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The Role of Thyroid Hormone in Blood Pressure Homeostasis: Evidence from Short-Term Hypothyroidism in Humans

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Arterial hypertension is known to be frequently associated with thyroid dysfunction, with a particularly high prevalence in chronic hypothyroidism. However, to our knowledge no comprehensive study addressed causal mechanisms possibly involved in this association. We here report the physiological relationships between blood pressure and neuro-humoral modifications induced by acute hypothyroidism in normotensive subjects. Twelve normotensive patients with previous total thyroidectomy were studied. Ambulatory 24-h blood pressure monitoring was performed, and free T_3, free T_4, TSH, PRA, aldosterone, cortisol, adrenaline, and noradrenaline were assayed 6 wk after oral L-T_4 withdrawal (phase 1) and 2 months after resumption of treatment (phase 2). During the hypothyroid state (TSH, 68.1 ± 27.7 μIU/ml; mean ± SD), daytime arterial systolic levels slightly, but significantly, increased (125.5 ± 9.7 *vs.* 120.4 ± 10.8 mm Hg; $P < 0.05$), and daytime diastolic levels (84.6 ± 7.9 *vs.* 76.4 ± 6.8 mm Hg; $P < 0.001$), noradrenaline (2954 ± 1578 *vs.* 1574 ± 962 pmol/liter; $P < 0.001$), and adrenaline (228.4 ± 160 *vs.* 111.3 ± 46.1 pmol/liter; $P < 0.05$) also increased. PRA remained unchanged (0.49 ± 0.37 *vs.* 0.35 ± 0.21 ng/ml·h; P = NS), whereas both aldosterone (310.3 ± 151 *vs.* 156.9 ± 67.5 pmol/liter; $P < 0.005$) and cortisol (409.2 ± 239 *vs.* 250.9 ± 113 pmol/liter; $P < 0.02$) significantly increased. By using univariate logistic regression daytime arterial diastolic values, noradrenaline and aldosterone were found to be significantly related to the hypothyroid state ($P < 0.02$, $P < 0.036$, and $P < 0.024$, respectively). In conclusion, our data show that thyroid hormones participate in the control of systemic arterial blood pressure homeostasis in normotensive subjects. The observed sympathetic and adrenal activation in hypothyroidism, which is reversible with thyroid hormone treatment, may also contribute to the development of arterial hypertension in human hypothyroidism. (*J Clin Endocrinol Metab* 87: 1996–2000, 2002)

THE ROLE OF thyroid hormone on heart and vessel physiology has been investigated since the description of the main cardiovascular symptoms in clinical dysthyroidisms. Arterial hypertension is frequently observed in both hyper- and hypothyroidism (1), thus suggesting different working mechanisms in the two conditions. Observational studies in the literature have pointed out a high prevalence of hypertension, particularly in chronic hypothyroidism (1–5), but underlying pathophysiological mechanisms have not been clarified.

In animal models T_3 has a positive direct inotropic effect by inducing a predominant synthesis of fast α-isoforms of heavy myosin chains and by increasing calcium-adenosine triphosphatase and cAMP levels, together with the number and sensitivity of β-adrenergic receptors (6–10). T_3 has also a vasodilatory effect on arterioles, which is mediated by a direct effect on vascular smooth muscle cells that promotes relaxation, by local heat production, and possibly by β_2-receptor stimulation (11–13).

Thyroid function also interacts with other systems involved in cardiovascular regulation. In fact, beside sympathetic system activity (14, 15), thyroid hormone can increase angiotensinogen (16) and atrial natriuretic peptide levels (17, 18) and respectively decrease vasopressin levels (19, 20). Even more complex is the effect of thyroid hormone on renal hemodynamics and sodium homeostasis. Thyroid hormone deficiency may be associated to a reduction of the glomerular filtration rate and renal blood flow (21, 22). On the other hand, in the hyperthyroid state the increase in renin release secondary to the hormone-dependent decrease in systemic vascular resistance may stimulate the angiotensin-aldosterone axis and consequently sodium reabsorption (13–23).

To our knowledge, there are no studies carried out on normotensive subjects showing the effect of a short-term variation in thyroid hormone levels on both blood pressure and some of its important regulatory mechanisms represented by renin, sympathetic, and adrenal systems. We addressed this issue by the use of a unique clinical model encompassing a short-term variation from a state of acute hypothyroidism to one of restoration of normal thyroid function in normotensive patients.

Materials and Methods

In a 10-month period we selected 12 patients suitable for the study. All of the patients (9 women and 3 men; mean age, 50.7 ± 8.4 yr; range, 36–67 yr) had undergone total thyroidectomy and radioiodine ablation for primary treatment of stage I differentiated thyroid cancer 6.50 ± 1.46 yr before the study. All of the patients had been disease-free for at least 3 yr and underwent routine follow-up at the time of the study. None of the patients had a family history of hypertension. They were informed of the purpose of the study. All of the patients were normotensive both before surgical intervention and during the clinical follow-up thereafter. No patient was affected by any other known disease or received any

Abbreviations: A, Adrenaline; ALDO, aldosterone; BP, blood pressure; CORT, cortisol; DBP, diastolic blood pressure; fT_3, free T_3; fT_4, free T_4; NA, noradrenaline; SBP, systolic blood pressure.

pharmacological treatment except L-T_4. In particular, no one presented cardiovascular diseases, as assessed by history, physical examination, electrocardiogram, and chest x-rays routinely performed in the follow-up. Informed consent was obtained from all patients, and the study was approved by the local review committee of our institution. Each patient was studied in 2 different conditions: the first study was carried out 6 wk after the withdrawal of L-T_4 replacement therapy to undergo ^{131}I whole body scintigraphy as a part of the routine clinical work-up (phase 1), and the second study was performed 2 months later under thyroid hormone replacement therapy consisting of oral intake of 1.5–2.5 μg/kg BW·d L-T_4 (phase 2). At both time points, 24-h ambulatory blood pressure (BP) monitoring was performed, and plasma levels of free T_3 (fT_3), free T_4 (fT_4), TSH, PRA, aldosterone (ALDO), cortisol (CORT), adrenaline (A), and noradrenaline (NA) were assayed. Blood samples for hormonal determinations were taken between 0730 and 0900 h before application of the BP-monitoring device, after 30 min at rest, in recumbent position.

A SPACE-LABS 90207 ambulatory blood pressure-monitoring device was used for BP determinations. The following laboratory methods were used for hormonal parameters assays: PRA, angiotensin I RENCTK RIA kit (DiaSorin, Inc., Saluggia, Italy); ALDO, ALDOCTK-2 RIA kit (DiaSorin, Inc.); CORT, TDx Abbott (Wiesbaden-Delkenheim, Germany); NA and A, automatic catecholamine analyzer HPLC-725-CA (TOSOH, Tokyo, Japan); and TSH, AIA-Pack third generation on TOSOH AIA System Analyzer (TOSOH). Free thyroid hormones (fT_3 and fT_4) were measured using both competitive enzyme immunoassay AIA-Pack 21 apparatus (TOSOH) and the gel equilibration procedure (Liso Phase RIA system, Techno Genetics, Milan, Italy). To improve the reliability of measurements and to reduce the effects of interassay variability, we assayed each serum sample on several occasions in the same experiment and in different sessions (at least three times) (24). All of the repeated measurements carried out for each hormone determination on a single blood sample were averaged. Only the single mean value obtained for the individual hormone assayed in the patients (n = 12) was used for the purpose of statistical analysis (see below).

Statistical analysis

Values are expressed as the mean ± SD. Continuous variables were compared by paired samples *t* test when their distributions were found to be normal, as assessed by Kolmogorov-Smirnov test. Otherwise, Wilcoxon nonparametric test was exploited. The relation between the acquired variables and the phases of the study was investigated by univariate logistic regression. The 95% confidence interval for the logistic regression coefficients was computed. $P < 0.05$ was considered statistically significant. A *t* test for paired values and linear regression analysis were used for results evaluation.

Results

The mean data of each parameter determined at both time points of the study (phases I and II) are reported in Table 1.

BP

A 24-h ambulatory BP monitoring in a typical subject in the hypothyroid state and during thyroid hormone replacement therapy is reported in Fig. 1.

In the hypothyroid state mean 24 h systolic BP (SBP) was less than 140 mm Hg in all patients; in four cases the mean diastolic BP (DBP) was 90 mm Hg or higher (see Fig. 2). After L-T_4 treatment, BP was in the normotensive range, except for one subject with 146 mm Hg systolic levels. A significant decrement was observed in daytime SBP ($P < 0.05$) and an even greater decrease in DBP ($P < 0.001$).

Sympatho-adrenal system

In the hypothyroid state mean values for plasma catecholamines were in the upper normal range; after L-T_4 replacement, NA decreased significantly ($P = 0.001$) as well as A, although to a lesser degree of significance ($P < 0.05$).

Adreno-cortical steroids and PRA

In the hypothyroid state mean ALDO and CORT levels were significantly higher ($P < 0.005$ and $P < 0.02$ respectively) compared with the corresponding values measured during L-T_4 treatment.

During hypothyroidism, PRA was at the lower normal limit in nine patients and was almost suppressed in the remaining three (<0.20 ng/ml·h). No significant changes were observed after L-T_4 treatment.

Linear regression analysis (Table 2)

Phase 1. During hypothyroidism, fT_3 and TSH correlated with NA levels; the regressions was negative for fT_3 and positive for TSH, respectively. The more marked the hypothyroidism, the more elevated the NA levels. Nighttime systolic BP was inversely related to morning CORT levels as well as DBP.

TABLE 1. Humoral parameters, blood pressure, and heart rate levels during acute hypothyroidism and after L-T_4 (n = 12)

Parameters	Hypothyroidism	L-T_4	*P* (paired *t* test)
fT_4 (pmol/liter)	3.30 ± 2.0	21.2 ± 5.7	<0.0001
fT_3 (pmol/liter)	1.19 ± 0.5	4.55 ± 1.2	<0.0001
TSH (μIU/ml)	68.1 ± 27.7	1.10 ± 2.05	<0.0001
SBP (mm Hg)			
Day	125.5 ± 9.7	120.4 ± 10.8	<0.05
Night	109.3 ± 8.5	107.3 ± 8.9	NS
DBP (mm Hg)			
Day	84.6 ± 7.9	76.4 ± 6.8	<0.001
Night	68.9 ± 7.8	64.7 ± 5.6	NS
HR (beats/min)			
Day	80.9 ± 6.7	81.0 ± 7.4	NS
Night	64.3 ± 5.9	67.4 ± 7.1	<0.005
Noradrenaline (pmol/liter)	2954 ± 1578	1574 ± 977	0.001
Adrenaline (pmol/liter)	228.6 ± 159.6	111.3 ± 46.1	0.05
PRA (ng/ml·h)	0.49 ± 0.38	0.35 ± 0.21	NS
Aldosterone (pmol/liter)	310.3 ± 151.3	156.8 ± 67.4	<0.005
Cortisol (pmol/liter)	409.11 ± 239	251.0 ± 113	<0.02

HR, Heart rate; PRA, plasma renin activity. Values are expressed as the mean ± SD.

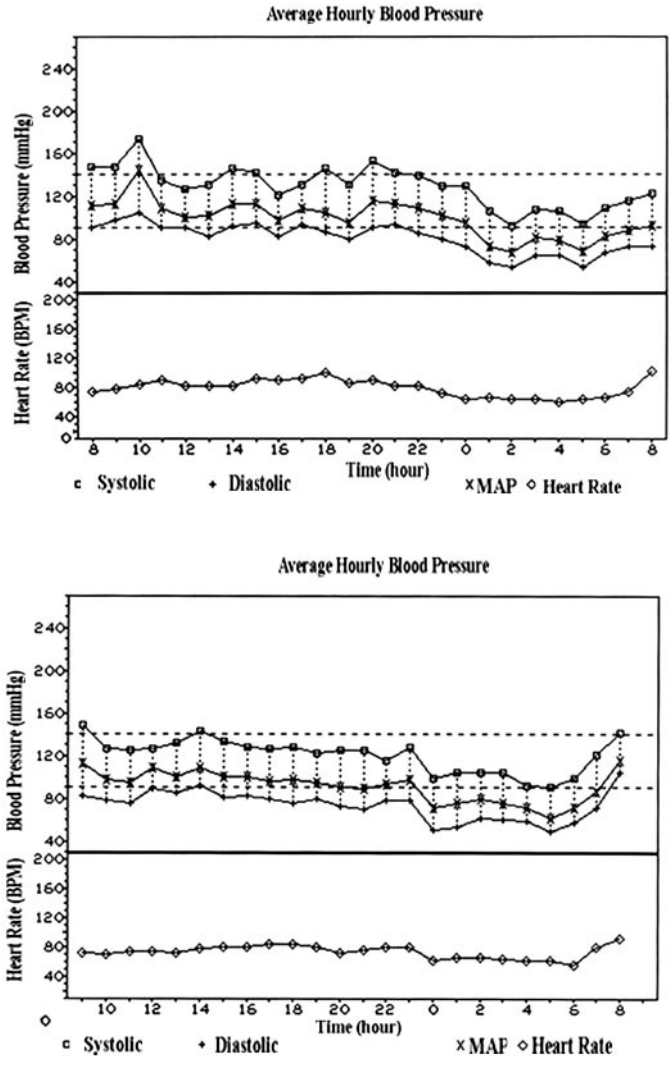

FIG. 1. Twenty-four-hour arterial BP monitoring in a typical patient during the hypothyroid state (*upper panel*) and during replacement therapy with L-T_4 (*lower panel*).

Phase 2. During thyroid hormone replacement therapy, fT_3 significantly correlated with daytime BP levels (fT_3 *vs.* DBP: $r = 0.61$; $P < 0.04$) as well as TSH, which also correlated with systolic levels (Table 2). The more efficiently the hypothyroidism status was corrected, the lower the resulting BP levels (Fig. 3 and Table 2). No significant correlations of TSH and fT_3 were observed with either NA, ALDO, or CORT levels.

Univariate logistic regression

The univariate logistic regression (Table 3) singled out the relation between the acquired variables and the hypothyroid state. Daytime DBP, NA, and ALDO values were significantly related to the hypothyroid state. A nonsignificant relation was found for CORT.

Discussion

The main purpose of the present study was to investigate the relationships between thyroid function and aspects of blood pressure physiology in the absence of cardiovascular disease. For this reason we selected a group of normotensive patients, all of them free from any pharmacological treatment. Our experimental design enabled us to study *in vivo* specifically the effects of changing thyroid hormone levels on blood pressure and the neuroendocrine parameters known to be involved in blood pressure regulation. A similar approach was recently adopted to evaluate the thyroid hormone-related changes in cardiac oxidative metabolism and contractile function (25).

Additionally, we chose only patients free from disease in previous clinical work-up to reduce the potential influence of disease stress condition on the neuroendocrine and BP parameters we measured. Moreover, we investigated BP levels by the use of 24-h ambulatory monitoring, which has been demonstrated to approximate more accurately than casual measures the actual intraarterial values (26).

The main finding of the study was that thyroid hormone withdrawal induced an increase in BP levels, particularly diastolic. The elevation in blood pressure levels was reversible with thyroid hormone replacement therapy. In addition, the highly significant correlation observed between fT_3 and DBP strongly suggest a direct cause-effect relationship. These findings taken as a whole indicate that thyroid hormone contributes to systemic arterial blood pressure homeostasis in physiological conditions.

It has long been known that chronic hypothyroid patients show an increase in peripheral arterial resistance (27). However, the ability of thyroid hormone to directly regulate systemic vascular resistance by changes in vascular smooth cell contractility has been recently demonstrated (28). In particular, the important role of T_3 as a direct novel vasodilator agent on skeletal muscle resistance has been reported in animal models (29). In this regard, very recent data have shown the presence in humans of deiodinase type II expression in peripheral vascular muscle cells (30); we speculate that locally produced T_3 from T_4 could contribute to the regulation of vascular tone in normal and possibly pathophysiological conditions.

The deprivation of thyroid hormone was also associated with a proportional increase in plasma NA and A, whereas the restoration of thyroid function abolished that stimulation and proportionally reduced BP levels. Sympatho-adrenal stimulation could thus contribute to sustain BP levels during acute hypothyroidism as a possible mechanism counteracting the decrease in myocardial inotropism and cardiac output (4, 14, 15).

The finding that no correlation was observed between A and NA levels in any phase of the study suggests the existence of separate regulatory mechanisms for the two neurohormones during hypothyroidism. Besides being activated by sympathetic stimulation, A can be released by ACTH and glucocorticoid hormones (31, 32). In this regard, during hypothyroidism we observed relatively higher levels of CORT as well as ALDO; adrenergic and adrenocortical stimulations may thus be synergistic mechanisms acting in hypothyroidism.

Whereas ALDO secretion was maintained, PRA was low during thyroid hormone withdrawal, similar to what observed in chronic hypothyroidism (1, 5). In the presence of a

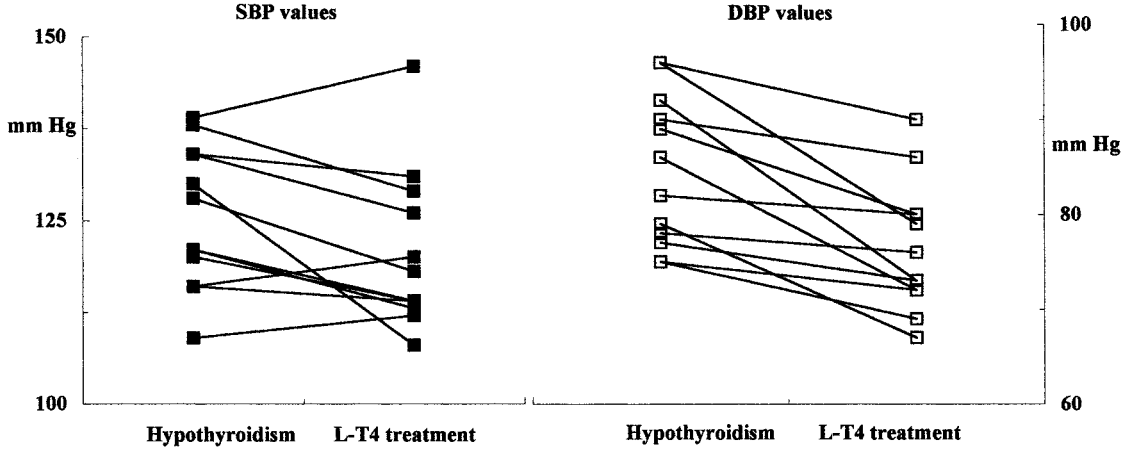

FIG. 2. Individual mean daytime SBP and DBP levels during the hypothyroid state (*left panel*) and L-T_4 treatment (*right panel*).

TABLE 2. Main significant correlations found in phase I and phase II

Phase I (n = 12)				Phase II (n = 12)			
Parameters	Pos/neg	r	*P*	Parameters	Pos/neg	r	*P*
NA *vs.* fT_3	Neg	0.60	<0.05	Daytime DBP *vs.* fT_3	Neg	0.61	<0.04
NA *vs.* TSH	Pos	0.71	<0.01	DBP *vs.* fT_3	Neg	0.70	<0.01
Night SBP *vs.* CORT	Neg	0.64	<0.03	DBP *vs.* TSH	Pos	0.74	<0.01
DBP *vs.* CORT	Neg	0.68	<0.02	Daytime SBP *vs.* TSH	Pos	0.90	<0.001

Pos/neg, Positive or negative.

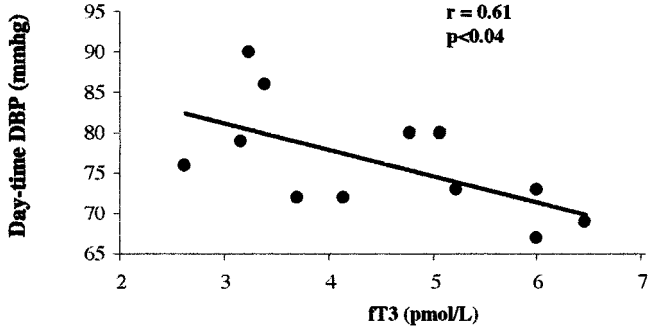

FIG. 3. Correlation between thyroid hormone (fT_3) and daytime DBP (day-t DBP) during replacement therapy with L-T_4.

reduced PRA, ALDO secretion could be sustained by the pituitary hormone ACTH; according to this finding, recent studies have reported a reactive increase in ACTH secretion in response to adrenal cortex dysfunction induced by acute hypothyroidism in experimental animals (33, 34). The compensation of an impaired adrenal cortex function may be important in hypothyroidism, in view of the hemodynamic effects of the steroids that can help in preserving cardiac output by sustaining blood volume and cardiac preload.

However, the observed changes in catecholamines, ALDO, and, although to a lesser extent, CORT levels are difficult to interpret *per se*. All of these changes that accompany the hypothyroid state should be also evaluated by taking into account the volume changes accompanying the hypothyroid state. Intravascular volume and red cell mass may be decreased in hypothyroidism (13), and patients with hypofunction appear to be more salt sensitive than normal subjects, thus implying important changes in volume regulation (35). Moreover, the increase in catecholamines and most likely the increase in ALDO and CORT may be at least partially a secondary response to their reduced clearance (15). On the other hand, other pathophysiological mechanisms favoring salt/water retention are activated during the hypothyroid state, such as an increase and a decrease in vasopressin and atrial natriuretic peptide secretion, respectively (17–20).

Finally, beside the clear advantages of the unique human model we adopted in providing new insights into the *in vivo* physiological role of thyroid hormone in BP control, some caution is needed in transferring results to the effects of long-term thyroid function abnormalities.

In conclusion, our data indicate that thyroid hormone deprivation promotes an increase in BP as well as activation of the sympathetic/adrenal systems. In addition, it is interesting that although all of our patients were normotensive both before and after thyroidectomy, BP increased into the hypertensive range in one third of them when hypothyroidism was induced.

The pathophysiological linkage between thyroid dysfunction and BP control appears even more relevant in clinical terms if we consider the consistent prevalence (3–4%) of hypothyroidism in the general nonselected hypertensive population (1, 2, 36) and, for comparison, that of renovascular hypertension (~1%), one of the most investigated forms of secondary hypertension (37).

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TABLE 3. Univariate logistic regression between the acquired variables (NA, daytime DBP, and ALDO) and the hypothyroid state (phase I)

Parameter	Regression coefficient (B)	Confidence interval (95% CI odds ratio)	Significance (*P*)	Coefficient of correlation (r)
NA	0.0062	1.0004–1.0121	0.0357	0.2962
Daytime DBP	0.152	1.0160–1.3341	0.0287	0.2894
ALDO	0.0397	1.0053–1.0768	0.0238	0.3059

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