CLINICAL STUDY

Endocrine factors related to changes in total peripheral vascular resistance after treatment of thyrotoxic and hypothyroid patients

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Abstract

Objective: Total peripheral vascular resistance (TPR) decreases in thyrotoxicosis and increases in hypothyroidism. Several mechanisms may be involved, including adaptation to changes in heat production and direct non-genomic effects of tri-iodothyronine (T_3) on vascular smooth muscle cells. The aim of this study was to see if changes in TPR are related to changes in plasma concentrations of the endothelial hormones adrenomedullin and endothelin-1 as well as other hormones affecting vasculature.

Design: A prospective study.

Subjects: Eleven hypothyroid patients (pretreatment: thyroid-stimulating hormone (TSH) 68 (38–201) mU/l, T_3 0.7 (0.35–1.5) nmol/l, fT_4 3.0 (2.0–5.9) pmol/l, median (range)) and 14 with hyperthyroidism (pretreatment: TSH 0.02 (<0.01–0.06) mU/l, T_3 6.4 (2.3–13.0) nmol/l, fT_4 56.1 (22.9–70.0) pmol/l) were studied before treatment and 3 months after reaching the euthyroid state. Blood collection was carried out simultaneously with the recording of finger arterial pressure (FINAP). Cardiac output and TPR were derived from stroke volume computations by modelling flow from the FINAP signal.

Results: Thyroid-function tests of hypothyroid and thyrotoxic patients did not differ after restoration of the euthyroid state. TPR, expressed in arbitrary units (AU), decreased after correction of hypothyroidism (from 1.32 ± 0.65 to 0.96 ± 0.36 AU, $P = 0.04$) and increased after correction of hyperthyroidism (from 0.75 ± 0.18 to 1.10 ± 0.35 AU, $P = 0.007$). Adrenomedullin concentrations did not change during the transition from the hypothyroid state $3.2(0.9–11.0)$ pmol/l to the euthyroid state $4.9(0.9–8.6)$ pmol/l, but decreased after treatment of hyperthyroidism, from $5.2(0.9–11.0)$ pmol/l to $2.2(0.9–5.4)$ pmol/l. Plasma endothelin-1 was undetectable in all samples. Changes in TPR upon treatment correlated with $\log \Delta fT_4$ ($r = -0.65$, $P = 0.001$), $\log \Delta T_3$ ($r = -0.57$, $P = 0.006$), Δ noradrenaline ($r = 0.54$, $P = 0.02$) and Δ ANP (atrial natriuretic peptide) ($r = -0.59$, $P = 0.004$). Multiple linear regression analysis indicated that only T_3 was an independent determinant of TPR. Changes in T_3 accounted for 46% of the variability in the changes in TPR.

Conclusions: TPR is reduced in thyrotoxicosis and increased in hypothyroidism. Restoration of the euthyroid state normalizes TPR. Changes in TPR are not related to plasma adrenomedullin concentrations, but 46% could be explained by changes in T_3 . Altered ANP secretion and adrenergic tone may contribute to the T_3 -induced changes in TPR.

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Introduction

Total peripheral vascular resistance (TPR) decreases in thyrotoxicosis and increases in hypothyroidism (1, 2). The mechanism involved is incompletely understood, but is probably multifactorial: changes in heat production may contribute, along with changes in Na^+/K^+ fluxes caused by modulation of the inward

rectifying potassium channels (3). Vascular smooth muscle cells relax acutely upon tri-iodothyronine (T_3) binding (4). A fast decrease in TPR has been observed after acute thyroid hormone administration in experimental animals and humans, even before changes in heart rate or cardiac contractility (1, 5–7). The speed of action favours direct, non-genomic effects of T_3 .

Changes in local release of vasoactive hormones by the endothelium may be another mechanism (8). Endothelial cells contain nuclear T_3 receptors (9, 10) and produce vasoconstricting (endothelin-1) as well as vasodilating (adrenomedullin) factors in proportion to the ambient T_3 concentrations (11, 12). Endothelium-dependent vasodilatation is modulated by T_3 , as illustrated by *in vitro* studies with vascular rings (13–15). Flow-mediated, endothelium-dependent vasodilatation is reduced in patients with subclinical or overt hypothyroidism, and the magnitude is related to thyroid-stimulating hormone (TSH) levels (16).

Changes in TPR may also be mediated by changes in non-thyroid hormones which affect the vasculature. In thyrotoxicosis, plasma catecholamines are unchanged or low, but the β -adrenergic receptor density is altered in a time- and tissue-dependent manner, raising tissue sensitivity to catecholamines. In hypothyroidism, plasma catecholamine concentrations are elevated whereas receptor densities are lowered (17). Cortisol has a permissive influence on catecholamine effects, but both hypothyroid and thyrotoxic patients have normal plasma cortisol levels (18, 19). Blood volume is increased in thyrotoxicosis and reduced in hypothyroidism (2). The effective circulating volume influences vascular tone and is partly controlled by the activities of the renin–angiotensin–aldosterone system, atrial natriuretic peptide and vasopressin. Plasma renin activity is positively correlated to thyroid hormone levels (20). Vasopressin concentrations can be increased in severe hypothyroidism, sometimes resulting in hyponatraemia (21). A higher cardiac preload in thyrotoxicosis might trigger secretion of atrial natriuretic peptide (ANP), but a stimulatory effect on ANP gene transcription by T_3 is also reported (22). In hypothyroidism, afterload is raised and atrial filling pressures are lowered.

The aim of this study was to evaluate whether changes in TPR in states of thyroid hormone excess or deficiency are related to changes in plasma levels of the endothelial hormones adrenomedullin and endothelin-1 or of other non-thyroid hormones. Therefore measurement of TPR was carried out, using a non-invasive method, simultaneously with the collection of venous blood samples for hormone assays, before and after restoration of the euthyroid state in hyper- and hypothyroid patients.

Subjects and methods

Patients

Twenty-five consecutive patients referred to the out-patient clinics of the Academic Medical Centre were studied. Fourteen had overt thyrotoxicosis (five men and nine women; mean age 38 years, range 23–59) and 11 had overt hypothyroidism (three men and eight women; mean age 47 years, range 30–65). Causes of

thyrotoxicosis were Graves' disease ($n = 12$) and toxic multinodular goitre ($n = 2$); causes of hypothyroidism were autoimmune thyroiditis ($n = 8$) and ^{131}I therapy ($n = 3$). Thyrotoxic patients were treated with anti-thyroid drugs (propylthiouracil or methimazole) in combination with levothyroxine, and hypothyroid patients were treated with levothyroxine replacement. None of the patients used any medication known to interfere with thyroid-hormone metabolism or with the cardiovascular system. In the thyrotoxic group, 75% were smokers, and in the hypothyroid group, 62% were smokers. The study protocol was approved by the local medical ethical committee.

After written informed consent had been obtained, patients were studied twice, i.e. before the start of treatment and three months after reaching the euthyroid state, between 0800 h and 1000 h, after an overnight fast in a room at a constant ambient temperature of 22 °C. They were given a catheter into an antebrachial vein for blood sampling while resting in the supine position. After 60 min, blood was collected and finger arterial pressure (FINAP) and an electrocardiogram were recorded continuously for 30 min.

Methods

Hormone assays Blood samples were immediately put on melting ice. Different anti-coagulants and additives were used according to the specific assays employed, as follows: heparin (for TSH, thyroid hormones, aldosterone and cortisol), EDTA (for plasma renin activity (PRA)), EGTA + glutathione in prechilled tubes (for adrenaline and noradrenaline) and EDTA + aprotinin (1400 Kallikrein inhibitor units Trasylol (Bayer, Leverkusen, Germany) per 7 ml blood collection tube, in prechilled tubes (for adrenomedullin, endothelin-1 (ET-1), arginine vasopressin (ADH) and atrial natriuretic peptide (ANP)). Plasma was prepared within 1 h after collection of the blood samples and was stored, until assay, at -20 °C.

Thyroxine (T_4) and T_3 were measured by in-house radioimmunoassay (RIA; intra-assay coefficient of variation (c.v.), 2–4%; detection limits, 5 nmol/l and 0.3 nmol/l respectively). Free T_4 (FT $_4$) was measured by a two-step fluoroimmunoassay (DELFA; Wallac, Turku, Finland), (intra-assay c.v., 6%; detection limit, 2 pmol/l) and TSH was measured by immunofluorometric assay (intra-assay c.v., 1–2%; detection limit, 0.01 mIU/l; DELFIA). Thyrotoxicosis was defined as reduced plasma TSH in combination with raised concentrations of plasma T_3 and free T_4 . Overt hypothyroidism was defined as raised plasma TSH in combination with reduced free plasma T_4 . The euthyroid state for previous thyrotoxic patients was defined as comprising normal plasma T_3 and free T_4 , but, for previous hypothyroid patients, as normal TSH in combination with normal plasma T_3 and free T_4 .

Pre- and post-treatment samples of each subject were assayed for all non-thyroid hormones in the same run in order to avoid interassay variation. PRA was measured by an in-house RIA for angiotensin I formation (intra-assay c.v., 4–6%; detection limit, 0.3 ng angiotensin I/ml/h. Aldosterone was measured by RIA (Coat-A-Count; Diagnostic Products Corporation (DPC), Los Angeles, CA, USA) (intra-assay c.v., 5–12%; detection limit, 0.03 nmol/l). Cortisol was measured by enzyme-immunoassay on a DPC Immulite analyser (intra-assay c.v., 2–4%; detection limit, 50 nmol/l). Noradrenaline and adrenaline were determined by an in-house HPLC method (noradrenaline intra-assay c.v., 6–8%; detection limit, 0.05 nmol/l; adrenaline intra-assay c.v., 6–8%; detection limit, 0.05 nmol/l).

Prior to the RIA of ET-1, adrenomedullin, ANP and ADH, plasma was extracted with Sep-Pak octadecyl solid-phase extraction cartridges (Waters, Milford, MA, USA) according to the manufacturer's instructions. ET-1 was measured by RIA (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA) with a total (extraction and RIA) inter-assay c.v. of 12% at 10 pg/ml and a detection limit of 2 pg/ml (0.8 fmol/ml). Adrenomedullin (amino acids 1–52) was measured by RIA (RK-010-01 (detection limit, 11 pg/ml (1.8 pmol/l)); Phoenix Pharmaceuticals, Inc. CA, USA). ANP was measured by RIA (Nichols Institute Diagnostics; intra-assay c.v., 8%; detection limit, 7.5 pg/ml). ADH was measured by in-house RIA (detection limit, 0.2 pmol/l).

Haemodynamic parameters FINAP was determined at the middle finger of the non-dominant arm and contra-lateral to the cannulated arm, with a Finapres (Model 5; Netherlands Organization for Applied Scientific Research, Biomedical Instrumentation TNO-BMI, Amsterdam). The Finapres is based on the volume clamp method of Peñáz and the Physiological criteria of Wesseling (23, 24), and reflects changes in systolic, mean and diastolic arterial pressure under variable conditions (25, 26). The cuffed finger was fixed in the anterior axillary line at heart level.

Beat-to-beat changes in stroke volume (SV) were computed by modelling flow from arterial pressure, simulating a non-linear, time-varying model of the aortic input impedance (27). The SV was obtained as the integral of the flow waveform for one beat. Tracking of changes in SV relative to non-invasive arterial pressure are accurate in both normal and pathological conditions (27–29). Cardiac output (CO) was the product of the SV and the heart rate (HR); TPR was calculated from the mean arterial pressure (MAP) and the CO.

Signals were sampled at 100 Hz, stored on a computer disk and also recorded on a Graphtec WR7700 recorder (Graphtec Corp., Yokohama, Japan) for on-line inspection. Signals to and from the computer were routed through an interface providing electrical isolation. Signals requiring offset and

sensitivity adjustments went through additional offset and gain amplifiers. Systolic arterial pressure (SAP) and diastolic arterial pressure (DAP) were collected from the FINAP signal, and MAP was computed as the integral of pressure over one beat divided by the beat interval and was expressed in mmHg. The HR was computed as the inverse of the inter-beat pressure interval and was expressed in beats per minute (bpm). If absolute values for SV are required, Modelflow (a three-element model describing the relation between aortic flow and pressure (29)) requires calibration against a 'golden standard', e.g. thermodilution. Otherwise SV can be expressed as relative changes or as changes in arbitrary units (AU). To calculate group means, a transformation from beat-to-beat results to equidistantly sampled data was necessary. Therefore the beat-to-beat data were interpolated at 2 Hz using a polynomial three-point interpolation algorithm (30). Group mean values were then calculated.

Statistical analysis Calculations were done with the statistical software package *SPSS* version 6.1 (SPSS, Inc. Chicago, Illinois, USA). Values are given as medians (range). Comparisons between groups were done by using the Wilcoxon matched pairs signed rank sum test or the Mann–Whitney test for paired or unpaired data, as appropriate. First, in order to study potential determinants of TPR in the untreated state, pretreatment plasma values for thyroid and other hormones were correlated with pretreatment values for TPR by using Spearman's rank correlation coefficients. Determinants that correlated with a *P* value of <0.10 were then entered into a forward multiple linear regression model to assess which determinant was the most important.

Thereafter, in order to disclose those variables which contribute to changes in TPR upon restoration of the euthyroid state, the differences (Δ) between pre- and post-treatment values for TPR, thyroid hormones and other hormones were calculated. Changes in fT_4 (or T_3) were expressed as an fT_4 (or T_3) post-treatment/ fT_4 (or T_3) pretreatment ratio and plotted on a logarithmic scale. Spearman's rank correlation coefficients were calculated for the relationship between Δ TPR on the one hand and Δ plasma hormones on the other hand. Again, those variables that correlated with a *P* value of <0.10 were then entered into a forward multiple linear regression model.

The level of statistical significance was set at *P* < 0.05.

Results

The results of the endocrine-function tests and haemodynamic variables are given in Table 1. After treatment, thyroid-function tests did not differ between the initially hypothyroid and hyperthyroid patients.

Table 1 Endocrine-function tests and haemodynamic parameters of 11 hypothyroid and 14 hyperthyroid patients in the untreated state and 3 months after restoration of the euthyroid state. Values given as medians (ranges are in parentheses).

	Hypothyroid	Euthyroid	Hyperthyroid	Euthyroid	Reference value
TSH	68(38–201)	2.2(0.1–11.5)	0.02(0.01–0.06)	0.73(0.03–8.1)	0.4–4.0 mU/l
T ₄	25(10–50)	130(95–160)	255(190–310)	110(80–150)	70–150 nmol/l
T ₃	0.7(0.35–1.5)	1.7(1.4–2.1)	6.4(2.3–13.0)	1.7(1.2–3.4)	1.3–2.7 nmol/l
fT ₄	3.0(2.0–5.9)	15.7(12.7–24.5)	56.1(22.9–70.0)	13.8(9.2–19.2)	10–23 pmol/l
P sys	127(100–156)	114(90–142) ^a	117(86–159)	121(100–143)	mmHg
MAP	91(62–108)	79(59–94)	79(48–106)	79(67–97)	mmHg
P dia	66(35–83)	57(41–69)	57(31–73)	59(51–78)	mmHg
HR	63(45–77)	70(58–78) ^b	86(74–113) [‡]	70(58–84) ^b	bpm
SV	71(34–170)	78(49–109)	75(48–103)	64(44–111)	ml
CO	4.2(2.5–8.0)	5.1(3.0–8.5)	6.2(5.0–8.4) [†]	4.7(3.0–7.7) ^b	l/min
TPR	1.12(0.49–2.37)	0.92(0.57–1.79) ^a	0.81(0.46–0.97) [†]	1.07(0.62–1.95) ^b	AU
PRA	1.40(0.5–6.0)	1.90(0.9–3.6)	2.15(1.10–5.30) [†]	1.80(0.60–8.30)	<0.3–3.2 µg A ₁ /l/hr
Aldosterone	0.20(0.03–0.34)	0.15(0.07–0.47)	0.34(0.03–0.68) [†]	0.16(0.03–0.82)	<0.03–0.35 nmol/l
PRA/aldo	7.8(3.7–46.7)	13.5(3.9–23.3)	7.1(3.2–60.0)	11.1(4.5–43.3)	
Cortisol	300(120–590)	305(120–570)	455(220–820)	290(140–540)	220–650 nmol/l
A	0.25(0.05–0.83)	0.20(0.09–0.42)	0.05(0.05–0.36) [‡]	0.08(0.05–0.15)	<0.55 nmol/l
NA	1.99(1.4–8.2)	1.55(0.99–3.25)	1.24(0.17–3.30) [‡]	1.64(1.02–2.80)	<3.25 nmol/l
ADM	3.2(0.9–11.0)	4.9(0.9–8.6)	5.2(0.9–11.0)	2.2(0.9–5.4) ^a	pmol/l
ET-1	<0.8	<0.8	<0.8	<0.8	pmol/l
ANP	25.6(18.1–42.0)	41.2(13.4–65.5) ^a	54.5(21.7–104) [‡]	32.6(3.5–50.7) ^b	22.0–65.0 ng/ml
ADH	1.8(0.7–5.9)	0.95(0.20–3.9) ^a	3.2(0.5–8.1)	1.5(0.1–5.2) ^a	<0.2–1.4 pmol/l

For comparison within groups: a = $P < 0.05$; b = $P < 0.01$. For pretreatment comparison between groups: † = $P < 0.05$; ‡ = $P < 0.01$. *For post-treatment comparison between groups, $P = 0.05$. P sys, systolic arterial pressure; MAP, mean arterial pressure; P dia, diastolic arterial pressure; HR, heart rate; SV, stroke volume; CO, cardiac output; TPR, total peripheral resistance; PRA, plasma renin activity; PRA/aldo, PRA/aldosterone ratio; A, adrenaline; NA, noradrenaline; ADM, adrenomedullin; ET-1, endothelin-1; ANP, atrial natriuretic peptide; ADH, arginine vasopressin.

Figure 1 Haemodynamic parameters, as recorded during 3 min (180 s) in 11 hypothyroid (a) and 14 hyperthyroid (b) patients before treatment (solid line) and when euthyroid (dotted line). Values are given as group means.

In the untreated state, the HR and CO were lower and total peripheral resistance was higher in hypothyroid patients compared with the hyperthyroid ones. After treatment, the differences in haemodynamic parameters between both groups had disappeared. The changes are presented graphically in Fig. 1. Peripheral vascular resistance, expressed in AU, decreased after correction of hypothyroidism (from 1.32 ± 0.65 to 0.96 ± 0.36 AU, $P = 0.04$) and increased after correction of hyperthyroidism (from 0.75 ± 0.18 to 1.10 ± 0.35 AU, $P = 0.007$). Smoking status did not affect pretreatment values for TPR in hyper- or hypothyroid patients, but, after treatment, smokers had higher TPR values (1.07, range 0.64–1.95) than non-smokers (0.73, range 0.57–1.25, $P = 0.03$). Smoking status did not influence adrenomedullin concentrations.

In the untreated state, PRA, aldosterone and ANP were lower and plasma catecholamines higher in the hypothyroid patients compared with the hyperthyroid patients, but adrenomedullin and ADH levels did not differ between the two groups. After treatment, no

differences between the two groups were noted any longer, except in the case of adrenaline levels, which were still higher in the previously hypothyroid patients. Adrenomedullin concentrations did not change during the transition from the hypothyroid state to the euthyroid state, but decreased after treatment of hyperthyroidism. Adrenomedullin concentrations in the euthyroid state differed between previous hyper- and hypothyroid patients ($P = 0.05$). ADH levels decreased after treatment of both hypo- and hyperthyroidism. In all plasma samples, the concentrations of ET-1 were below the detection limit of the assay (2 pg/ml or 0.8 pmol/l).

Pretreatment TPR correlated with pretreatment $\log T_4$ ($r = -0.48$, $P = 0.02$), $\log T_3$ ($r = -0.48$, $P = 0.02$) and noradrenaline ($r = 0.50$, $P = 0.03$); there was a trend towards a correlation with adrenaline ($r = 0.45$, $P = 0.06$) and ANP ($r = -0.40$, $P = 0.06$) (see Fig. 2). The changes in TPR upon treatment correlated with $\log \Delta T_4$ ($r = -0.65$, $P = 0.001$), $\log \Delta T_3$ ($r = -0.57$, $P = 0.006$), Δ noradrenaline ($r = 0.54$, $P = 0.02$) and Δ ANP ($r = -0.59$,

Figure 2 Graphical representation of the relationship between TPR and plasma concentrations of T_3 , ANP, adrenaline and noradrenaline in hypothyroid (●) and thyrotoxic (○) patients.

Figure 3 Graphical representation of the relationship between changes in TPR and changes in plasma concentrations of T_3 , ANP and noradrenaline, occurring upon treatment of hypothyroid (●) and thyrotoxic (○) patients.

$P = 0.004$) (see Fig. 3). Multiple linear regression analysis showed that pretreatment TPR was predicted by $\log T_3$ (regression equation $TPR = 1.38 - 0.75 \log T_3$, $r = 0.68$, $P = 0.002$), and the changes in TPR by $\log \Delta T_3$ values (regression equation $\Delta TPR = -1.39 - 0.75 \log \Delta T_3$, $r = 0.68$, $P = 0.002$). Determination of the residual sum of squares (RSQ) in this regression analysis showed

that $\log (\Delta T_3)$ accounted for 46% of the variability in ΔTPR .

Discussion

Peripheral vascular resistance in this study was measured by FINAP and by the application of Modelflow. Previous studies measuring TPR in thyroid dysfunction applied invasive measures. The observed changes in TPR in this study, measured using non-invasive techniques, were in agreement with the literature.

We could not establish a direct relationship between changes in TPR and changes in plasma concentrations of the endothelial hormones ET-1 or adrenomedullin. ET-1 gene expression is regulated by T_3 (11), and plasma ET-1 concentrations are raised in hyperthyroid patients (31). We could not confirm this latter finding because in all our plasma samples, concentrations of ET-1 were below the detection limit of the assay (2 pg/ml or 0.8 pmol/l). Several explanations for this phenomenon are possible. (i) Plasma concentrations of ET-1 in normal individuals are very low (1–2 pg/ml). The increase in ET-1 levels reported in hyperthyroidism was less than twofold and was measured with another RIA kit (31). (ii) During collection and handling of samples, premature destruction of the ET-1 protein could have happened; this is a less likely explanation because the other labile proteins (adrenomedullin, ANP and ADH) would have been equally destroyed (they could be readily measured). The improper performance of extraction and the assay procedure were ruled out by the use of internal controls and a good recovery rate. (iii) ET-1 secretion occurs abnormally (80% or more). Changes in plasma ET-1, in response to altered thyroid hormone concentrations, may be too small to be detected with confidence using our RIA (because of its limited sensitivity). Any increase in plasma endothelin is, however, in view of its vasoconstricting properties, hard to reconcile with the reduced TPR in thyrotoxicosis. In contrast, adrenomedullin, with its vasodilating effects, T_3 -dependent gene expression (32) and increased plasma concentrations in thyrotoxicosis (33), could be a determinant of TPR in thyroid-function disorders. However, no relationship between TPR and plasma adrenomedullin concentrations could be established, although adrenomedullin levels in the untreated hyperthyroid patients were higher than that in patients after treatment.

Changes in non-thyroid hormone concentrations in the transition from hypo- or hyperthyroidism to the euthyroid state were in accordance with the literature. When correlations were studied, changes in TPR were associated with changes in thyroid hormone, catecholamines and ANP. Using regression analysis, TPR was predicted independently only by thyroid hormones.

It is striking that both PRA and ANP concentrations were higher in the hyperthyroid state compared with the hypothyroid state. This resembles the situation in heart failure, when both PRA and ANP (and ADH) concentrations are increased (34). However, in heart failure, TPR is raised and the effective circulating volume is reduced, which triggers the release of renin and non-osmotic ADH secretion. The cardiac hypertrophy that accompanies myocardial failure and the stretching of atrial and ventricular myocardium lead to increases in circulating ANP (35). In thyrotoxicosis, in contrast, TPR is reduced and the effective circulating volume is presumably normal in the absence of (clinical) high output failure. The increased plasma concentrations of renin, ANP and ADH may be due to a direct effect of T_3 on their gene expression. In animals, sustained low-dose infusions of ANP reduce peripheral vascular resistance and lower blood pressure (36). Thus, increased levels of ANP may contribute to the decrease in TPR.

In conclusion, 46% of the variability in the change of TPR upon restoration of the euthyroid state could be explained by changes in T_3 concentration. No relationship between TPR and plasma adrenomedullin is observed. Changes in ANP secretion and adrenergic tone induced by thyroid hormone excess or deficiency may contribute to the reduced TPR in thyrotoxicosis and the raised TPR in hypothyroidism.

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