Thyroid hormone attenuates cardiac remodeling and improves hemodynamics early after acute myocardial infarction in rats

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Abstract

Objective: Cardiac remodeling of viable myocardium occurs after acute myocardial infarction (AMI) and further contributes to cardiac dysfunction. The present study explored whether thyroid hormone (TH) administered shortly after AMI in rats can attenuate cardiac remodeling and improve cardiac function. TH regulates important structural and regulatory proteins in the myocardium including myosin isoform expression and calcium cycling proteins.

Methods: AMI was induced in Wistar male rats by ligating left coronary artery (AMI, n = 10), while sham-operated rats were used as controls (SHAM, n = 10). Animals with acute myocardial infarction were also treated with 0.05% thyroid powder in food (AMI-THYR, n = 10). Within 2 weeks, cardiac function was impaired as assessed by echocardiography and under isometric conditions in Langendorff preparations. Results: Ejection fraction (EF%) was 71.5 (SEM, 2.7) in SHAM versus 30.0 (2.0) in AMI, P < 0.05. +dP/dt was 3886 (566) in SHAM versus 2266 (206) in AMI hearts, P < 0.05 and –dP/dt was 1860 (46) in SHAM versus 1633 (120) in AMI hearts, P = ns. Such changes were associated with alterations in myosin isoform expression in the non-infarcted area; AMI hearts expressed 34% α-MHC and 66% β-MHC versus 52% α-MHC and 48% β-MHC in SHAM, P < 0.05, while the expression of SERCA and phospholamban (PLB) remained unchanged. Furthermore, a mismatch of left ventricular size and cardiac mass (2*Posterior Wall thickness/LVIDd was decreased) was observed. After TH treatment, AMI-THYR hearts expressed 71% α-MHC and 29% β-MHC, P < 0.05 versus SHAM and AMI and the ratio of SERCA/PLB was increased by 2.0-fold, P < 0.05 versus SHAM and AMI. These changes corresponded to a marked improvement in cardiac function; EF% was raised to 45.8 (1.7), P < 0.05 versus AMI while +dP/dt and –dP/dt were 3800 (435) and 2600 (200), respectively, in AMI-THYR hearts, P < 0.05 versus AMI. The ratio of 2*Posterior Wall thickness/LVIDd was normalized.

Conclusions: Thyroid hormone administration early after infarction attenuates cardiac remodeling and significantly improves myocardial performance.

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Keywords: Thyroid hormone; Acute myocardial infarction; Cardiac remodeling; Myosin; PKC; Thyroid hormone receptors

1. Introduction

It is now recognized that cardiac dysfunction after acute myocardial infarction (AMI) is not only due to the extent of myocardial necrosis but also to the remodeling of viable myocardium. During this process, a fetal-like phenotype is recapitulated including a shift to fetal pattern of myosin isoform expression with an increase in β-MHC and decrease in α-MHC expression. Among the various neuro-hormonal factors which are thought to contribute to this response is thyroid hormone. In fact, changes in thyroid hormone—thyroid hormone nuclear receptors axis can occur after myocardial infarction, cardiac hypertrophy or heart failure and may, at least in part, contribute to fetal phenotype which characterizes these conditions [1–3]. Furthermore, low thyroid hormone levels appears to be an independent predictor of mortality and morbidity in patients with heart disease [4, 5]. Thyroid hormone critically regulates cardiac performance, since several genes encoding important structural and regulatory proteins in the myocardium, including myosin isoform expression [6], calcium cycling proteins [7] and protein kinases (such as PKCα and PKCε known to phosphorylate cardiac contractile proteins) are thyroid hormone responsive [8–10]. Thus, thyroid analogs are suggested as potential therapeutic agents for treating heart failure [11, 12].

Based on this evidence, the present study further explored the effects of thyroid hormone on cardiac remodeling and cardiac function administered shortly after acute myocardial infarction, cardiac hypertrophy or heart failure and may, at least in part, contribute to fetal phenotype which characterizes these conditions [1–3]. Furthermore, low thyroid hormone levels appears to be an independent predictor of mortality and morbidity in patients with heart disease [4, 5]. Thyroid hormone critically regulates cardiac performance, since several genes encoding important structural and regulatory proteins in the myocardium, including myosin isoform expression [6], calcium cycling proteins [7] and protein kinases (such as PKCα and PKCε known to phosphorylate cardiac contractile proteins) are thyroid hormone responsive [8–10]. Thus, thyroid analogs are suggested as potential therapeutic agents for treating heart failure [11, 12].

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injury in rats. This issue is of clinical and therapeutic relevance.

2. Materials and methods

2.1. Animals

Fifty male Wistar rats, weighing 280–360 g, were used for this study. The rats were handled in accordance with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health Guide (NIH Pub. No. 83–23, Revised 1996).

2.2. Experimental model of myocardial infarction

Myocardial infarction was induced by ligation of the left coronary artery as previously described [2]. Rats were anesthetized with an intraperitoneal injection of ketamine (70 mg/kg) and midazolam (0.1 mg/kg), intubated and ventilated via a tracheal cannula using a constant-volume rodent ventilator (Harvard Apparatus, Inspira, 50 breaths/min, 1 ml/100 g tidal volume). Anesthesia was maintained by inhalation of small doses of sevoflurane (2—3%). Left thoracotomy was performed at the fourth intercostal space followed by pericardiotomy. Left coronary artery was then ligated with a 6—0 silk round-bodied suture. The heart was followed by pericardiotomy. Left coronary artery was then ligated with a 6—0 silk round-bodied suture. The heart was quickly returned to the chest cavity, the chest was closed and rats were allowed to recover using assistant mode ventilation. Atelectasis was prevented by producing positive end-expiratory pressure at the end of the surgical procedure. Continuous ECG recording was used to monitor heart rate and ECG ischemic changes after coronary artery ligation. Body temperature was maintained at 37°C by using a heating blanket (Harvard Homeothermic Blanket, 50-7061). The mortality was up to 40% for the infarction group within the first 24 h. Myocardial infarctions which produced a scar area 35—55% of the left ventricle. The animals were left to recover for 2 weeks after myocardial infarction. This group of animals was designated as AMI. The same procedure was followed for sham-operated control animals, but the coronary artery was not ligated. These animals were designated as SHAM.

2.3. Thyroid hormone administration

Rats subjected to coronary artery ligation were randomly divided in two groups 24 h after the operation. The first group received standard rat chow (AMI), while the second group received food containing thyroid powder 0.05% (Sigma, T1251, containing 0.42 μg/mg T3 and 1.7 μg/mg T4) for 2 weeks (AMI-THYR). The dose of thyroid powder was selected after pilot studies looking at beneficial effects without major side effects. Mean daily intake of thyroid hormone per rat was 4 μg T3 and 16 μg T4, while it is known that gastrointestinal absorption of thyroid hormone varies from 50 to 75%.

2.4. Echocardiography

At 2 weeks after coronary artery ligation, rats were sedated with ketamine hydrochloric acid (100 mg/kg) and heart function was evaluated by echocardiography. Short- and long-axis images were acquired using a digital ultrasound system (Sonosite 180Plus, 21919 30th Drive SE, Bothell, WA, USA) with a 7.0-MHz sector-array probe. Left ventricular internal diameter at diastolic phase (LVIDd), LV internal diameter at systolic phase (LVIDs), posterior wall thickness at diastolic phase (LVPW), posterior wall velocity of shortening (PWV) and ejection time (ET) were measured. Ejection fraction was calculated as follows EF% = [(LVIDd3 — LVIDs3)/ LVIDd3] × 100. Fractional shortening was measured using the equation FS = [(LVIDd — LVIDs)/LVIDd] × 100. Furthermore, the ratio (2*Posterior Wall thickness/LVIDd) was measured as an indirect assessment of myocardial wall stress. All measurements were averaged for at least three consecutive cardiac cycles. Echocardiographic studies were performed blindly.

2.5. Isolated heart preparation

A non-ejecting isolated rat heart preparation was perfused at a constant flow according to the Langendorff technique [13,14]. An intraventricular balloon allowed measurement of contractility under isovolumic conditions. Left ventricular balloon volume was adjusted to produce an average initial left ventricular end-diastolic pressure of 6—7 mmHg in all groups and was held constant thereafter throughout the experiment.

Rats were anesthetized with ketamine hydrochloric acid and heparin 1000 IU/kg was given intravenously before thoracotomy. The hearts were rapidly excised, placed in ice-cold Krebs—Henseleit buffer (composition in mmol/l: sodium chloride 118, potassium chloride 4.7, potassium phosphate monobasic 1.2, magnesium sulfate 1.2, calcium chloride 1.4, sodium bicarbonate 25, and glucose 11) and mounted on the aortic cannula of the Langendorff perfusion system. Perfusion with oxygenated (95% O2/5% CO2) Krebs—Henseleit buffer was established within 60 s after thoracotomy. The perfusion apparatus was heated to ensure a temperature of 37°C throughout the course of the experiment. Hearts were paced at 320 beats/min with a Harvard pacemaker. The water-filled balloon, connected to a pressure transducer and coupled to a Gould RS 3400 recorder, was advanced into the left ventricle through an incision in the left atrium. Pressure signal was transferred to a computer using a data analysis software (IOX, Emka Technologies) which allowed continuous monitoring and recording of heart function.

As intraventricular volume was maintained at a constant value, diastolic fiber length, which represented preload, did not change. Thus, the left ventricular developed pressure (LVDP), defined as the difference between left ventricular peak systolic pressure and left ventricular end-diastolic pressure, represented a contractility index obtained under isometric conditions. Left ventricular systolic function was assessed by recording the left ventricular developed pressure (LVDP, mmHg) and the positive and negative first derivative of LVDP; +dp/dt (mmHg/s), −dp/dt (mmHg/s). All preparations were perfused for 30 min and measurements were performed at the end of this period. All preparations included in this study were stable for at least the last 15 min of the perfusion period. Isolated hearts that did not produce stable measurements of LVDP, LV end-diastolic pressure and perfusion
pressure for the last 15 min of the perfusion period were excluded from analysis.

2.6. Experimental protocol

Sham-operated rats (SHAM, n = 10) and rats subjected to coronary artery ligation without and with thyroid hormone treatment (AMI, n = 10 and AMI-THYR, n = 10 respectively) after 2 weeks were anesthetized and subjected to echocardiography analysis. Heart rates were recorded using surface ECG (lead I, II, III, aVR, aVL, aVF) (Cardiograpapid K111, 50 mm/s). Five rats from each group were used to measure contractile function in Langendorff preparation, while five additional rats from each group were used for protein analysis. Blood was collected from the left atrium in order to measure total T3 and T4 in serum. The left ventricle was isolated from each heart, scar tissue was dissected out and the non-infarcted left ventricle was immediately frozen in liquid nitrogen. Weights of the scar tissue and the viable left ventricular tissue were measured. The area of the scar tissue was measured in mm².

2.7. Measurement of thyroid hormones

Plasma l-thyroxine and 3,5,3’ triiodothyronine quantitative measurements were performed with ELISA, using kits obtained from Alpha Diagnostic International, Texas, USA (No. 1100 for total T4 and No. 1700 for total T3), as previously described [2]. l-Thyroxine and 3,5,3’ triiodothyronine levels were expressed as nmol/l of plasma. Absorbance measurements were performed at 450 nm with Tecan Genios ELISA reader (Tecan, Austria).

2.8. Protein isolation, sodium dodecyl sulfate–protein polyacrylamide (SDS–PAGE) gel electrophoresis and immunodetection

Approximately 0.2 g of left ventricular tissue was homogenized in ice-cold buffer (A) containing 10 mM Hepes (pH 7.8), 10 mM KCl, 0.1 mM EDTA, 0.1 mM EGTA, 0.5 mM PMSE, 1 mM DTT and 10 μg/ml leupeptin. Two hundred microliter of 10% Igepal was added and samples were left in ice for 30 min. Homogenization was repeated and a small fraction of total lysis was kept for PKCζ, PKCε and myosin heavy chain isoform analysis. The rest of the homogenate was centrifuged at 1000 x g for 5 min, 4 °C and the supernatant representing the cytosol-membrane fraction was kept for SERCA and phosphorylamban protein analysis, while the pellet containing the nuclear fraction was washed again in buffer (A) with 1% Igepal. The final pellet was resuspended in 300 μl buffer (B) containing 20 mM Hepes (pH 7.8), 420 mM NaCl, 1 mM EDTA, 1 mM EGTA, 0.5 mM PMSE, 1 mM DTT, 10 μg/ml leupeptin and 10% glycercine and samples were incubated at 4 °C for 60 min followed by centrifugation at 10,000 x g for 5 min, 4 °C. The supernatant containing the nuclear fraction was separated and stored at −80 °C, while the pellet containing cellular debris and cytoskeleton was discarded [2]. TRα1, TRβ1 and TRα2 protein expression was determined in nuclear fraction. Protein concentrations were determined by the BCA method.

Samples were prepared for sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS–PAGE) by boiling for 5 min in Laemmli sample buffer containing 5% 2-mercaptoethanol. Forty or 20 μg (nuclear fraction) of total protein was loaded onto 10% (w/v) acrylamide gels and subjected to SDS–PAGE in a Bio-Rad Mini Protein gel apparatus. For Western blotting, following SDS–PAGE, proteins were transferred electrophoretically to a nitrocellulose membrane (Hybond ECL) at 100 V and 4 °C for 1.5 h using Towbin buffer. After Western blotting, filters were probed with specific antibodies against TRα1 (Affinity Bioreagents, PA1-211A, dilution 1:1000, 2 h at 37 °C), TRβ1 (Affinity Bioreagents, MA1-216, dilution 1:1000, o/n at 4 °C), TRα2 (Affinity Bioreagents, PA1-216, dilution 1:500, 2 h at 37 °C), histone H3 (Cell Signaling, #9715, dilution 1:1000, o/n at 4 °C), SERCA (Affinity Bioreagents, MA3-919, dilution 1:1000, o/n at 4 °C), phosphorylamban (Affinity Bioreagents, MA3-922, dilution 1:1000, o/n at 4 °C), PKCα (BD Biosciences, 610108, dilution 1:1000, 2 h at RT) and PKCζ (Affinity Bioreagents, BD Biosciences, 610086, dilution 1:1000, o/n at 4 °C). Filters were incubated with appropriate anti-mouse (Amersham) or anti-rabbit (Cell Signaling) HRP secondary antibodies and immunoreactivity was detected by enhanced chemiluminescence using Lumiglo reagents (New England Biolabs) and exposed to Hyperfilm paper (Amersham). Five samples from each group were loaded on the same gel. Histone H3 protein expression was used in order to normalize slight variations in nuclear protein loading. Immunoblots were quantified using the AlphaScan Imaging Densitometer (Alpha Innotech Corporation, 14743, Catalina Street, San Leandro, CA).

2.9. Measurement of myosin heavy chain isoform content

Homogenates of all samples were diluted 40-fold with Laemmli sample buffer containing 5% 2-mercaptoethanol. The composition and preparation of the gels was carried out as previously described [15,16]. Briefly, the stacking and separating gels consisted of 4 and 8% acrylamide (w/v) respectively, with acryl:bis-acryl in the ratio of 5:1. The stacking and separating gels included 5% (v/v) glycerol. The upper running buffer consisted of 0.1 M Tris (base), 150 mM glycine, 0.1% sodium dodecyl sulfate (SDS) and 2-mercaptoethanol at a final concentration of 10 mM. The lower running buffer consisted of 0.05 M Tris (base), 75 mM glycine and 0.05% SDS. The gels were run in Biorad Protein II xi electrophoresis unit at a constant voltage of 240 V for 21 h at 8 °C. The gels were fixed and silver-stained (Biorad silver stain kit). Gels were scanned and quantified using the AlphaScan Imaging Densitometer (Alpha Innotech Corporation, USA).

2.10. Statistics

Results are presented as mean (SD). Unpaired t-test and Mann–Whitney U-test were used to evaluate differences between groups. One-way analysis of variance with Bonferroni or Dunnnett correction was used for multiple comparisons. Significance was set at 0.05.

3. Results

3.1. Thyroid hormones levels in plasma and heart rate

T3 and T4 plasma levels and heart rate are shown in Table 1. Thyroid hormone levels did not change significantly.
at 2 weeks after coronary artery ligation. In addition, thyroid hormone treatment in post-infarcted rats caused a modest but significant increase in $T_3$ and $T_4$ levels. Heart rate was found to be increased by 15% in AMI-THYR as compared to AMI hearts, $P < 0.05$, but without significant difference as compared to SHAM hearts (Table 1).

### 3.2. Cardiac hypertrophy

Although scar area and weight were not different between AMI and AMI-THYR hearts, viable left ventricular weight was significantly greater in AMI-THYR hearts (Table 1). Protein content of viable heart tissue was found to be increased by 40% in AMI-THYR hearts as compared to SHAM hearts, indicating the development of cardiac hypertrophy, while there was no significant difference between SHAM and AMI hearts (Table 1). Furthermore, left ventricular posterior wall thickness was increased in post-infarcted hearts at 2 weeks only with thyroid hormone treatment (Table 2).

### 3.3. Echocardiographic study

Echocardiographic measurements are shown in Table 2. Post-infarcted hearts at 2 weeks after coronary artery ligation showed significant dilation of the left ventricle with reduced contractile function. Thyroid hormone treatment in post-infarcted rats resulted in a modest decrease in LVIdd and significant increase in all contractile indexes. The ratio $(2\times\text{Posterior Wall thickness/LVIdd})$ was reduced in post-infarcted hearts, indicating increased myocardial wall stress. Thyroid hormone treatment resulted in normalization of this ratio.

### 3.4. Contractile function assessed in Langendorff preparation

LVDP was found to be 116.0 (8) in SHAM hearts versus 84.6 (17) in AMI hearts, $P = 0.024$. In AMI-THYR hearts, LVDP was 118.6 (22), $P = 0.015$ versus AMI hearts (Fig. 1A). $+dp/dt$ was 3886 (1000) in SHAM versus 2266 (500) in AMI hearts, $P = 0.03$, while it was 3800 (950) in AMI-THYR, $P = 0.04$ versus AMI. In addition, $-dp/dt$ was 1860 (180) in SHAM versus 1633 (250) in AMI-THYR.

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**Table 1**

<table>
<thead>
<tr>
<th>Scar area (mm$^2$)</th>
<th>SHAM (n=10)</th>
<th>AMI (n=10)</th>
<th>AMI-THYR (n=10)</th>
</tr>
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<tbody>
<tr>
<td>109 (20)</td>
<td>112 (15)</td>
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**Table 2**

<table>
<thead>
<tr>
<th>Scar weight (mg)</th>
<th>SHAM (n=10)</th>
<th>AMI (n=10)</th>
<th>AMI-THYR (n=10)</th>
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<tbody>
<tr>
<td>181 (53)</td>
<td>165 (29)</td>
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**Table 2**

<table>
<thead>
<tr>
<th>Heart rate (bpm)</th>
<th>SHAM (n=10)</th>
<th>AMI (n=10)</th>
<th>AMI-THYR (n=10)</th>
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<tbody>
<tr>
<td>322 (27)</td>
<td>307 (38)</td>
<td>353 (32)</td>
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**Table 2**

<table>
<thead>
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<th>T3 (nM)</th>
<th>SHAM (n=10)</th>
<th>AMI (n=10)</th>
<th>AMI-THYR (n=10)</th>
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<td>1.48 (0.15)</td>
<td>1.3 (0.2)</td>
<td>2.2 (0.6)</td>
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**Table 2**

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<thead>
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<th>T4 (nM)</th>
<th>SHAM (n=10)</th>
<th>AMI (n=10)</th>
<th>AMI-THYR (n=10)</th>
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<tr>
<td>80.6 (15)</td>
<td>80.7 (18)</td>
<td>129.3 (11)</td>
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</table>

**Table 2**

<table>
<thead>
<tr>
<th>Protein content (μg/mg tissue)</th>
<th>SHAM (n=10)</th>
<th>AMI (n=10)</th>
<th>AMI-THYR (n=10)</th>
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<tbody>
<tr>
<td>633 (19)</td>
<td>421 (75)</td>
<td>525 (38)</td>
<td></td>
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**Table 2**

<table>
<thead>
<tr>
<th>LVIdd (mm)</th>
<th>SHAM (n=10)</th>
<th>AMI (n=10)</th>
<th>AMI-THYR (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.7 (0.3)</td>
<td>9.2 (0.26)</td>
<td>8.8 (0.3)</td>
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**Table 2**

<table>
<thead>
<tr>
<th>PW (mm/s)</th>
<th>SHAM (n=10)</th>
<th>AMI (n=10)</th>
<th>AMI-THYR (n=10)</th>
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<tr>
<td>35.4 (8.8)</td>
<td>21.7 (6.9)</td>
<td>33.9 (5.0)</td>
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**Table 2**

<table>
<thead>
<tr>
<th>EF%</th>
<th>SHAM (n=10)</th>
<th>AMI (n=10)</th>
<th>AMI-THYR (n=10)</th>
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<tr>
<td>71.5 (6.8)</td>
<td>30.0 (6.0)</td>
<td>45.8 (4.9)</td>
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**Table 2**

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<tr>
<th>LVDP (mmHg)</th>
<th>SHAM (n=10)</th>
<th>AMI (n=10)</th>
<th>AMI-THYR (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>116.0 (8)</td>
<td>84.6 (17)</td>
<td>118.6 (22)</td>
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</table>
AMI hearts, not statistically different, while it was 2600 (400) in AMI-THYR, \( P = 0.001 \) versus AMI and SHAM (Fig. 1B).

3.5. Expression of thyroid hormone receptors

Previous studies have shown that the expression of thyroid hormone receptors is important for the regulation of contractile proteins, while changes have been reported in relation to acute myocardial infarction [2,3].

In the present study, after AMI, TRa2 protein expression was found to be slightly increased but not to a statistically significant level, while no change was found in TRa1 protein expression. Thyroid hormone treatment resulted in 2.6- and 2.3-fold increase in TRa2 and TRa1 protein expression, respectively, \( P < 0.05 \) (Fig. 2). TRb1 protein expression was found to decrease 1.35-fold in AMI hearts, \( P = 0.08 \), while there was a 1.9-fold increase in AMI-THYR hearts, \( P < 0.05 \) (Fig. 2).

3.6. SERCA, phospholamban and MHC isoform protein expression

AMI hearts were found to express 34% \( \alpha \)-MHC and 66% \( \beta \)-MHC as compared to 52% \( \alpha \)-MHC and 48% \( \beta \)-MHC expression observed in SHAM hearts, \( P < 0.05 \). Thyroid hormone treatment in post-infarcted hearts resulted in a shift from \( \beta \)-MHC to \( \alpha \)-MHC. In fact, AMI-THYR hearts expressed 71% \( \alpha \)-MHC and 29% \( \beta \)-MHC, \( P < 0.05 \) versus SHAM and AMI (Fig. 3A).

In the post-infarcted hearts, no change was found to occur in SERCA and phospholamban protein expression at 2 weeks. Thyroid hormone treatment resulted in 2.0-fold increase in the ratio of SERCA to phospholamban, \( P < 0.05 \) versus SHAM and AMI. This increase was mainly due to the decrease in phospholamban protein expression caused by thyroid hormone (Fig. 3B).

3.7. PKCa and PKCe protein expression

In post-infarcted hearts, PKCe decreased 1.35-fold, \( P < 0.05 \) versus SHAM, while PKCa protein expression was found to be slightly increased but not to a statistically significant level. Thyroid hormone treatment resulted in 2.3- and 3.0-fold decrease in PKCe and PKCa, respectively, \( P < 0.05 \) versus SHAM and AMI (Fig. 4).

4. Discussion

The present study, using an experimental model of AMI in rats, demonstrated that thyroid hormone administration...
Lamban remained unchanged. The latter probably indicates that, at this stage, calcium uptake by sarcoplasmic reticulum may not be severely compromised. This is further supported by the fact that the rate of left ventricular relaxation was not shown to be significantly reduced.

Our study was further extended to explore whether other mechanisms known to be involved in the regulation of cardiac contractility have also contributed to cardiac remodeling of viable myocardium. PKC and particularly certain isoforms are now shown to serve an important role in cardiac contractility. In fact, PKC\(\varepsilon\) and PKC\(\alpha\) affect contractile function directly through myofilament phosphorylation \[8,10\]. Cardiac dysfunction is observed in transgenic animals overexpressing PKC\(\varepsilon\), while PKC\(\alpha\) is overexpressed in the hypothyroid hearts which are hypo-contractile \[10,17\]. Furthermore, pharmacological and gene therapy-based inhibition of PKC\(\alpha\) enhances cardiac contractility and attenuates heart failure \[8\]. In the present study, PKC\(\varepsilon\) expression was significantly decreased in viable myocardium, while PKC\(\alpha\) protein expression was found to be slightly increased, although not to a statistically significant level. Taken together, it could be suggested that, at this early stage, PKC\(\varepsilon\) may have a protective role against functional decompensation.

Evidence of chamber remodeling was provided by echocardiography analysis showing that the size of left ventricular cavity was increased without a concomitant significant increase in cardiac mass. Thus, the ratio (2*Posterior Wall thickness/LVIDd) was found to be significantly reduced. Such a mismatch between the left ventricular cavity size and wall thickness may be responsible for the increased systolic left ventricular wall stress which subsequently increases myocardial oxygen consumption with unfavorable effects on cardiac hemodynamics.

4.2. Effects of thyroid hormone on cardiac remodeling and cardiac function

In the present study, we have not observed significant changes in thyroid hormone signaling at this early stage after myocardial infarction. A trend though towards lower expression of TR\(\beta\)1 receptor was seen. Thyroid hormone signaling probably plays an important role in pathophysiology of cardiac remodeling at later stages after myocardial infarction \[2,3\]. However, thyroid hormone administration shortly after left coronary ligation displayed striking effects on cardiac remodeling and consequently on cardiac function. In fact, in viable myocardium, the expression of \(\alpha\)-MHC and the ratio of SERCA/PLB were increased, while \(\beta\)-MHC expression was decreased. Furthermore, PKC\(\alpha\) expression was significantly reduced while PKC\(\varepsilon\) expression further declined. Both PKC\(\alpha\) and PKC\(\varepsilon\) are regulated by thyroid hormone \[9\].

The observed changes at the molecular level were translated to a marked improvement in cardiac function in thyroid hormone treated animals; EF\%, FS\%, \(+dp/dt\) and \(--dp/dt\) under isometric conditions were all significantly increased as compared to untreated hearts. However, this functional improvement may also be due to the thyroid hormone vasodilating effect on peripheral vasculature \[18\]. Thus, the increase in parameters, such as EF\%, which are load dependent, could be attributed both to thyroid hormone effects on the myocardium and to reduced afterload.
Thyroid hormone treatment was associated with marked effects on chamber remodeling. Chamber diameter was significantly reduced, while the cardiac mass was increased and the ratio (2°Posterior Wall thickness/LVIDd) reached the control value. Similar effects have previously been observed in hypertensive rats near heart failure. In fact, thyroid hormone significantly reduced myocardial wall stress, a response attributed to its unique effect on cardiac myocyte shape [19]. Interestingly, we have recently shown that thyroid hormone has the ability to change cardiac myocyte shape and geometry through the activation of ERK pathway independently of its effect on cell growth [3,20].

4.3. TH as potential therapeutic treatment

Recent clinical and experimental studies suggest that thyroid hormone may prove suitable treatment for cardiac diseases. Apart from its well known inotropic effect, thyroid hormone seems to induce cardioprotection against ischemia in various experimental settings [14,21,22]. More importantly, this finding has been recently confirmed even in patients undergoing CABG. T3 administration in those patients significantly improved the post-ischemic cardiac hemodynamics and reduced the extent of myocardial injury [23]. Thyroid hormone is shown to upregulate important hemodynamics and reduced the extent of myocardial injury significantly improved the post-ischemic cardiac performance. This may be of important diseases. Apart from its well known inotropic effect, thyroid hormone changes cardiomyocyte shape and geometry via ERK signaling pathway: potential therapeutic implications in reversing cardiac remodeling? Mol Cell Biochem 2007;297:65—72.

In conclusion, thyroid hormone administration early after infarction can attenuate cardiac remodeling and significantly improve myocardial performance. This may be of important clinical and therapeutic relevance.

References


