Thyroid hormone metabolism and cardiac gene expression after acute myocardial infarction in the rat

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Ojamaa, Kaie, Agnes Kenessey, Rajesh Shenoy, and Irwin Klein. Thyroid hormone metabolism and cardiac gene expression after acute myocardial infarction in the rat. Am J Physiol Endocrinol Metab 279: E1319–E1324, 2000.—In a rat model of acute myocardial infarction (MI) produced by coronary artery ligation, thyroid hormone metabolism was altered with significant reductions (54%) in serum triiodo-L-thyronine (T₃), the cellular active hormone metabolite. T₃ has profound effects on the heart; therefore, rats were treated with T₃ after acute MI for 2 or 3 wk, at either replacement or elevated doses, to determine whether cardiac function and gene expression could be normalized. Acute MI resulted in a 50% (P < 0.001) decrease in percent ejection fraction (%EF) with a 32–35% increase (P < 0.01) in compensatory left ventricle (LV) hypertrophy. Treatment of the MI animals with either replacement or elevated doses of T₃ significantly increased %EF to 64 and 73% of control, respectively. Expression levels of several T₃-responsive genes were altered in the hypertrophied LV after MI, including significant decreases in α-myosin heavy chain (MHC), sarcoplasmic reticulum calcium-activated ATPase (SERCA2), and Kv1.5 mRNA, whereas β-MHC and phospholamban (PLB) mRNA were significantly increased. Normalization of serum T₃ did not restore expression of all T₃-regulated genes, indicating altered T₃ responsiveness in the postinfarcted myocardium. Although β-MHC and Kv1.5 mRNA content was returned to control levels, α-MHC and SERCA2 were unresponsive to T₃ at replacement doses, and only at higher doses of T₃ was α-MHC mRNA returned to control values. The present study showed that acute MI in the rat was associated with a fall in serum T₃ levels, LV dysfunction, and altered expression of T₃-responsive genes and that T₃ treatment significantly improved cardiac function, with normalization of some, but not all, of the changes in gene expression.

triiodothyronine; left ventricular ejection fraction; myosin; calcium ATPase; cardiac gene expression

Thyroid hormone has profound effects on cardiac contractile function as well as on cardiovascular hemodynamics, including blood pressure and systemic vascular resistance (7, 24, 39). The cellular-active metabolite of thyroid hormone, triiodo-L-thyronine (T₃), regulates expression of specific cardiomyocyte genes independent of its effects on cardiac growth and protein synthesis (37, 40). Certain T₃-responsive cardiac genes, including, but not limited to, the myosin heavy chains (MHC), phospholamban (PLB), and sarcoplasmic reticulum calcium-activated ATPase (SERCA2), are important determinants of cardiac contractility (14, 16, 19, 22). Their expression has been shown to be altered similarly in hypothyroidism and in various models of heart failure (1, 17, 28, 43).

Acute myocardial infarction (MI) is the major cause of heart failure in the adult American population (11). After acute MI, the remaining viable left ventricle (LV) undergoes hypertrophy and remodeling to compensate for the loss of the infarcted nonfunctional myocardium. Previous studies by Yue et al. (45) have reported alterations in cardiac phenotype after MI that may potentially contribute to the observed impairment in LV function. Ultimately, this compensation determines whether cardiac function is maintained or heart failure ensues.

Thyroid hormone metabolism has been reported to be abnormal in patients with chronic heart failure, with an impairment of t-thyroxine (T₄)-to-T₃ conversion resulting in a low T₃ state (13, 15). A significant decrease in serum T₃ was observed in humans after acute MI, which reached a nadir on the 4th day and persisted throughout the 10-day period of observation (8). Serum thyrotropin (TSH) levels remained unaltered during this period. Thus acute and chronic cardiac dysfunction can be characterized as nonthyroidal illnesses in which low serum T₃ levels can alter the expression of cardiac genes (5). In the present study, we addressed the hypothesis that the low T₃ state after acute MI may contribute to the changes in cardiac specific gene expression and further compromise the cardiac myocyte in its response to the ischemic injury. The low T₃ syndrome has not previously been reported in an animal model of ischemic heart disease.

MATERIALS AND METHODS

Animal treatment protocols. MI was produced by ligation of the left coronary artery of adult male Sprague-Dawley rats weighing between 180 and 200 g (Charles River Laborato-

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ries, Raleigh, NC). To assess the extent of the infarct, at 1 wk after MI surgery, the animals were sedated (100 mg/kg ketamine, 1.5 mg/kg xylazine) to obtain electrocardiographic (EKG) tracings and two-dimensional echocardiographic analysis (7.5 mHz probe; Acuson, Mountain View, CA). Ejection fraction (EF) and percent fractional shortening were measured by use of M-mode analysis. Heart rates were obtained from the EKG tracings. At that time, a randomly assigned subgroup of the MI animals received T3 (Sigma, St. Louis, MO). T3 was delivered subcutaneously by constant infusion via a miniosmotic pump (Alza, Palo Alto, CA) set to deliver 1.2 μg/day for 2 wk. A subgroup of these animals received 10 μg of T3 delivered twice daily by subcutaneous injection for an additional 1 wk. Blood from all animals was obtained from the ocular space at 1, 3, and 4 wk after the coronary artery ligation surgery to measure serum levels of total T4 and T3 by radioimmunoassay (DiaSorin, Stillwater, MN). Animals were weighed weekly.

Immediately before animals were killed, at either 3 or 4 wk after the MI surgery, EKG and echocardiographic measurements were reassessed. At death, a midline thoraocotomy exposed the heart, which was then removed; the atria and major vessels were removed, and the LV including the septum and the right ventricle (RV) were isolated, immediately frozen in liquid nitrogen, and then weighed. The area of infarct was visually identified and dissected away from the remaining LV and weighed. Blood was collected, and the serum was retained for analysis.

Tissue preparation and RNA analysis. Frozen LV and RV tissues were pulverized with a mortar and pestle placed in liquid nitrogen and then homogenized with a Potter-Elvehjen homogenizer in guanidinium thiocyanate for RNA extraction as previously described (2). RNA was quantified by A260 nm, and its integrity was verified by ethidium bromide intercalation of the ribosomal RNA resolved by denaturing gel electrophoresis. Conditions for Northern blot analysis of the α-and β-MHC, SERCA2, and PLB mRNAs were as previously described (2, 32). Isoform-specific radiolabeled oligodeoxynucleotide probes were used for the MHC mRNA quantitation, whereas cDNA probes for SERCA2 and PLB were radiolabeled by random priming. Individual mRNA values were normalized by the amount of 18S rRNA in each sample measured on the same Northern blot. 18S rRNA was quantified by a radiolabeled oligodeoxynucleotide probe.

A competitive quantitative RT-PCR (QRT-PCR) method was developed to determine the copy number of Kv1.5 mRNA per microgram of total RNA from cardiac tissue, as previously described (36).

Statistical analysis. All results are expressed as means ± SE. Unpaired Student’s t-test was used for statistical comparison of two groups.

RESULTS

Experimental myocardial infarction. All animals showed evidence of a significant area of MI as determined by the presence of a Q wave on standard EKG limb lead III and impaired systolic EF measured 1 wk after surgery (40 ± 5 vs. 81 ± 2% EF). Echocardiography using M-mode analysis showed that the mean percent ejection fraction (%EF) in the MI group was reduced significantly by ~50% compared with control or sham animals throughout the 4-wk period after coronary artery ligation (Fig. 1). EFs were not different between sham-operated and control animals, and their values have been combined. A trend toward an improvement in %EF in the MI group occurred over the 4 wk after surgery (40 ± 5 to 46 ± 4%), suggesting some compensation of LV function after infarction. The size of the infarct was determined at death by weighing the infarcted LV tissue and expressing its weight as a percentage of the weight of the total LV of body weight-matched control animals at the time of coronary artery ligation surgery. Although this measure, based on necrotic tissue weight, underestimated infarct size, the mean percent infarction of the 14 animals was 28 ± 6% (range 18–40%).

Mean body weights, LV and RV weights, and heart rates at 3 and 4 wk after MI are summarized in Table 1. No significant differences were found in body weights among the groups, although the MI animals tended to have lower body weights than controls. The LV mass in the MI group was significantly increased by 32% compared with control (P < 0.01). The weight of the RV in the MI group was increased by about twofold (P < 0.001) at 4 wk after infarction compared with control animals. The observation that RV weight increased to a greater extent than the LV weight in the MI animals may be the result of increased left ventricular end-diastolic pressures leading to increased pulmonary pressures and edema, as reflected by increased lung weights (1.525 ± 0.66 and 1.175 ± 0.22 g, MI and control groups, respectively).

Heart rates measured at the time of death were not significantly different among control and MI groups at 300 ± 1 vs. 283 ± 8 and 313 ± 22 beats/min, respectively (Table 1).

Thyroid hormone metabolism after acute MI and effects of T3 treatment. To assess changes in thyroid hormone metabolism after acute MI, serum total T3 and T4 levels were measured during the 4-wk period after coronary artery ligation. Serum T3 levels fell within 1 wk of the acute infarct, and remained >40%
lower than control (62 ± 4 vs. 33 ± 5 ng/dl) 4 wk after the MI (P < 0.01; Table 3). Serum T4 levels were unchanged after acute MI and throughout the 4-wk study period (5.1 ± 0.2 and 4.6 ± 0.3 µg/dl, control and MI, respectively; Table 2). The observation that serum T4 was unaltered suggests that serum TSH was also normal. The low serum T3 in the presence of normal serum T4 levels is characteristic of the low T3 syndrome (5, 6).

To determine whether normalization of serum T3 levels after MI would affect cardiac function and specific gene expression, animals were administered T3 by continuous infusion at a dose chosen to achieve normal serum T3 levels. This dose increased serum T3 to control levels at 60 ± 5 ng/dl and did not significantly inhibit endogenous production of T4 (3.9 ± 1.2 µg/dl), indicating that TSH was not suppressed. This replacement dose of T3 had no effect on heart rate (Table 1). A second T3 dosage regimen was administered to a subgroup of MI animals, in which the serum levels of T3 were increased 7.5-fold to 453 ± 20 ng/dl measured 3 h (peak level) after subcutaneous injection (Table 2). After 1 wk at this dose regimen of T3, serum T4 levels were significantly decreased to 1.8 ± 0.1 µg/dl. Because of the rapid half-life of T3 (68 ± 1 ng/dl at 10 h post-T3 injection), animals were injected with T3 every 12 h to maintain elevated serum levels. This dose of T3 significantly increased heart rate to 367 ± 8 beats/min compared with control, 300 ± 1 beats/min (Table 1) (23).

Effects of T3 treatment on cardiac mass and LV function after acute MI. Neither treatment dose of T3 had an effect on LV or RV mass beyond that caused by compensated hypertrophy after infarction (Table 1). LV EF measured by M-mode echocardiography averaged ~80% in sham-operated and control animals and was decreased by ~50% in the MI group throughout the period of study (Fig. 1). Administration of replacement dose of T3 by continuous infusion for 2 wk enhanced systolic function to 52 ± 2%EF, which was significantly higher than that of the untreated MI animals (42 ± 3%EF, P < 0.05; Fig. 1). Treatment of the MI animals for an additional 1 wk at a higher dose of T3 (20 µg/day) further increased %EF to ~73% of the control/sham EF (59 ± 2 vs. 82 ± 3%EF, MI + T3 vs. sham, respectively; Fig. 1). This higher-dose T3 treatment regimen of infarcted rats significantly improved LV function compared with the untreated MI group with EF of 46 ± 4% (Fig. 1).

Table 1. Cardiac chamber sizes and heart rates after MI and with T3 treatment

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Body Wt, g</th>
<th>LV, mg</th>
<th>RV, mg</th>
<th>LV/Body Wt</th>
<th>RV/Body Wt</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>6</td>
<td>330 ± 6</td>
<td>503 ± 23</td>
<td>184 ± 6</td>
<td>1.52 ± 0.04</td>
<td>0.56 ± 0.03</td>
<td>300 ± 1</td>
</tr>
<tr>
<td>MI</td>
<td>3</td>
<td>315 ± 4</td>
<td>681 ± 39</td>
<td>227 ± 21</td>
<td>2.16 ± 0.13</td>
<td>0.72 ± 0.07</td>
<td>283 ± 8</td>
</tr>
<tr>
<td>4 wk</td>
<td>3</td>
<td>316 ± 13</td>
<td>664 ± 18</td>
<td>372 ± 17</td>
<td>2.10 ± 0.03</td>
<td>1.18 ± 0.07</td>
<td>313 ± 22</td>
</tr>
<tr>
<td>MI + T3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low dose</td>
<td>4</td>
<td>319 ± 11</td>
<td>620 ± 24</td>
<td>307 ± 31</td>
<td>1.90 ± 0.07</td>
<td>0.98 ± 0.13</td>
<td>303 ± 17</td>
</tr>
<tr>
<td>High dose</td>
<td>3</td>
<td>334 ± 16</td>
<td>665 ± 16</td>
<td>343 ± 13</td>
<td>2.00 ± 0.05</td>
<td>1.03 ± 0.08</td>
<td>367 ± 8§</td>
</tr>
</tbody>
</table>

Values are means ± SE. MI, myocardial infarction; T3, triiodo-L-thyronine; LV and RV, left and right ventricle; HR, heart rate. *P < 0.01 vs. control; †P < 0.001 vs. control; ‡P < 0.01 vs. MI after 3 wk; §P < 0.01 vs. all groups.

Table 2. Serum total T3 and T4 in control/sham rats and rats with MI with and without T3 treatment

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>T3, ng/dl</th>
<th>T4, µg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>6</td>
<td>62 ± 4</td>
<td>5.1 ± 0.2</td>
</tr>
<tr>
<td>Sham</td>
<td>6</td>
<td>60 ± 4</td>
<td>4.5 ± 0.1</td>
</tr>
<tr>
<td>MI</td>
<td>3</td>
<td>38</td>
<td>5.8</td>
</tr>
<tr>
<td>1 wk</td>
<td>6</td>
<td>35 ± 5</td>
<td>4.2 ± 0.4</td>
</tr>
<tr>
<td>4 wk</td>
<td>3</td>
<td>33 ± 5</td>
<td>4.6 ± 0.3</td>
</tr>
<tr>
<td>MI + T3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low dose</td>
<td>5</td>
<td>60 ± 5</td>
<td>3.9 ± 1.2</td>
</tr>
<tr>
<td>High dose</td>
<td>3</td>
<td>453 ± 20</td>
<td>1.8 ± 0.1*</td>
</tr>
</tbody>
</table>

Values are means ± SE. T3, t-thyroxine. *P < 0.01 vs. control/sham; †P < 0.01 vs. control/sham; ‡3 h post-T3 injection; †*10 h post-T3 injection.

THYROID HORMONE AFTER MYOCARDIAL INFARCTION

Alterations in cardiac gene expression in response to MI and T3 treatment. Specific cardiac gene expression was determined in left ventricular tissue 3 and 4 wk after acute myocardial infarction and compared with MI animals treated with T3 during the same period with either a replacement (low, L) or a higher dose (high, H) of hormone. Figure 2 shows a representative Northern blot of the specific cardiac genes studied, and Table 3 summarizes the mRNA concentrations normalized for 18S ribosomal RNA. α-MHC mRNA in the MI animals decreased by ~65% of control values (P < 0.001), and this was accompanied by a three- and eightfold increase in β-MHC mRNA content after T3 and 4 wk after acute MI, respectively (P < 0.01). Similarly, ventricular SERCA2 mRNA content was significantly decreased by 40 and 65% at 3 and 4 wk after acute MI, whereas PLB mRNA increased by 40% (P < 0.01) 4 wk after MI. The ratio of SERCA2 to PLB mRNA was decreased by 76% (P < 0.01) after MI compared with control animals. We also examined the expression of a voltage-gated K+ channel, Kv1.5, known to be rapidly T3 responsive (36). Using QRT-PCR methodology, Kv1.5 mRNA was decreased significantly by 66% after acute MI (Table 3).

Thyroid hormone treatment was initiated to determine whether T3 could reverse the changes in cardiac gene expression after acute MI. The major finding was the selective responsiveness of specific genes to T3 treatment in this model of cardiac dysfunction. T3 normalized the expression of Kv1.5 mRNA content in the MI animals treated at both doses. In contrast, treatment of the MI rats with replacement doses of T3

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did not increase α-MHC mRNA to control levels, whereas expression of the β-MHC mRNA was normalized (Table 3). However, treatment of the MI animals with a higher dose of T₃ normalized α-MHC mRNA expression and further decreased β-MHC mRNA content to levels below control level (0.06 ± 0.01 vs. 0.31 ± 0.10, P < 0.05). T₃ treatment of the MI rats at either dose regimen significantly decreased expression of PLB compared with both MI and control animals. In contrast, T₃ treatment did not alter expression of SERCA2 in the MI hearts, which remained ~50% (P < 0.01) lower than control. However, the summation of these effects of T₃ at either dose was to increase the ratio of SERCA2 to PLB mRNA in the MI animals to control levels (Table 3).

Measurements of MHC and SERCA2 mRNA content in the RV of MI and T₃-treated animals showed similar responses to what was observed in the LV. Specifically, β-MHC expression increased fivefold, whereas α-MHC mRNA decreased ~40% after MI, and only the β-MHC mRNA levels were normalized with T₃ treatment. Similarly, SERCA2 mRNA in the RV of the MI animals was significantly decreased and remained unchanged by T₃ treatment.

To control for a potential hemodynamic effect of thyroid hormone in this setting (34, 40), expression of a cardiac gene not responsive to T₃, β-tropomyosin, was measured. β-Tropomyosin was increased significantly after acute MI compared with control animals (0.96 ± 0.04 vs. 0.70 ± 0.06, respectively, P < 0.05), and T₃ treatment had no additional effect on expression of this gene (0.77 ± 0.9).

**DISCUSSION**

Numerous reports document altered thyroid hormone metabolism with low serum T₃ levels in patients with congestive heart failure, those undergoing coronary artery bypass graft surgery, and after acute MI (8, 13, 15, 25). Increased severity of cardiac disease (NY Heart Association class II-IV congestive heart disease) has been shown to correlate inversely with serum total T₃ levels (13). The cause for the decrease in serum T₃ (total and free T₃) is multifactorial and can be attributed to 1) decreased hepatic conversion of T₄ to T₃, especially with advanced heart failure, as a result of a decrease in activity of the 5′ monodeiodinase, 2) a decrease in binding to serum proteins, 3) an expanded volume of distribution, and 4) a shortened half-life (3, 12, 30). Serum interleukin 6 (IL-6), which has been shown to be increased in the low T₃ syndrome, appears to inhibit the hepatic 5′ monodeiodinase activity (3). Cardiac myocytes in the border zone of reperfused viable myocardium, as well as monocytes and macrophages in this area, produce IL-6, which may in part mediate the changes in serum T₃ level after an acute MI (12). Although the low T₃ syndrome was previously thought to represent a euthyroid condition not requiring thyroid hormone treatment, recent investigations have questioned this conclusion (6, 13, 21, 25).

In the present model of acute MI, LV mass increased significantly within 3 wk, reflecting hypertrophy and remodeling (41). Serial echocardiography measurements of EF and fractional shortening showed a 50% reduction by 1 wk post-MI that remained unchanged for up to 4 wk. Coronary artery ligation has been used to produce LV dysfunction in a variety of animal species, and the decrease in contractility reflects the magnitude of the infarct and the extent of LV remodeling.

**Table 3. Alterations in cardiac gene expression (mRNA) in response to MI and T₃ treatment**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>α-MHC</th>
<th>β-MHC</th>
<th>Kv1.5 × 10⁻²¹</th>
<th>SERCA2</th>
<th>PLB</th>
<th>SERCA2/PLB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>7</td>
<td>4.24 ± 0.30</td>
<td>0.31 ± 0.10</td>
<td>5.38 ± 0.12</td>
<td>4.42 ± 0.45</td>
<td>3.05 ± 0</td>
<td>1.45 ± 0.15</td>
</tr>
<tr>
<td>MI</td>
<td>3 wk</td>
<td>1.81 ± 0.20ᵃᵇ</td>
<td>1.02 ± 0.12ᶜ</td>
<td>1.83 ± 0.21ᵈ</td>
<td>2.72 ± 0.24ᵉ</td>
<td>ND</td>
<td>0.35 ± 0.03ᶠ</td>
</tr>
<tr>
<td></td>
<td>4 wk</td>
<td>1.10 ± 0.29ᵃᵇ</td>
<td>2.68 ± 0.35ᵉ</td>
<td>ND</td>
<td>1.54 ± 0.12ᵈ</td>
<td>4.28 ± 0.07ᶜ</td>
<td>1.44 ± 0.09</td>
</tr>
<tr>
<td>MI + T₃</td>
<td>Low dose</td>
<td>1.85 ± 0.11ᵃᵇ</td>
<td>0.30 ± 0.05</td>
<td>4.26 ± 0.69</td>
<td>2.26 ± 0.14ᵉ</td>
<td>1.57 ± 0.08ᵉ</td>
<td>1.44 ± 0.09</td>
</tr>
<tr>
<td></td>
<td>High dose</td>
<td>3.28 ± 0.44</td>
<td>0.06 ± 0.01ᵈ</td>
<td>6.60 ± 0.22</td>
<td>2.77 ± 0.38ᵉ</td>
<td>1.73 ± 0.09ᵉ</td>
<td>1.60 ± 0.14</td>
</tr>
</tbody>
</table>

Values are means ± SE. α-MHC, myosin heavy chain; SERCA2, sarcoplasmic reticulum Ca²⁺-activated ATPase; PLB, phospholamban; Kv1.5, a K⁺ channel gene. ᵇP < 0.001 vs. control; ᵇP < 0.05 vs. MI + T₃ high dose; ᵇP < 0.01 vs. control, MI + T₃ low and high doses; ᵇP < 0.05 vs. all groups; ᵇP < 0.01 vs. control; ᵇP < 0.01 vs. all groups.
The present results are similar to those results described by Yue et al. (45), in which the decline in function in the postinfarcted mycardium was accompanied by changes in expression of α- and β-MHC and SERCA2, known thyroid hormone-responsive genes, resulting in alterations in excitation-contraction coupling similar to those seen in hypothyroidism and heart failure (17, 43, 44).

In the present study, we were able to produce the low T₃ syndrome after acute MI, which had not been previously documented in this animal model. Serum T₃ levels fell by 50%, whereas serum T₄ was maintained at control levels. Accompanying this decline in T₃ were changes in expression of known thyroid hormone-responsive genes, including the MHCs, SERCA2, and PLB, as well as a potassium channel gene, Kv1.5, similar to that of hypothyroidism (14, 22, 34, 36). To test whether these phenotypic changes were at least in part the result of altered thyroid metabolism, animals were treated with a constant infusion of T₃ to restore serum T₃ levels to normal. The T₃ replacement dose did not completely restore expression of these genes, contrary to our previous report in another model of the low T₃ syndrome (21) or as would be expected when hypothyroid animals are rendered euthyroid (2). α-MHC and SERCA2 genes, both containing well-delineated thyroid-responsive DNA elements (7), were unresponsive to T₃ replacement, and only at higher treatment doses of T₃ was α-MHC mRNA returned to control levels, whereas SERCA2 mRNA remained relatively unaffected. In contrast, the negatively regulated β-MHC and PLB genes responded as predicted to replacement T₃ treatment, with expression falling to or below control levels (32, 34). Thus, in contrast to the coordinated phenotypic expression well documented in thyroid disease states (18), the hypertrophic remodeled myocardium showed varied and gene-specific T₃ responsiveness. The mechanisms underlying these observations could include changes in thyroid hormone receptor expression (42) or transcriptional activity, as reported for pressure overload, hypertrophic growth (18), cardiac unloading and atrophy (35), and with mutant thyroid hormone receptors (38).

Previous studies by Gay and colleagues (9, 10) have tested whether T₄ treatment could improve LV function when administered to rats after acute MI. Short-term (1–2 days) T₄ treatment improved LV function (10); however, similar to the present study, restoration of normal MHC isoform distribution required higher doses of T₄ than the dose required in the hypothyroid rat. In a rat model of heart failure due to pressure overload, Chang et al. (4) showed that T₄ treatment increased LV systolic and diastolic functions and improved calcium handling consistent with changes in thyroid hormone-responsive genes. In that model and in the present study, the improvement in LV function in response to thyroid hormone treatment occurred despite the persistence of ventricular hypertrophy. It is interesting to speculate that thyroid hormone can reverse the pathological phenotype in both hypertensive and ischemic hypertrophic heart disease and thereby improve myocardial contractility. In chronic congestive heart failure in humans, studies have shown that T₄ treatment for 3 mo increased the LV EF, lowered systemic vascular resistance, and improved the patient’s functional status (31).

We have reported that, in hypothyroidism, cardiac PLB content, an inhibitor of SERCA2, was significantly increased (32). T₃ treatment of hypothyroidism decreased PLB content and promoted phosphorylation of PLB, thereby decreasing its inhibitory action on sarcoplasmic reticulum calcium uptake and improving LV function (32). Therefore, it is plausible that, as a result of the low serum T₃ after acute MI, cardiac PLB was similarly altered and that T₃ replacement improved myocyte contractility through this pathway.

In conclusion, we observed that acute myocardial infarction in the rat produced by coronary artery ligation was associated with a fall in serum T₃ levels, development of significant left ventricular dysfunction, and alterations in specific thyroid hormone-responsive genes. Thyroid hormone treatment at doses sufficient to normalize serum T₃ significantly improved cardiac function and reversed some but not all of the changes in gene expression. We propose that T₃ treatment in the setting of cardiac disease and altered thyroid hormone metabolism may have potential beneficial effects (25). The effect of long-term treatment on survival in congestive heart disease remains to be determined (26).

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REFERENCES


