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Thyroid Function Disturbance and Type 3 Iodothyronine Deiodinase Induction after Myocardial Infarction in Rats—A Time Course Study

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In humans, there is a significant decrease in serum T_3 and increase in rT_3 at different time points after myocardial infarction, whereas serum TSH and T_4 remain unaltered. We report here a time course study of pituitary-thyroid function and thyroid hormone metabolism in rats subjected to myocardial infarction by left coronary ligation (INF). INF- and sham-operated animals were followed by serial deiodination assays and thyroid function tests, just before, and 1, 4, 8, and 12 wk after surgery. At 4 and 12 wk after INF, liver type 1 deiodinase activity was significantly lower, confirming tissue hypothyroidism. Type 3 deiodinase (D3) activity was robustly induced 1 wk after INF only in the infarcted myocardium. Reminiscent of the consumptive hypothyroidism observed in patients with large D3-expressing tumors, this induction of cardiac D3 activity was associated with a decrease in both serum T_4 (~50% decrease) and T_3 (37% decrease), despite compensatory stimulation of the thyroid. Thyroid stimulation was documented by both hyperthyrotropinemia and radioiodine uptake. Serum TSH increased by 4.3-fold in the first and 3.1-fold in the fourth weeks ($P < 0.01$), returning to the basal levels thereafter. Thyroid sodium/iodide-symporter function increased 1 wk after INF, accompanying the increased serum TSH. We conclude that the acute decrease in serum T_4 and T_3 after INF is due to increased thyroid hormone catabolism from ectopic D3 expression in the heart. (*Endocrinology* 148: 4786–4792, 2007)

THYROID HORMONES EXERT a broad range of effects on the heart and cardiovascular hemodynamics, and are important regulators of blood pressure and vascular resistance (1–3). The principal bioactive hormone, T_3, regulates cardiac genes that encode proteins involved in myocardium contractility, such as the myosin heavy chain, phospholamban, and the sarcoplasmatic reticulum calcium pump (4–6). In addition, similar changes in the pattern of expression of these proteins occur in both hypothyroidism and heart failure models (7–10).

In general, severe diseases produce a down-regulation of the thyroid hormone (TH) economy. In patients with acute myocardial infarction (MI), low-serum T_3 and/or high rT_3 is commonly associated with a severe clinical course (11, 12). Some authors (13, 14) have previously suggested that thyroid function might be normal in patients with chronic heart failure and hypothesized that impaired T_4 to T_3 conversion by deiodinases should result in the low T_3 state. New insights from deiodinase knockout mouse models have demonstrated that serum T_4 is even higher than in wild-type animals, and T_3 is normal in the absence of type 1 deiodinase (D1) (15). Thus, D1 might not be essential for the maintenance of a normal serum T_3 level, and the decreased D1 activity might be the consequence of the so-called low T_3 syndrome rather than its cause. A time course study could highlight the primary site affected after MI and, thus, lead to a better understanding of the mechanisms involved in the low T_3 syndrome that accompanies this clinical entity.

Ojamaa *et al*. (16) have recently demonstrated that the low-serum T_3 syndrome also occurs in an animal model of MI after left anterior coronary ligation. However, the time course of changes in serum TH levels and in D1 activity during the development of heart failure has not been studied so far. Thus, the aim of the present study was to investigate the pituitary-thyroid axis and the extrathyroidal metabolism of THs in a model of MI and progressive heart failure in rats.

We show here that type 3 deiodinase (D3) is robustly induced in the heart after MI. This is associated with an acute decrease in serum T_4 and T_3, despite compensatory stimulation of the thyroid gland that is evidenced by both hyper-

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Abbreviations: Ao, Aorta internal dimension; D1, type 1 deiodinase; D3, type 3 deiodinase; DTT, dithiothreitol; ECG, electrocardiogram; EF, ejection fraction; INF, infarction; LA, left atrium; LV, left ventricle; LVDd, left ventricular internal end-diastolic dimension; MI, myocardial infarction; NIS, thyroid sodium/iodide symporter; RWT, relative wall thickness; TH, thyroid hormone.

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thyrotropinemia and increased thyroid sodium/iodide-symporter (NIS) function. D1 activity is decreased after MI, consistent with tissue hypothyroidism. These data support the concept that increased TH inactivation catalyzed by ectopic cardiac D3 is the major cause of the acute decrease in serum T_4 and T_3 after infarction (INF).

Materials and Methods

Animals

The experiments were conducted on male Wistar rats weighting 200–250 g at surgery. All animals were housed at controlled temperature (23 C) with daily exposure to a 12-h light-dark cycle, and free access to water and standard rat chow. This investigation conforms to the Guide for the Care and Use of Laboratory Animals published by the U.S. National Institutes of Health (NIH Publication No. 85-23, revised 1996) and was approved by the institutional animal welfare committee.

Experimental MI

Left ventricular MI was induced after the procedure described by Johns and Olson (17), and modified in our laboratory (18). Briefly, male Wistar rats (200–250 g) were anesthetized with halothane PA (Merck, Darmstadt, Germany), and a 2-cm incision was made on the left side of the thorax, parallel to the sternum. The fifth and sixth ribs were separated, exposing the heart, and the left anterior coronary artery was permanently occluded by a 6–0 silk thread as it passed underneath the left atrial appendage. The chest was then closed with continuous silk stitch, and the rats were allowed to recover. The sham-operated group was subjected to the same surgical procedure as the infarcted group (MI) but without left anterior coronary artery occlusion.

Experimental protocol

In the first part of this study, male Wistar rats (~200–250 g) underwent left coronary ligation (MI, n = 12) or sham operation (n = 12). Serial cardiac functional assessment and measurements of serum TSH, T_4, and T_3 were performed just before, and 1, 4, 8, and 12 wk after surgery. Type 1 iodothyronine deiodinase activity was measured 4 (three per group) or 12 wk (nine per group) after sham or INF surgery. In the second part of experiments, short-term radioiodide uptake (NIS activity) was assessed in infarcted (n = 24) and sham (n = 14) rats 1 d, or 1 and 12 wk after surgery. Basal and *in vivo* TRH-stimulated serum TSH was assessed 1 and 8 wk after sham (n = 6) or infarct (n = 6) surgery.

RIA for serum TSH, and total T_4 and T_3

Blood was always collected at approximately 0800 h from the jugular vein under anesthesia with ketamine (50 mg/kg, ip) and xylazine (5 mg/kg, ip), during the periods described previously. Thereafter, blood was centrifuged (3000 rpm for 20 min), and sera were separated and stored at −20 C. The measurement of serum TSH levels was performed using a specific RIA for rat TSH obtained from the National Institute of Diabetes, Digestive and Kidney Diseases (Bethesda, MD), and expressed in terms of reference preparations 3. Serum T_3 and T_4 were determined by specific coated-tube RIA kits: T_3, 3100 Active; and T_4, 3200 Active (Diagnostic System Laboratory, Webster, TX). Hormone-stripped rat serum was used for the standard curves of total TSH, T_4, and T_3. All procedures were performed following the recommendations of the kit.

Type 1 iodothyronine deiodinase activity

The D1 activity was determined as previously published (19, 20). In short, each thyroid, pools of two pituitary glands, and 25 mg liver and kidney were homogenized in 1 ml 0.1 M sodium phosphate buffer containing 1 mM EDTA, 0.25 M sucrose, and 10 mM dithiothreitol (DTT) (pH 6.9). Homogenates (150 μg protein for pituitary samples, and 30 μg protein for liver, thyroid, and kidney) were incubated, in duplicate, for 1 h at 37 C with 1 μM rT_3 (Sigma-Aldrich, St. Louis, MO), freshly (Sephadex LH20; Sigma-Aldrich) purified tracer [^{125}I] rT_3 (PerkinElmer Life and Analytical Sciences, Inc., Waltham, MA), and 10 mM DTT (Invitrogen Life Technologies, Carlsbad, CA) in 100 mM potassium phosphate buffer (pH 6.9), containing 1 mM EDTA. Total reaction volume was 300 μl. Blank incubations were performed in the absence of protein. The reaction was stopped in an ice bath, followed by immediate addition of 200 μl fetal bovine serum (Cultilab, São Paulo, Brazil) and 100 μl trichloroacetic acid (50%, vol/vol). After thorough mixing (Vortex Ventures Inc., Houston, TX), the samples were centrifuged at 10,000 rpm for 3 min, and an aliquot of the supernatant was collected for measurement of ^{125}I liberated during the deiodination reaction. The specific enzyme activity was expressed as picomoles of rT_3 deiodinated/min × mg protein. Although type 2 deiodinase can also be present in the pituitary glands, only D1 activity was measured because under our assay conditions, deiodinase activity was completely blocked in the presence of 100 mM 6N-propylthiouracil, a specific D1 inhibitor (data not shown).

Protein was measured by the Bradford method (21), after incubation of homogenates with NaOH (2.5 N) for 30 min at room temperature.

Type 3 iodothyronine deiodinase activity

D3 activity was evaluated in the heart and liver samples from infarcted (n = 6) and sham (n = 3) operated rats 1 wk after surgery. Frozen tissues were homogenized and sonicated in 0.1 M phosphate and 1 mM EDTA (pH 6.9), with 10 mM DTT and 0.25 M sucrose. D3 activity was measured as previously described (22) using 150 μg cellular protein, 200,000 cpm 3, 5, [^{125}I]3′-triiodothyronine (PerkinElmer), 1 mM 6N-propylthiouracil, 10 mM DTT, and 10 nM unlabeled T_3 in each reaction. Reactions were stopped by the addition of methanol and the products of deiodination quantified by HPLC (23). D3 velocities are expressed as femtomole of T_3 inner-ring deiodinated per milligram sonicate protein per minute. Individual tissue specimens were assayed in duplicate.

Short-term radioiodide uptake: in vivo NIS function

We have previously demonstrated that the measurement of radioiodide uptake 15 min after ^{125}I-NaI administration (short-term iodide uptake) reflects iodide transport through the NIS without the influence of *in vivo* thyroid iodine organification activity (24) because methylmercaptoimidazole administration before radioiodine injection does not modify the measurement of iodide uptake. Thus, to evaluate the *in vivo* NIS function using thyroid radioiodine uptake measurements without the influence of thyroperoxidase iodine organification reaction, the animals received ^{125}I-NaI (250,000 dpm, ip; Amersham, Buckinghamshire, UK) 15 min before decapitation. The thyroids were removed and weighed. The radioactivity of the thyroid glands was measured using a γ-counter and expressed as percentage of total ^{125}I injected per milligram of thyroid.

Basal and in vivo TRH-stimulated serum TSH

After anesthesia with ketamine (50 mg/kg, ip) and xylazine (5 mg/kg, ip), rats received a single ip injection of TRH (1.5 μg/animal; Sigma-Aldrich), and blood samples were collected from the jugular vein 15 min before and after TRH injection to obtain basal and TRH-stimulated TSH values. Serum TSH levels were measured as described previously, and data are expressed in relation to basal serum TSH (= TRH-stimulated TSH/basal TSH).

Cardiac functional assessment

To ascertain MI surgery efficacy, an electrocardiogram (ECG) was registered 1 d after surgery under anesthesia with ketamine and xylazine, as described before (18).

The echocardiogram was also performed as described before (18). In this study an echocardiograph color system (Megas; Esaote, Firenze, Italy) equipped with a 10 MHz electronic-phased array transducer was used. Under ketamine and xylazine anesthesia, the chests of the animals were shaved, and they were maintained either in left lateral decubitus or supine position. All echocardiogram analysis was performed blind by the same echocardiographer, and included morphological and functional parameters. Images were obtained from the left parasternal and apical windows. Short-axis two-dimensional views of the left ventricle (LV) were taken at the level of the papillary muscles to obtain the M-mode recordings. Anterior and posterior end-diastolic and end-systolic wall thickness, LV, left atrium (LA) to aorta internal dimension (Ao)

ratio, and relative wall thickness (RWT) [2 × posterior end-diastolic wall thickness/LV internal end-diastolic dimension (LVDd)] were measured following the American Society of Echocardiography leading-edge method. The systolic function was expressed by the ejection fraction (EF), calculated by Simpson's method, after left ventricular volume calculation. Systolic and diastolic LV long axes were measured on the long-axis view, and systolic and diastolic LV short axis, traced at papillary muscle level, were measured on the transversal view. The pulsed-wave Doppler spectrum of mitral inflow was recorded from the apical four-chamber view with the guidance of the color Doppler. All Doppler spectra (mitral flow velocity pattern: peak early diastolic filling velocity, E velocity; peak filling velocity at atrial contraction, A velocity; and their ratio: E/A) were recorded, and morphological parameter values were measured during the echocardiographic examination.

Postmortem study

Rats were anesthetized and killed by cervical dislocation 12 wk postoperatively. The heart, lung, liver, and thyroid were removed, and their weights measured and corrected by the body weight of the animal and expressed as the heart, lung, liver, and thyroid index.

Histopathology

After macroscopic analysis, the heart was perfused with 4% paraformaldehyde in phosphate buffer. The percentage of scar tissue in LV was calculated as described by Spadaro *et al.* (25). Briefly, the LV was cut into four slices from apex to base. The slices had approximately the same thickness (1–2 mm) and were named slices A (at the apex), B, C, and D, respectively. Histological analysis with hematoxylin-eosin and Picrosirius staining was performed in representative sections obtained from slice C, described as the most representative (25) and confirmed by a previous study from our group (unpublished data) of the total infarcted length, using an Axiovert 100 microscope (Zeiss Inc., Göttingen, Germany). Sections stained with Picrosirius were recorded with a digital camera and stored for posterior analysis. The digital files were analyzed with the ImageJ software (version 1.27z; National Institutes of Health, Bethesda, MD), which allowed us to quantify the relative infarct size of the LV. The length of the infarcted endocardium was measured, as well as the total perimeter of the endocardial surface. From the ratio of these values, the percentage value of infarcted endocardium was calculated. The same procedure was done for the epicardial surface, obtaining the value of the percentage of infarcted epicardium. From these two values, the average percentage infarct size was estimated.

Statistical analyses

The results are expressed as mean ± SEM. Data from total T_3, T_4, and deiodinase activities were analyzed by two-way ANOVA using the SuperANOVA program (Abacus Concept, Berkeley, CA), by one-way ANOVA, or by unpaired *t* test using the Graphpad Prism software (version 4; Graphpad Software, Inc., San Diego, CA). The results of serum TSH were analyzed by nonparametric ANOVA (Kruskal-Wallis test) or the Mann-Whitney *U* test, using the Graphpad Prism software. A value of $P < 0.01$ or $P < 0.05$ was considered statistically significant.

Results

Cardiac function

The ECGs recorded showed a large MI at any time of observation in infarcted animals, as previously described by our group (18, 26). There was a significant rightward deviation of the frontal QRS axis (ÂQRS), the Q wave was observed in L1, and the I-QRS decreased in all infarcted animals, compared with data obtained in these animals before surgery and those of the sham-operated rats at the same time of observation (data not shown). The animals not presenting these ECG signs of MI 1 d after surgery were excluded from the study. Heart rate was continuously monitored by ECG during echocardiography and was not statistically different among the groups studied, ranging from 250–300 beats per minute under anesthesia.

As shown in Fig. 1, infarcted and sham groups had similar baseline echocardiographic values (before surgery). However, clear signs of severe heart failure were observed only in the infarcted group from 1–12 wk after surgery. There was a significant increase in the LA/Ao ratio and LVDd, as well

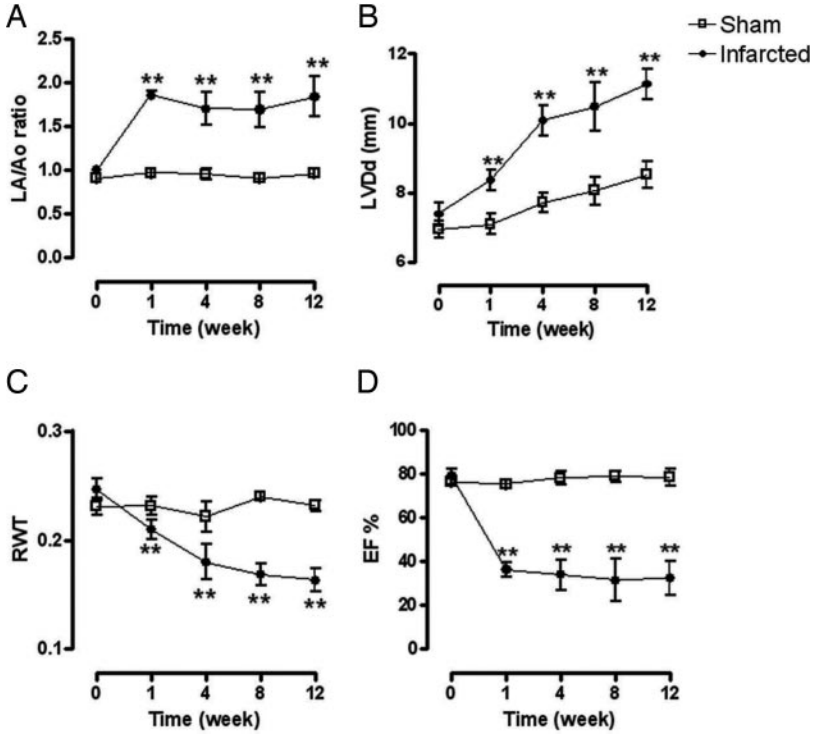

FIG. 1. LA/Ao ratio (A), LVDd (B), RWT (C), and EF obtained by Simpson's method (D) assessed by echocardiography in sham and infarcted groups before (0 wk), and 1, 4, 8, and 12 wk after surgery. *, $P < 0.05$ *vs.* infarcted group before surgery and sham group at the same week.

as a significant decrease in both RWT and EF, when compared with sham and baseline values of the infarcted group. No major changes were detected in other echocardiographic parameters.

Postmortem study and histopathology

Table 1 shows the macroscopic study undertaken in both groups. Secondary to the severe left ventricular damage in this model, heart and lung indexes were increased in all rats from the infarcted group. No changes were observed in the liver and thyroid index in both groups. The planimetric study showed a large transmural post-infarct scar in all hearts from the infarcted group (~40% of scar tissue in the anterolateral left ventricular wall). Figure 2 shows representative cross-sections of heart slices taken at the papillary muscle level, obtained from sham and infarcted rats 12 wk after surgery.

Type 1 iodothyronine deiodinase activity and RIA for TSH, and total T_4 and T_3

After MI, although serum TSH increased after 1 and 4 wk after infarct (basal = 0.93 ± 0.07 ng/ml; 1 wk INF = 3.99 ± 0.47 ng/ml; and 4 wk INF = 2.87 ± 0.60 ng/ml; Fig. 3A), T_4 remained low during the entire investigation (basal = 2.35 ± 0.24 μg/dl; 1, 4, 8, and 12 wk INF, respectively, = 1.20 ± 0.28 μg/dl, 1.12 ± 0.39 μg/dl, 1.63 ± 0.33 μg/dl, and 1.19 ± 0.19 μg/dl; Fig. 3B). T_3 levels decreased after 1 and 4 wk INF (basal = 135.5 ± 8.62 ng/dl; 1 wk INF = 83 ± 2.87 ng/dl; and 4 wk INF = 97.89 ± 3.09 ng/dl), returning back to the control level after 8 (126 ± 12.73 ng/dl) and 12 wk INF (130.2 ± 8.3 ng/dl; Fig. 3C). The sham-operated animals did not show any changes in serum TSH, T_4, and T_3 values during the experimental period (Fig. 3). These data indicate a preserved hypothalamus-pituitary axis after MI.

D1 activity in the pituitary, thyroid, liver, and kidney was significantly lower in infarcted rats compared with sham operated ($P < 0.05$), as analyzed 4 and 12 wk after INF (Fig. 4). Under physiological conditions, hepatic and renal D1 activities are mainly modulated by serum T_4 and T_3 (27), and might be decreased in these animals due to the significantly decreased serum T_4 levels. At present we have no explanation for the decreased thyroid D1 activity that occurs 4 wk after INF, despite high-serum TSH.

Type 3 iodothyronine deiodinase activity

We next wanted to determine if increased D3-mediated TH inactivation could contribute to the decrease in serum T_4 and T_3 observed after MI. To test this, we measured D3 activity in cardiac tissue from infarcted *vs.* sham-operated rats. As in a previously published rat model of congestive heart failure (28), D3 activity in sham-control animals was uniformly low (<0.1 fmol/min·mg). In contrast, there was high D3 activity in the infarcted myocardium, ranging from 0.22–0.77 fmol/min·mg. There was no difference in hepatic D3 activity between the sham (0.91 ± 0.17 fmol/min·mg) and

TABLE 1. Body weight, and heart, lung, liver, and thyroid index 12 wk after surgery

	Sham	Infarcted
Body weight (g)	363.50 ± 10.17	320.50 ± 15.88[a]
Heart index (mg/g)	3.27 ± 0.08	5.01 ± 0.38[b]
Lung index (mg/g)	4.30 ± 0.34	6.68 ± 0.68[b]
Liver index (mg/g)	30.10 ± 1.10	28.70 ± 1.25
Thyroid index (μg/g)	30.72 ± 1.77	30.29 ± 1.16

[a] $P < 0.05$ *vs.* sham group.
[b] $P < 0.01$ *vs.* sham group.

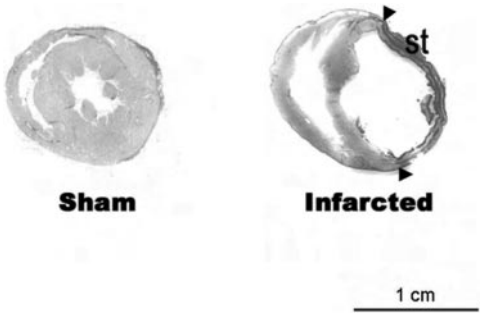

FIG. 2. Representative cross-section of heart slice from a sham and infarcted animal stained with Picrosirius red. The *arrowheads* delimit the scar tissue (st) in the LV.

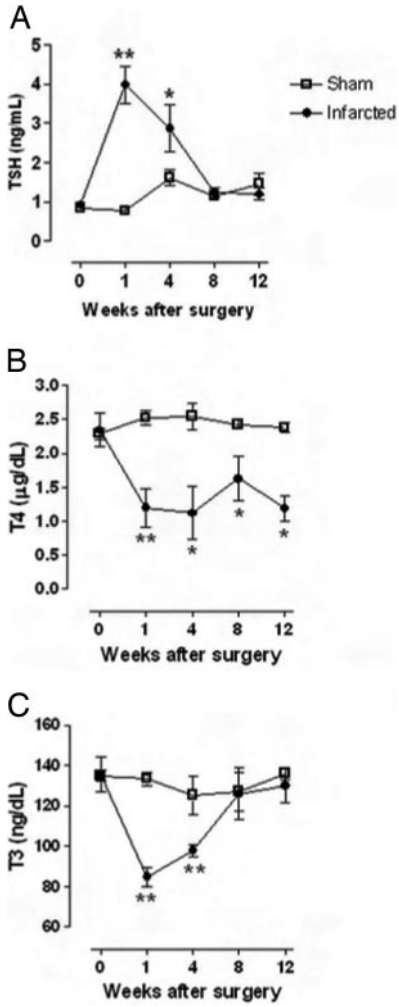

FIG. 3. Serum TSH (A), T_4 (B), and T_3 (C) determined by RIA in sham and infarcted groups before (0 wk), and 1, 4, 8, and 12 wk after surgery. *, $P < 0.05$ and **, $P < 0.01$ *vs.* infarcted group before surgery and sham group at the same week.

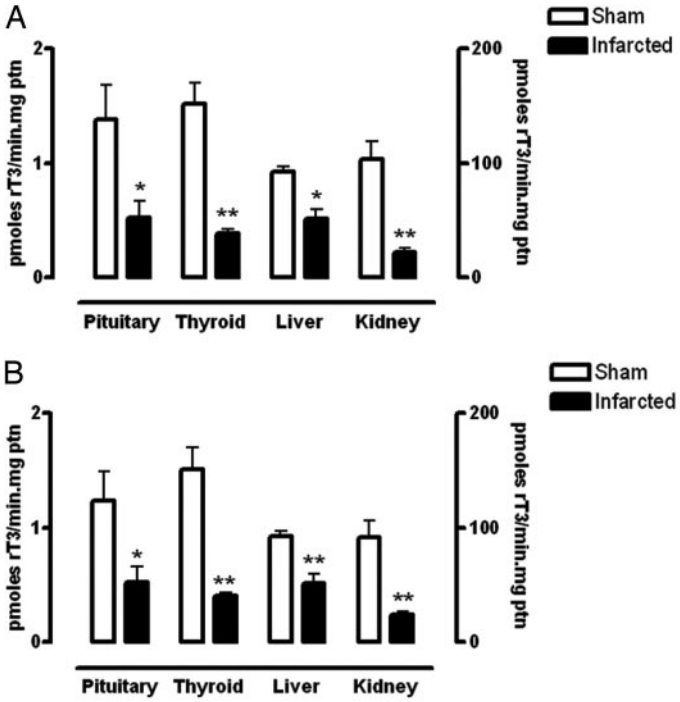

FIG. 4. D1 activity assessed in sham and infarcted group 4 (A) and 12 (B) wk after surgery. The *left* y-axis refers to pituitary activity, and the *right* y-axis to the thyroid, liver, and kidney activities. *, $P < 0.05$ and **, $P < 0.01$ *vs.* sham group.

infarcted (1.23 ± 0.38 fmol/min·mg) groups, illustrating the tissue specificity of this D3 induction.

Short-term radioiodide uptake: NIS activity

One day after MI, no differences in short-term thyroid radioiodide uptake were detected when compared with sham-operated rats (INF = 19.1 ± 1.53% I/g thyroid; sham = 15.1 ± 4.59% I/g thyroid; Fig. 5). However, 1 wk after surgery, infarcted rats showed a significant increase in short-term thyroid radioiodide uptake compared with sham-operated rats (INF = 39.9 ± 3.0% I/g thyroid; sham = 18.7 ± 8.10% I/g thyroid; $P < 0.05$). On the other hand, 12 wk after surgery, NIS function was significantly decreased after INF (INF = 14.2 ± 1.83% I/g thyroid; sham = 20.0 ± 1.11% I/g thyroid; $P < 0.05$; Fig. 5). These findings show that thyroid gland function is preserved shortly after MI and is even increased secondary to the high-serum TSH levels but seems to be strikingly impaired late during cardiac dysfunction, notwithstanding normal serum TSH.

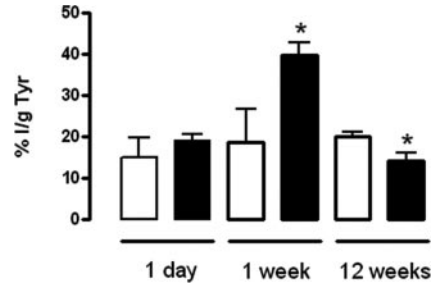

FIG. 5. Short-term radioiodide uptake study performed in sham and infarcted groups 1 d, and 1 and 12 wk after surgery. *, $P < 0.05$ *vs.* sham group. Tyr, Thyroid.

Basal and TRH-stimulated TSH in vivo

The serum TSH level was significantly increased after TRH injection in all groups studied (data not shown). Comparing the ratio of TSH response to TRH (TSH after/TSH before TRH stimulation), the infarcted rats had a significantly higher TSH response to TRH 1 wk after surgery (Fig. 6). However, despite the persistent low T_4 during the whole experimental period, the TSH response to TRH normalized in the infarcted group 8 wk after surgery (Fig. 6), when basal serum TSH had also returned to the levels found in sham-operated animals. Altogether, our data indicate that the decreased thyroid function is not secondary to pituitary failure and that serum TSH better correlates with T_3 rather than with T_4 in these animals.

Discussion

The vast majority of studies in which thyroid function has been studied after MI were performed in humans, and do not allow a time course-controlled evaluation due to the differences in outcome and drugs used. Thus, the mechanism underlying the normal serum TSH and low T_3 levels after MI in humans is largely unknown, and could be related to changes in the hypothalamus-pituitary axis, concomitant pathologies, use of drugs, and hospitalization. As assessed by functional and pathological studies, we show here that severe cardiac dysfunction in rats induces an early decrease in serum T_4 levels, which remained low until the end of the study, *i.e.* 12 wk after INF. The early decrease of both T_4 and T_3 together with high-serum TSH indicates that the transient hypothyroidism is established secondary to modifications in the peripheral TH metabolism. In fact, not only was serum TSH elevated, but also the *in vivo* TSH response to TRH was increased, as in other hypothyroid states. In addition, thyroid NIS function is increased 1 wk after MI, indicating stimulation of the thyroid gland.

A decrease in D1 activity, as seen in the present study, has been implicated in the pathogenesis of the low T_3 syndrome during illness (29). The mechanism underlying low D1 activity in our model could include the decrease in serum T_4 and/or be a result of increased cytokine action, which has been induced after acute MI (30) and inhibited hepatic 5′ monodeiodinase activity (31). However, the induction of high ectopic D3 activity in infarcted cardiac tissue supports the concept that D3-mediated inactivation is the major cause

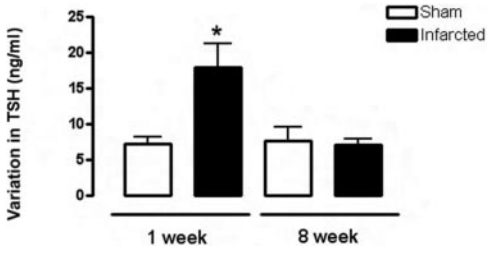

FIG. 6. Variation in serum TSH level after TRH injection in sham and infarcted groups 1 and 8 wk after surgery. *, $P < 0.05$ *vs.* sham in 1 wk.

of the abrupt decrease in serum TH levels after MI. D3 is a catabolic enzyme that is induced in many models of tissue injury, including a previously reported rat model of cardiac hypertrophy (28), and its reactivation has been correlated with changes in systemic thyroid status during critical illness (32). The induction of D3 we show here after MI further supports its role as a modulator of thyroid status in the euthyroid sick syndrome. However, a unique feature of the current model is the documentation of thyroid stimulation, evidenced by both hyperthyrotropinemia (Fig. 3) and increased short-term radioiodide uptake (Fig. 5). This is in sharp contrast to other models of nonthyroidal illness that share suppression of the hypothalamic-pituitary-thyroid axis as a common feature. This indicates that altered deiodination is the primary cause of low-serum T_4 and T_3 after acute MI, and that hypothyroidism occurs despite compensatory changes in the central axis physiology that has previously been reported only in the context of consumptive hypothyroidism from large D3-expressing tumors (33).

In contrast to the present findings, Ojamaa *et al.* (16) have previously described low T_3 syndrome, *i.e.* unaltered serum T_4 and low T_3 after 1 wk MI in rats, which were maintained throughout the 4 wk-period of study. In this previous study, serum TSH was not evaluated. Considering the same level of cardiac dysfunction (mean EF reduced by ~50%), we suggest that the differences observed in serum T_4 levels are the result of the distinct protocols used. Our analyses were performed in the same infarcted animals at different time points, whereas Ojamaa *et al.* (16) have used different rats at different periods. Another possibility to explain these controversial results is based on the compensatory state presented by failing hearts. It has been described that a 40–60% reduction of plasma T_4 and T_3 with normal TSH levels in rats with congestive heart failure (decompensate state) and normal T_4, T_3, and TSH in rats with cardiac hypertrophy without signs of heart failure (compensatory hypertrophy) in chronic overload induced a right ventricular hypertrophy model (28). In line with this, all rats included in this work presented congestive heart failure, as demonstrated in the postmortem study. In addition, we have extended the follow-up to assess thyroid status for a longer period of time and observed low-serum T_4 throughout the period of a 12-wk study.

The failing heart might functionally and phenotypically resemble the hypothyroid heart (5, 7, 9, 10). Furthermore, numerous reports document altered TH metabolism with low-serum T_3 levels in patients with congestive heart failure (34–37). Considering that T_3 might be important for heart function reestablishment, several mechanisms might be involved in the permanent cardiac failure despite normalization of serum T_3. Despite intrinsic changes from the cardiac remodeling process and deleterious neurohumoral activation after ischemic insult, part of the cause for the persistent impairment of cardiac function despite recovery of serum T_3 to control levels is multifactorial and can be ascribed to: 1) an impairment of TH signaling on cardiac tissue, as a downregulation in TRα1 and TRβ1 reported in the MI model (38) and/or changes in transcriptional activity of the TH receptor as described for pressure overload-induced hypertrophy (39); 2) a decrease in TH uptake; 3) altered T_4 to T_3 conversion in cardiomyocytes; and 4) increased degradation of TH by type 3 iodothyronine, which occurs in heart hypertrophy (36). Conversely, decreased serum T_3 could in turn correspond to a protective mechanism that occurs immediately after acute injury.

Our data indicate that an acute decrease in both serum T_4 and T_3 occurs after MI as the result of altered TH metabolism, with increased TH inactivation from ectopic cardiac D3 activity as the major cause. Unlike other animal models of thyroid status derangement during systemic illness, we observed compensatory stimulation of the hypothalamic-pituitary-thyroid axis evidenced by both hyperthyrotropinemia and increased radioiodine uptake. These features are uniquely reminiscent of the pathophysiology of the consumptive hypothyroidism, which has previously been described in patients with large D3-expressing tumors. The possible mediator(s) of these changes in thyroid function economy and whether the transient hypothyroidism could be implicated in the pathophysiology of heart failure after MI or is conversely protective, are currently under study by our group.

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