Synthesis and Degradation of Myocardial Protein during the Development and Regression of Thyroxine-Induced Cardiac Hypertrophy in Rats

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SUMMARY Cardiac hypertrophy was induced in rats by daily injections of L-thyroxine (1.0 mg/kg). Regression from hypertrophy was studied 4 days after discontinuing thyroxine. Isolated, Langendorff-perfused hearts were perfused with Krebs-Henseleit buffer, glucose, insulin, and amino acids. To measure protein synthesis, left ventricular tissue was assayed for incorporation of tritiated phenylalanine into protein. Indices of rates of protein degradation were obtained by measuring the release of cold phenylalanine after blocking protein synthesis with cycloheximide. After 3 days of thyroxine (when cardiac growth was maximally increased), the rate of protein synthesis increased by 22% (P < 0.001). After 1 week, synthesis was 8% greater than control (P < 0.05), and by 2 weeks (when hypertrophy was stable and the rate of cardiac growth was similar to controls), synthesis had returned to control levels. In hearts regressing from hypertrophy, synthesis was reduced to 68% of control (P < 0.001). The rate of protein degradation was decreased by 12% (P < 0.05) after 3 days of thyroxine, but was not different from control at 1 or 2 weeks. During regression, degradation was 12% below control (P < 0.05). Changes in the release of several amino acids that are synthesized or metabolized in heart (e.g., alanine, glycine, serine) were different from changes in phenylalanine release. In conclusion thyroxine-induced cardiac hypertrophy and regression are accompanied by changes in protein synthesis and degradation, and amino acid metabolism. The predominant change in hypertrophy is increased protein synthesis with a minor contribution from reduced degradation. Regression of hypertrophy is accompanied by decreased synthesis, not increased degradation.

THEORETICALLY, cardiac hypertrophy may occur as a consequence of increased protein synthesis, reduced protein degradation, or both. Similarly, a decrease in heart size, as in regression of hypertrophy, might be brought about by accelerated protein degradation, a decreased rate of synthesis, or both.

The relative importance of these factors is defined imprecisely. There is a general agreement that protein synthesis is accelerated during the development of hypertrophy," but reports differ regarding whether rates of degradation are retarded" or not." The type and magnitude of changes that occur may depend on the nature, intensity, and duration of the stress imposed on the heart, and on whether or not the hypertrophic process is accompanied by cellular damage and/or repair.

To clarify the roles of altered synthesis and degradation of cardiac protein in one experimental model of hypertrophy and regression, we have measured their rates in vitro following induction and cessation of a well-defined stimulus to hypertrophy—daily injections of L-thyroxine in rats. The regimen employed produces rapid growth of the heart (over and above that observed in age-matched controls), predominantly involving myocardial cells and without evidence of significant cellular damage, fibroblast overgrowth, or disproportionate collagen deposition." Also, cessation of treatment produces a well-documented and reproducible loss of myocellular protein mass over a period of a few days." Methods

Seven-week-old male albino rats (Charles River Co., outbred) were maintained on standard Purina chow ad libitum. Control rats received daily intraperitoneal injections of 0.9% NaCl, and experimental rats received similar injections of L-thyroxine (1.0 mg/kg per day). Some of the rats that received thyroxine subsequently were switched to saline injection, to allow regression of the thyroid-induced cardiac hypertrophy. For studies of protein synthesis and degradation, injection schedules were timed so that rats of all groups studied (control, 3-day treatment, 1-week treatment, 2-week treatment, and 4-day recovery after 2-week treatment) were studied on the same day and at the same age.

The rats were given sodium heparin, 2.5 mg,
intraperitoneally, and anesthetized with ether. Hearts were excised rapidly, dropped into 0.9% NaCl (4°C), and mounted on a modified Langendorf perfusion apparatus. For study purposes, preliminary perfusion was performed for 30 minutes with amino acid-rich "BGJ" solution (Grand Island Biological Co.) in Krebs-Henseleit buffer, containing 50 μg/ml bovine insulin (Sigma Chemical Co.), 15 mM glucose and 0.80 mM phenylalanine, and gassed with 95% O₂ + 5% CO₂. The perfusion pressure was 65 mm Hg throughout the study, and beating rates were held constant at 350/min by atrial pacing. After the preliminary perfusion, the solution was changed to a single one containing 0.80 mM [³H]phenylalanine (1.3 x 10^6 dpm/μmol). This perfusate was recirculated over the next hour (during which time the rate of incorporation of label was linear). The first 10 ml of radioactive buffer to pass through the heart were discarded to minimize dilution of phenylalanine specific activity. At the end of perfusion, hearts were removed, weighed, and placed in beakers containing 0.15 M NaCl at 4°C.

Incorporation of radioactive phenylalanine into cardiac protein was estimated as described previously. Left ventricular sections were homogenized in ice-cold 20 mM NaCl-2 mM phosphate buffer (pH 7.4) in a tightly fitting Dounce homogenizer. Protein was precipitated from samples of the homogenate in ice-cold 20 mM NaCl-2 mM phosphate buffer (pH 7.4) and once more in 0.80 mM trichloroacetic acid (TCA), collected on glass fiber filters (Whatman GF/C), washed twice with cold TCA, and solubilized with NCS solubilizer (Amersham/Searle). Samples were counted in a Packard 2425 Tricarb scintillation counter in toluene/PPO/POPOP and the rate of protein synthesis was calculated.

When phenylalanine (phe) perfusate levels are 0.80 mM, specific activities of perfusate, intracellular, and tRNA-bound phenylalanine are equal and rates of protein synthesis can be calculated accurately using any of the three. For any intervention, however, the equality of specific activities in the pools needs to be confirmed, so for each group of rats we measured intracellular as well as extracellular specific activities and calculated synthesis rates using both, as described previously. For all groups, intracellular specific activities (S.A.) were similar. Extracellular S.A. was 1.30 x 10^6 dpm/μmol phe in all groups. Intracellular S.A. averaged 1.22 x 10^6 dpm/μmol in control hearts, 1.25 x 10^6 dpm/μmol in hearts treated with thyroxine for 3 days, 1.26 x 10^6 dpm/μmol in hearts treated for 1 week, 1.22 x 10^6 dpm/μmol in hearts treated for 2 weeks, and 1.24 x 10^6 dpm/μmol in hearts recovering from thyrotoxicosis. Thus, differences in protein synthesis between the groups were similar using either intracellular or extracellular values; results reported here were calculated from intracellular values.

To measure differences in protein degradation in hypertrophying, regressing, and control hearts, isolated hearts were perfused at 65 mm Hg, as described above, with Krebs-Henseleit solution containing 50 μg/ml insulin, 15 mM glucose, and 10 μM cycloheximide, (an amount that inhibits cardiac protein synthesis by >90%). Perfusion concentrations of 14 amino acids were measured using a Durrum analyzer at the beginning and end of a 90-minute test period, after a preliminary 30-minute "washout period." Since, in heart, phenylalanine is involved only in protein synthesis and degradation, being neither synthesized nor converted to other compounds, its net balance is a reflection of net protein balance. When protein synthesis is blocked, the net rate of release of phenylalanine as measured by concentration differences in the perfusate becomes essentially a reflection of the rate of protein degradation alone. Adverse disadvantage of this method should be noted, namely that cycloheximide, itself, causes some alteration in cardiac proteolytic rates as may the use of an amino acid-deficient medium. Thus, as discussed in detail previously, primary inhibition of protein synthesis can secondarily produce a less severe but progressive inhibition of protein breakdown (possibly via alterations in lysosomal lability, depletion of proteins with short half-lives that may be important in regulating proteolysis, or accumulation of metabolites that may influence proteolysis). Nevertheless, if both control and experimental hearts are exposed to cycloheximide, its influence on protein degradation can be assumed to be similar in both, and qualitative differences reasonably can be attributed to the experimental intervention.

For all measurements, comparisons between groups were made using Student's t-test for unpaired samples.

**Results**

Treatment with l-thyroxine caused a large increase in the ratio of heart weight to body weight, and cessation of treatment produced a rapid return toward control values (Fig. 1). This change was produced by an increase in heart weight, as compared to age-matched controls, as well as by a relative reduction in body weight (Fig. 2). Cessation of treatment caused a rapid gain in body weight, coupled with an absolute decrease in heart weight (Fig. 2). Because the hearts of normal control rats of the ages studied are growing steadily (i.e., are in a state in which protein synthesis exceeds protein degradation), and because of major abnormalities in body weight in thyrotoxic rats, comparisons between actual cardiac growth patterns of control and experimental animals at a given time can best be ascertained by estimating the tangent of the cardiac growth curve at that time, rather than by the more conventionally used ratio of heart to body weight. Thus, it is apparent from Figure 2 that the net rate of cardiac and total body growth is fairly constant in control animals over the 3-week period measured. In rats given thyroxine, on the other hand, the rate of growth slowed significantly, as measured by the ratio of heart weight to body weight. After cessation of treatment, the rats initially showed a large increase in heart weight relative to body weight, followed by a return toward control values. Therefore, it is apparent that the effect of thyroxine on cardiac growth is due to an increase in protein synthesis and the effect of thyroxine on total body growth is due to an increase in protein synthesis, and a decrease in protein degradation.
of cardiac growth is maximal after 3 days of treatment, still elevated (though less so) at 1 week, but approximately the same as control at 2 weeks, despite the fact that the heart-to-body weight ratio has increased continuously over that entire period. During recovery from thyrotoxicosis, the heart is actually in a state of negative protein balance whereas the rest of the body is gaining weight even more rapidly than normal.

Figure 3 illustrates changes in the rate of left ventricular protein synthesis during the development of and regression from thyroxine-induced cardiac hypertrophy. Control hearts had synthesis rates of $1.19 \pm 0.021$ (SEM; $n = 11$) $\mu$mol phenylalanine/g protein per hour. With a protein concentration of 0.2 g/g tissue, this value is equal to approximately $0.24 \mu$mol/g left ventricular weight. After three daily injections of L-thyroxine, the rate of synthesis had increased by 22% to $1.45 \pm 0.41 \mu$mol phe/g protein per hour ($n = 11$; $P < 0.001$). After 1 week of therapy, synthesis was still greater than control ($1.28 \pm 0.037 \mu$mol phe/g protein per hour; $n = 12$; $P < 0.05$), but the difference was only 8%. At 2 weeks, when cardiac hypertrophy was stable and the rate of cardiac growth was approximately the same as in control rats, the rate of synthesis was $1.12 \pm 0.026 \mu$mol phe/g protein per hour ($n = 11$), a value which was not significantly different from control ($P > 0.10$). Four days after the last injection of thyroxine, while cardiac size was regressing rapidly, protein synthesis was $0.81 \pm 0.034 \mu$mol phenylalanine/g protein per hour ($n = 11$), or 32% less than control ($P < 0.001$). It should be noted that, because of the experimental design used, any contribution to increased protein synthesis by the hyperdynamic circulatory state thyroxine produces would be minimized. Thus, the relative rates of synthesis during thyrotoxicosis may be an underestimation of the situation in vivo, compared to control or regression values, insofar as hemodynamic factors may contribute to the changes induced. Also, the experimental design used would minimize any effects of thyrotoxicosis that might be caused secondarily by altered circulating levels of other hormones or substrates, since the perfusion fluids used were identical for all hearts.

Simultaneous changes in the rates of protein degradation, as estimated from phenylalanine release during blockade of protein synthesis, are shown in Figure 4. Degradation averaged $0.17 \pm 0.006 \mu$mol phe/g heart weight per hour in control hearts ($n = 12$). Degradation was decreased by 12% to $0.15 \pm 0.005$ ($n = 10$) after 3 days of thyroxine ($P < 0.05$), but was not significantly different from

![Figure 1](image1.png)

**Figure 1** Influence of progressive thyrotoxicosis (L-thyroxine, 1 mg/kg per day) and recovery on the ratio of heart weight to body weight. Each point represents one rat and the bar represents the mean. * = $P < 0.05$ compared to control; † = $P < 0.05$ compared to preceding group.

![Figure 2](image2.png)

**Figure 2** Effect of thyrotoxicosis and recovery on absolute heart and body weights. Each point represents data from a minimum of five matched rats whose body weights were 210–220 g at the beginning of the experiment. The solid lines and filled circles represent periods when no thyroxine was given and the broken lines and unfilled circles represent periods in which the rats received daily injections of thyroxine (1 mg/kg per day).

![Figure 3](image3.png)

**Figure 3** Influence of progressive thyrotoxicosis and recovery on the rate of left ventricular protein synthesis. Conditions and symbols as in Figure 1.
control after 1 week (0.18 ± 0.012; n = 12) or 2 weeks (0.18 ± 0.011; n = 12). During the recovery phase, the rate of degradation again decreased slightly to 0.15 ± 0.007 μmol phe/g per hour (n = 12; P < 0.05). It should be noted that these measured values for protein degradation rates cannot be related directly to the values obtained for protein synthesis in the same thyroid state, because different hearts were used for the two determinations and because the perfusion fluids were different for the two determinations. Also, the synthesis data were obtained for sections of left ventricle alone, whereas the degradation data were for the entire heart mounted on the perfusion apparatus.

Changes in the rates of release of other amino acids, as summarized in Table 1, were similar to those for phenylalanine in some instances (e.g., tyrosine), but markedly different in other instances. Of special interest were alanine, the release of which increased steadily and markedly during thyrotoxicosis before returning to normal during recovery, and serine and glycine, whose release became progressively reduced during thyroxine administration before returning toward normal during recovery. The branched-chain amino acids, whose cardiac metabolism is altered markedly by many hormones, including glucagon, insulin, and hydrocortisone,27,28 were relatively unaffected by thyroid hormone.

**Discussion**

For cardiac hypertrophy to develop there must occur an increase in protein synthesis, a decrease in protein degradation, or both. Similarly, atrophy or regression of hypertrophy must result from reduced synthesis, increased degradation, or both. There is much evidence to indicate that the development of cardiac hypertrophy is accompanied by an increased rate of protein synthesis, but data are less consistent regarding changes in degradation rates. In some studies, certain proteins have been observed to be broken down more slowly than normal during development of hypertrophy,5 but in other experiments, turnover of some proteins, notably myosin, appears to be increased as the heart enlarges.3 Whether these apparent disparities are due to species differences, different degrees of stress and hypertrophy imposed, or true differences in responses of different proteins remains unclear.

Recently, Morgan and his colleagues25 used techniques almost identical to those employed in the present study to determine changes in total protein synthesis and degradation during the development of left ventricular hypertrophy secondary to aortic banding. They observed increases in protein synthesis of 46% at 3 days and 23% at 1 week. Also, at 3 days there was a 33% increase in protein degradation, with no change at 1 week.

Results in our study disclose interesting similarities and differences between hearts made hypertrophic by thyroxine and those subjected to aortic banding. Alterations in synthesis were similar fol-

### Table 1  Amino Acid Release from Rat Hearts Perfused in the Presence of Cycloheximide (10 μM)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>T&lt;sub&gt;r&lt;/sub&gt; × 3 days</th>
<th>T&lt;sub&gt;r&lt;/sub&gt; × 1 week</th>
<th>T&lt;sub&gt;r&lt;/sub&gt; × 2 weeks</th>
<th>Recovery × 4 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tau</td>
<td>0.22 ± 0.012</td>
<td>0.21 ± 0.021</td>
<td>0.22 ± 0.022</td>
<td>0.21 ± 0.022</td>
<td>0.22 ± 0.024</td>
</tr>
<tr>
<td>Lys</td>
<td>0.33 ± 0.018</td>
<td>0.37 ± 0.036</td>
<td>0.40 ± 0.016*</td>
<td>0.42 ± 0.025*</td>
<td>0.27 ± 0.010†</td>
</tr>
<tr>
<td>His</td>
<td>0.11 ± 0.009</td>
<td>0.09 ± 0.005</td>
<td>0.11 ± 0.010</td>
<td>0.09 ± 0.012</td>
<td>0.09 ± 0.009</td>
</tr>
<tr>
<td>Arg</td>
<td>0.21 ± 0.011</td>
<td>0.21 ± 0.014</td>
<td>0.25 ± 0.013†</td>
<td>0.24 ± 0.011</td>
<td>0.18 ± 0.011†</td>
</tr>
<tr>
<td>Thr</td>
<td>0.20 ± 0.013</td>
<td>0.21 ± 0.008</td>
<td>0.23 ± 0.016</td>
<td>0.21 ± 0.017</td>
<td>0.18 ± 0.010</td>
</tr>
<tr>
<td>Ser</td>
<td>1.15 ± 0.078</td>
<td>0.86 ± 0.040 †</td>
<td>0.83 ± 0.063*</td>
<td>0.86 ± 0.061*</td>
<td>0.84 ± 0.064*</td>
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<tr>
<td>Gly</td>
<td>0.45 ± 0.032</td>
<td>0.38 ± 0.019</td>
<td>0.35 ± 0.039</td>
<td>0.28 ± 0.039*</td>
<td>0.36 ± 0.026*</td>
</tr>
<tr>
<td>Ala</td>
<td>1.08 ± 0.074</td>
<td>1.45 ± 0.076†</td>
<td>1.56 ± 0.104*</td>
<td>1.82 ± 0.106*</td>
<td>1.17 ± 0.046†</td>
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<tr>
<td>Val</td>
<td>0.16 ± 0.012</td>
<td>0.17 ± 0.006</td>
<td>0.20 ± 0.015*</td>
<td>0.17 ± 0.011</td>
<td>0.15 ± 0.010</td>
</tr>
<tr>
<td>Met</td>
<td>0.11 ± 0.008</td>
<td>0.09 ± 0.003†</td>
<td>0.11 ± 0.007†</td>
<td>0.10 ± 0.005</td>
<td>0.10 ± 0.006</td>
</tr>
<tr>
<td>Ile</td>
<td>0.17 ± 0.010</td>
<td>0.17 ± 0.006</td>
<td>0.19 ± 0.009</td>
<td>0.18 ± 0.007</td>
<td>0.15 ± 0.006†</td>
</tr>
<tr>
<td>Leu</td>
<td>0.30 ± 0.017</td>
<td>0.28 ± 0.009</td>
<td>0.32 ± 0.021</td>
<td>0.30 ± 0.013</td>
<td>0.26 ± 0.001†</td>
</tr>
<tr>
<td>Tyr</td>
<td>0.14 ± 0.007</td>
<td>0.12 ± 0.008</td>
<td>0.14 ± 0.010</td>
<td>0.13 ± 0.011</td>
<td>0.12 ± 0.006*</td>
</tr>
<tr>
<td>Phe</td>
<td>0.17 ± 0.006</td>
<td>0.15 ± 0.005†</td>
<td>0.18 ± 0.012†</td>
<td>0.18 ± 0.011</td>
<td>0.15 ± 0.007†</td>
</tr>
</tbody>
</table>

* Each value represents the mean ± 1 SEM for 10-12 hearts. Units are μmol phe/g per hour. T<sub>r</sub> = L-thyroxine (1 mg/kg per day).
* P < 0.05 compared to control.
† P < 0.05 compared to the preceding value.
lowing the two interventions (i.e., maximal increases by 3 days with lesser elevations later). On the other hand, changes in protein degradation at 3 days were opposite, being accelerated after aortic banding but retarded slightly after thyroxine treatment. The reason for this difference remains obscure. Bishop et al. have reported that aortic banding produces some cell damage and initiation of repair processes along with cellular hypertrophy per se. Although thyroxine may produce apparent myocellular damage after severe, chronic treatment, it does not appear to cause such changes early in the course of treatment (R.S. Decker and K. Wildenthal, unpublished data, and refs. 10-12). Thus, one possible but unproved reason for the differences in protein degradation in the two experimental models of hypertrophy may be a contribution to enhanced proteolytic rates by the repair process.

Regression of hypertrophy has been studied much less extensively than has the development of hypertrophy. Protein degradation is thought to be increased significantly during some interventions that produce net catabolism of skeletal muscle; it often has been assumed that the heart responds similarly, although few actual measurements have been available. In a study closely related to the present one, but dealing with primary atrophy rather than regression of hypertrophy, Hjalmarson, Morgan, and their co-workers measured rates of protein synthesis and degradation following hypophysectomy. They observed a significant decrease in protein synthesis as cardiac atrophy developed. Both the atrophy and the change in synthesis could be prevented by replacement therapy with thyroxine. Protein degradation was unchanged from control. Similarly, in the present study, regression of thyrotropic hypertrophy was accompanied by a marked decrease in protein synthesis. The rate of protein degradation not only failed to increase but actually decreased slightly.

In contrast to phenylalanine, whose fate in the heart is confined to involvement in protein synthesis and degradation, several amino acids are actively synthesized or metabolized. One such amino acid is alanine, whose release from heart was markedly and progressively increased during the evolution of thyrotoxicosis. The release of alanine has been reported previously to be increased in skeletal muscle of thyrotoxic animals, independent of changes in proteolysis. The mechanism for this alteration is uncertain. Changes in alanine amino transferase activity seem not to be responsible, and an excessive accumulation of pyruvate has been postulated to be the cause. If so, the possibility must be considered that the accumulation of pyruvate and synthesis of alanine are consequences of tissue hypoxia. It seems at least theoretically possible that the increased metabolic demands of thyrotoxic hearts would be so severe that delivery of oxygen by Langendorff perfusion might be inadequate, leading to accumulation of potentially oxidizable substrates, including pyruvate and alanine. This possibility seems unlikely, however, when one examines other amino acids that are readily transaminated and oxidized in heart, such as the branched-chain amino acids. The pattern of release of valine, leucine, and isoleucine in thyrotoxic hearts was quite different from that of alanine (Table 1) and, specifically, there was no parallel or consistent increase in their release as would be expected if oxidative processes had been inhibited significantly by inadequate perfusion. Other major changes of interest in amino acid metabolism unrelated to proteolysis were a progressive increase in lysine release, followed by a reduction below normal during the recovery phase, and progressive, reversible decreases in the release of serine and glycine. The cellular mechanisms responsible for these changes are uncertain and deserve further study.

It is impossible on the basis of the present data alone to quantify the relative contributions of the direct cellular effects of thyroid hormone on protein synthesis vs. indirect effects produced by hyperdynamic contraction and altered humoral factors. The influence of secondary humoral factors was minimized in these studies by the use of identical perfusion fluids. The perfusate contained high concentrations of insulin, which itself stimulates cardiac protein synthesis and retards degradation, and which therefore might theoretically tend to obscure somewhat the full potential effect of a second intervention that tends to accelerate synthesis or inhibit degradation. The influence of altered contractile function was minimized by prevention of variations in heart rate and cardiac output. There was no way to eliminate the increased velocity of contraction that accompanies hyperthyroidism, however. Nevertheless, since the hyperdynamic contractile state persisted throughout the 2-week period, it is unlikely that increased contractility, alone, was the predominant cause of the observed changes. Because thyroid hormone reportedly accelerates protein synthesis in vitro and in vivo before evidence of enhanced contractile performance appears, it seems probable that a major component of the increased synthesis that occurs during the development of hypertrophy is mediated directly by thyroid hormone, independent of circulatory changes.

The magnitude of the decrease in synthesis observed during regression of hypertrophy is so great that it is impossible to conceive of it having been mediated by any minor difference in contractile function compared to control hearts. Accordingly, it seems certain that reduced synthesis is a direct consequence of the cellular reaction to withdrawal of the hormone. The nature of such a reaction cannot be deduced from the present study, but on the basis of work by Morgan and others it seems reasonable to postulate that alterations in the amount of cellular RNA may play a fundamental role.
The mechanisms responsible for the small transient alterations observed in protein degradation are unknown. Several interventions that alter cardiac proteolysis have been postulated to do so via changes in the activities and/or availability of lysosomal proteinases. The increased proteolysis that accompanies early hypertrophy after aortic banding is one such example. Also, changes in skeletal muscle proteolysis during alterations in thyroid state have been suggested to be caused by lysosomal alterations. In heart, however, Wildenthal and Mueller have shown that thyrotoxicosis causes sustained decreases in the specific activity and availability of lysosomal cathepsin D (i.e., changes which, if important in regulating protein breakdown, should lead to sustained decreases in proteolysis), and that regression of hypertrophy is accompanied by a marked increase in catabolic activity (i.e., a change that would be expected to have no effect or increase proteolysis). Thus, as with hypophysectomy and treatment with corticosteroids, there appears to be no correlation between known changes in lysosomal properties and protein breakdown in myocardium during thyrotoxicosis and recovery; it therefore seems unlikely that thyroid-mediated alterations in cathepsin D activity play a rate-limiting role in the shifts in proteolytic rates observed in the present study.

In summary, thyroxine-induced cardiac hypertrophy is accompanied primarily by a marked increase in the rate of total protein synthesis, with a small, transient contribution from retarded degradation. Regression of hypertrophy following cessation of thyroid treatment is accompanied by a marked reduction in the rate of protein synthesis, with no acceleration of proteolysis. It should be emphasized that these changes have been documented in isolated hearts in which many of the secondary changes that accompany thyrotoxicosis in vivo (e.g., hemodynamic changes and alterations in circulating levels of substrates and hormones) have been eliminated or minimized. Thus, insofar as such secondary alterations may themselves affect protein balance, the present study may not provide a full picture of the total effects of changes in thyroid status on cardiac protein synthesis and degradation in a living animal. Rather, these experiments were designed to disclose primarily the changes that are produced by intrinsic alterations in the myocardium per se, which persist even in a controlled environment in vitro. It is of special interest that the direction and magnitude of the changes observed under the experimental conditions imposed appear to be able to account for most if not all of the hypertrophy and the regression of hypertrophy that occur in vivo.

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