inhibitor of NOS may provide support for the notion that NO is not the sole mediator of endothelium-dependent responses to acetylcholine (Fulton et al., 1992; Moroe et al., 2004). Thus the release of the vasodilator endothelium-derived hyperpolarizing factor (Chen et al., 1991) may also be implicated in the dissociation between the response to L-NOARG and to acetylcholine.

The suppressive response induced by isoprenaline was not significantly different between the groups at any time. We previously reported that the isoprenaline-induced relaxation of rat isolated aortic rings significantly increased the sensitivity of dose–response curve but the maximum relaxation was not different in hypothyroid rats after 2 and 6 weeks as compared to their controls (Ampong et al., 2002). It is well known that blood pressure responses are mainly dependent on resistance vessels rather than elastic vessels such as the aorta. This is one reason why there is a difference in isoprenaline-induced responses between blood pressure in vivo and aortic relaxing responses in vitro. Another possible mechanism for the luck of significant differences in isoprenaline-induced suppressive responses between the groups may be due to the sum of the supersensitivity of β-adrenoceptors in the vasculature and the decrease in the number of β-adrenoceptors in the heart in hypothyroidism.

In conclusion, our results indicate that methimazole-induced hypothyroidism has little influence on hypotensive responses induced by a β-adrenoceptor, a NO-producer, and a NO donor; however, it has a time-dependent influence on α-adrenoceptor-mediated and a time-independent influence on NO synthase inhibitor-mediated hypertensive responses. It has been suggested that the decrease in α-adrenoceptor-mediated pressor responses occurs progressively in hypothyroidism whereas the decrease in basal NO production and/or release in the peripheral vasculature occurs at an early stage of hypothyroidism.

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