Thyroxine-Induced Redistribution of Isoenzymes of Rabbit Ventricular Myosin

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SUMMARY We examined ventricular myosin isoenzymes in hearts of normal and thyroxine (T4)-treated rabbits by polyacrylamide gel electrophoresis using non-dissociating conditions as described by Hoh et al. (1977). The rabbits received daily injections of T4 (150 μg/kg) or saline and were killed at 1 to 17 days. A myosin-enriched fraction was prepared from each ventricle by extraction in 100 mM pyrophosphate. Myofibrils were also prepared from each heart for the measurement of myofibrillar actomyosin and myosin ATPase activity. In normal and thyrotoxic rabbit ventricles, there were three distinct isoenzymes (R-V1, R-V2, and R-V3) in decreasing order of mobility analogous to the myosin isoenzymes V1, V2, and V3 present in rat ventricle. In hearts of normal rabbits, R-V3 was the predominant species, whereas, in the thyrotoxic hearts, R-V1 was the predominant species. The redistribution of isoenzymes was apparent within 2 days of T4 administration and was complete within 5-7 days of T4 injections. Associated with the maximum shift in myosin isoenzyme profiles there was an increase of approximately 90% in the myofibrillar myosin Ca2+-activated ATPase activity and an increase of approximately 30% in the Mg2+-ATPase activity of myofibrillar actomyosin. The Ca2+-activated myosin ATPase of the myofibrils was correlated with the percent R-V1 in the preparations. Co-electrophoresis of mixtures of rat and rabbit heart myosins showed four separate bands, resulting from a difference in mobility between R-V1 and V1, as well as R-V3 and V3. Our data indicate that rabbit heart myofibrils have three isoenzymes, some of which may be structurally distinct from rat heart myosin isoenzymes, and that T4 administration induces preferential synthesis of a preexisting isoenzyme, R-V1.


SUSTAINED stress, such as that produced by a pressure overload or thyroxine administration, produces fundamental alterations in the contractile elements of cardiac muscle (Alpert et al., 1979; Morkin, 1979). These changes are reflected in alterations of the Ca2+-activated myosin ATPase activity and the actin-activated myosin ATPase activity. Moreover, the rate of cross-bridge cycling, as measured by tension-dependent heat development, or unloaded velocity of shortening, has been correlated with increases and decreases in the Ca2+-activated myosin ATPase activity (Alpert et al., 1979).

How pressure-volume work is linked to alterations in the ATPase activity of cardiac myosin is not yet clear, but it now seems plausible that the adjustments of contractile function to chronic stresses may involve changes in the primary structure of the myosin heavy chain. There is evidence that isoenzymes of myosin exist in the heart and that long-term stresses are associated with a redistribution of these forms of myosin. Hoh et al. (1977) have identified three isoenzymes of rat ventricular myosin, which they call V1, V2, and V3, on the basis of their mobility in non-dissociating gel electrophoresis and their relative Ca2+-activated ATPase activities (the order of mobility and Ca2+-ATPase activity is V1>V2>V3). In normal rats, V1 predominates and myosin Ca2+-ATPase activity is relatively high, but Lompre et al. (1979) have shown that there is a redistribution of ventricular myosin isoenzymes associated with the hypertrophy resulting from chronic pressure overload so that the proportion of V3 is increased. Concomitant with this change in isoenzyme population, there is a reduction of the Ca2+-activated myosin ATPase activity.

The distribution of myosin isoenzymes also appears to be determined by serum levels of thyroid hormone. Although thyroxine administration does not increase the Ca2+-activated myosin ATPase activity or affect the myosin isoenzyme population of normal rat heart, perhaps due to the high ATPase activity associated with the predominating V1 isoenzyme, hypophysectomy does induce a change in the myosin isoenzyme population to predominantly V3 (Hoh et al., 1977). This change can be reversed with thyroxine treatment. In rabbits, on the other hand, thyroxine increases the Ca2+-activated myosin ATPase activity and Flink et al. (1979) have reported the presence of a different form of myosin in thyrotoxic rabbit heart by the mapping of cyanogen bromide peptides of myosin heavy chain isolated from both normal and thyrotoxic hearts. The question arises whether the changes in the primary
structure of the myosin molecule in response to thyroxine treatment are the result of a shift in the myosin isoenzyme population, as occurs in response to a pressure overload, or the synthesis of a new myosin isoenzyme by a direct effect on gene transcription as postulated by Flink et al. (1979).

Our objective in this study was to examine the population of myosin isoenzymes in normal rabbit heart and to determine whether thyroxine administration induces the synthesis of a novel form of myosin not present in normal rabbit heart or causes a change in the relative proportions of preexisting myosin isoenzymes.

Methods

We injected male New Zealand rabbits (1.0–2.0 kg; Dutchland Laboratories) daily, for up to 17 days, with either L-thyroxine (150 μg/kg body weight) or saline. Animals were weighed daily and the dose of L-thyroxine reduced to one-half, or omitted, if the body weight fell to less than 80% of the initial value.

The animals were killed at 1, 2, 3, 5, 7, and 17 days of daily thyroxine treatment. Control animals were killed at 2, 5, 7, and 17 days. Hearts were excised rapidly from stunned animals and placed in ice-cold saline. The heart was then trimmed of atria and connective tissue and in some instances blotted on moistened filter paper and weighed. The heart was minced in ice-cold saline and divided into two portions; one portion was used for the preparation of myofibrils, as described by Solaro et al. (1971), and the other for analysis of myosin isoenzymes.

Myosin Extraction

Approximately 300 mg of the minced ventricular tissue were homogenized in 7 ml of 40 mM NaCl, 3 mM sodium phosphate buffer, pH 7.0, with a MSE blade homogenizer. All procedures were carried out at 0–4°C unless otherwise stated. The homogenate was centrifuged at 800 g for 10 minutes, and the pellet was resuspended once in the homogenizing buffer and centrifuged. This pellet was suspended in 3 ml of 0.1 M Na₃P₂O₇, 5 mM EGTA, 5 mM dithiothreitol, 5 μg leupeptin/ml, pH 8.6, for 1 hour at 2°C as described by Hoh et al. (1979). The suspension was centrifuged at 100,000 g for 3 hours and the pellet was discarded. Glycerol was added to the supernatant fraction to give a final concentration of 50% and the samples were stored at −80°C.

Electrophoretic Separation of Myosin Isoenzymes

Myosin isoenzymes were separated by electrophoresis on polyacrylamide gels, using non-dissociating conditions, following the procedure described by Hoh et al. (1977). Electrophoresis was carried out on 4% polyacrylamide gels, in a cold room set at 2°C, using a Pharmacia GE4 electrophoresis chamber. The electrophoresis buffer was recirculated between the lower and upper chamber, and 50% ethanol was circulated through coils in the lower chamber. Electrophoresis was carried out for 16 hours at a voltage gradient of 14 V/cm, using a buffer containing 20 mM Na₃P₂O₇ and 10% (vol/vol) glycerol, pH 8.8.

The gels were fixed in a solution of 10% trichloroacetic acid and 50% methanol for 4 hours prior to staining with Coomassie Blue R (0.03% in 25% isopropanol and 10% acetic acid). The gels were destained in a diffusion destainer in 7.5% acetic acid and 30% methanol for several hours. The destained gels were scanned on a Zeinhe Soft Laser Scanning Densitometer at 520 nm.

ATPase Activity Measurements

ATPase activities were measured at 37°C in a final volume of 1.0 ml. The Mg²⁺-ATPase activity of the myofibrils was determined in 60 mM KCl, 7.5 mM MgCl₂, 5.0 mM Na₂ATP, 10 mM Na₃citrate, 20 mM imidazole, pH 7.0, 1.0 mM CaCl₂ and 1.03 mM EGTA (free Ca²⁺ = 1 x 10⁻⁷ M using a K₅ of 2.51 x 10⁶ M⁻¹ for the reaction of Ca²⁺ with EGTA at pH 7.0). The myosin ATPase of the myofibrillar preparations was measured in 450 mM KCl, 45 mM imidazole, pH 7.5, 5.0 mM Na₂ATP, 10 mM NaN₃ in the presence of either 10 mM CaCl₂ (Ca²⁺-activated myosin ATPase activity), or 10 mM EDTA (K⁺-EDTA myosin ATPase activity).

The protein concentrations in the reaction mixtures, which ranged from 0.25 to 0.35 mg/ml, were adjusted so that less than 20% of the ATP was hydrolyzed. The reaction was stopped by adding 1 ml of ice cold 10% trichloroacetic acid, and the precipitated protein was pelleted by centrifugation. Inorganic phosphate in the supernatant fraction was measured by the method of King (1938).

Separation of Myosin Heavy and Light Chains

Myosin isoenzyme bands that had been separated by electrophoresis, as described above, were stained with Coomassie Blue R, excised, and equilibrated overnight with 1% β-mercaptoethanol, 1% sodium dodecyl sulfate and 0.625 M Tris-HCl pH 6.8. The gel slices then were stacked on top of disc gels consisting of 2.5 cm of 12.5% acrylamide, 5 cm of 5% acrylamide, and a 2.5 cm 3% stacking gel. Electrophoresis was carried out according to the procedure of Laemmli (1970).

Results

We have identified three myosin isoenzymes in normal and thyrotoxic rabbit heart. The electrophoretic profiles and densitometric gel scans of the myosin isoenzymes, which we have designated R-V₁, R-V₂, and R-V₃ in descending order of mobility, are shown in Figure 1. In normal rabbit, R-V₂ was the predominant myosin isoenzyme; however, with thyroxine treatment for 7 days, we observed a shift
in the myosin isoenzyme population to predominantly R-Vi. Concomitant with the redistribution of myosin isoenzymes in the thyrotoxic rabbit ventricle, there was a 25% increase in the Mg2+-ATPase activity of the myofibrils and an approximate 90% increase in the Ca2+-activated myosin ATPase activity (Table 1). Our results indicate that R-Vi has a higher Ca2+-activated myosin ATPase activity than R-V3, similar to the relation between the Ca2+-activated myosin ATPase activity of V1 and V3 isoenzymes in rat ventricle (Hoh et al., 1977).

We have examined the temporal relation between the ventricular myosin isoenzyme population and administration of thyroxine. The distribution of ventricular myosin isoenzymes from rabbits treated 1, 2, 3, and 5 days with thyroxine and separated electrophoretically on polyacrylamide gels is shown in Figure 2. After 2 days of thyroxine administration, there was a slight increase in the proportion of R-Vi relative to R-V3. On day 3, the increase in R-Vi was more pronounced, with approximately equal amounts of R-Vi and R-V3 present. On day 5, the distribution of ventricular myosin isoenzymes was similar to that observed at 7 days (Fig. 1), and R-V1 was the predominant species.

The changes in the Ca2+-activated myosin ATPase activity closely paralleled the increases in the proportion of R-Vi present in the ventricle (Fig. 3). A maximal increase in Ca2+-activated myosin ATPase activity was observed after 7 days of thyroxine treatment and remained at this level at 17 days of thyroxine treatment. The K+-EDTA myosin ATPase activity for each preparation is given in nmol P,i mg myofibrillar protein min and is the mean ± SEM. Extensively washed and triton-treated myofibrils were used for these assays. Myofibrillar actomyosin Mg2+-ATPase was measured at 37°C in a medium containing 60 mM KCl, 5.0 mM ATP, 7.5 mM MgCl2, 10 mM NaN3, 1.0 mM CaCl2, 1.0 mM EGTA, 20 mM imidazole, pH 7.0. The calculated free calcium concentration was 1 × 10^-5 M. The Ca2+-ATPase activity was measured at 37°C in medium containing 450 mM KCl, 5 mM ATP, 10 mM NaN3, 10 mM CaCl2, 45 mM imidazole, pH 7.5. The CaCl2 was replaced by 10 mM EDTA for the measurement of K+-EDTA activity.

**TABLE 1 Actomyosin and Myosin ATPase Activity* of Myofibrils from Normal and Thyrotoxic Rabbit Hearts**

<table>
<thead>
<tr>
<th>Thyroid state</th>
<th>n</th>
<th>Myofibrillar actomyosin Mg2+-ATPase</th>
<th>Myofibrillar myosin Ca2+-ATPase</th>
<th>Myofibrillar myosin K+-ATPase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>13</td>
<td>205 ± 7</td>
<td>220 ± 10</td>
<td>230 ± 30</td>
</tr>
<tr>
<td>Thyrotoxic</td>
<td>6</td>
<td>250 ± 18</td>
<td>419 ± 18</td>
<td>260 ± 55</td>
</tr>
<tr>
<td>7 days</td>
<td>6</td>
<td>273 ± 13</td>
<td>414 ± 27</td>
<td>260 ± 38</td>
</tr>
<tr>
<td>17 days</td>
<td>6</td>
<td>230 ± 30</td>
<td>260 ± 55</td>
<td>260 ± 38</td>
</tr>
</tbody>
</table>

*ATPase activity for each preparation is given in nmol Pi/mg myofibrillar protein/min and is the mean ± SEM. Extensively washed and triton-treated myofibrils were used for these assays. Myofibrillar actomyosin Mg2+-ATPase was measured at 37°C in a medium containing 60 mM KCl, 5.0 mM ATP, 7.5 mM MgCl2, 10 mM NaN3, 1.0 mM CaCl2, 1.0 mM EGTA, 20 mM imidazole, pH 7.0. The calculated free calcium concentration was 1 × 10^-5 M. The Ca2+-ATPase activity was measured at 37°C in medium containing 450 mM KCl, 5 mM ATP, 10 mM NaN3, 10 mM CaCl2, 45 mM imidazole, pH 7.5. The CaCl2 was replaced by 10 mM EDTA for the measurement of K+-EDTA activity.

**FIGURE 1** Comparison of ventricular myosin isoenzymes from normal and thyroxine-treated rabbits. A and B are densitometric profiles of gels shown in C. A = myosin from a saline injected rabbit; B = myosin from a rabbit given daily injections of l-thyroxine, (150 µg/kg). C = pyrophosphate gels showing ventricular myosins from normal (a) and thyroxine-treated (b) rabbits. Electrophoresis was carried out in 4% polyacrylamide gels at a voltage gradient of 14 V/cm at 2°C for 16 hours.
ase activity appeared to be independent of the ventricular myosin isoenzyme population.

Despite the consistency of the increase in the Ca\(^{2+}\)-activated myosin ATPase with time following thyroxine administration (results presented in Fig. 2 are the mean of values obtained from two or more animals), there was variability in the myosin isoenzyme population between individual animals, as illustrated in Figure 4. Analysis of the ventricular myosin isoenzyme population in two normal rabbits, treated with saline injections for 5 days, shows that, in one (panel B), there was considerably more R-V\(_1\) (37%) present than in the other (5% R-V\(_1\); panel A). This difference was reflected in variations in the measured Ca\(^{2+}\)-activated myosin ATPase activities which were 178 nmol Pi/mg myofibrillar protein/min (panel A) and 260 nmol Pi/mg myofibrillar protein/min (panel B). A similar variability was observed in the ventricular myosin isoenzyme population from animals treated for 5 days with daily injections of thyroxine. Again, the values for the Ca\(^{2+}\)-activated myosin ATPase activity (301 and 409 nmol Pi/mg myofibrillar protein/min; panel C and D, respectively) corresponded to the proportion of R-V\(_1\) present in the myosin isoenzyme population (53% and 71%, respectively).

We also examined the different myosin isoenzymes from normal and thyrotoxic rabbit ventricles by electrophoresis of the excised myosin isoenzyme bands in the presence of sodium dodecyl sulfate. All samples gave an identical pattern of myosin heavy chain and two myosin light chains with the same mobility. No contaminating proteins were present.

It is evident from our results that there are three isoenzymes of myosin present in rabbit ventricle analogous to the three myosin isoenzymes identified in rat ventricle. To determine whether the ventricular myosin isoenzyme in rat and rabbit are similar,
we co-electrophoresed rat and rabbit myosin, extracted under identical conditions, on polyacrylamide gels using non-dissociating conditions (Hoh et al., 1977). The results are presented in Figure 5. In panel A, we show gel scans of myosin from adult rat ventricle, predominantly V₁, that was mixed with myosin from normal rabbit ventricle, predominantly R-V₃. Four bands are visible on the gel and in the densitometric scan of the gel. In the results shown in panel B, myosin from normal adult rat ventricle was mixed with myosin from thyrotoxic rabbit ventricle, predominantly R-V₁. Again, four distinct bands are visible and rabbit R-V₁ does not co-electrophorese with rat V₁, but with rat V₂. Rabbit R-V₃ isoenzyme comigrates with V₃ of rat ventricle. However, it is not possible to be sure that they are identical without supporting evidence from comparative analysis of the primary structure by peptide mapping.

We obtained approximate values for the Ca²⁺-ATPase activity of R-V₁ and R-V₃ by mathematical analysis of the data. Although Hoh et al. (1977) measured the Ca²⁺-activated myosin ATPase activity of the individual myosin isoenzymes of rat ventricle directly on polyacrylamide gels, it was not
possible for us to use this procedure due to the smaller differences in mobility between the rabbit isoenzymes compared to the rat isoenzymes. We integrated the area under the peaks in the densitometric scans of the gels to determine the relative amounts of R-V1, R-V2, and R-V3 present in each sample. The outer edges of the scan were used to define a symmetrical peak for R-V1 and R-V3. R-V2 was fitted, using R-V1 or R-V3, whichever was most appropriate, as a pattern. Based on Hoh's (1979) analysis of rat ventricular myosin isoenzymes, we made the assumption that R-V1 and R-V3 each consisted of two identical myosin heavy chains, aa and bb, respectively, whereas R-V2 contained an equal mixture of a and b (ab). This assumption is supported by the identification of two species of myosin heavy chain in rabbit ventricle by Sartore et al. (1979) using immunochemical fractionation procedures. We therefore distributed the relative amount of R-V2 equally between R-V1 and R-V3.

Another assumption in our analysis is that there are no cooperative interactions between the myosin heads in R-V2.

The relation between the percentage of R-V1 and the total Ca\(^{2+}\)-activated myosin ATPase activity was examined by linear least squares regression analysis using the following equation:

\[
V_t = a_1x_1 + a_2x_2
\]

where \(V_t\) is the total Ca\(^{2+}\)-activated myosin ATPase activity of the ventricular isoenzyme population, \(a_1\) is the Ca\(^{2+}\)-ATPase activity of R-V1, \(x_1\) is the fraction of R-V1 present in the total population, \(a_2\) is the Ca\(^{2+}\)-ATPase of R-V3, \(x_2\) is the fraction of R-V3 present in the total population, and \(x_1 + x_2 = 1\).

Therefore,

\[
V_t = a_1x_1 + a_2(1 - x_1) \quad \text{and,}
\]

\[
V_t = (a_1 - a_2)x_1 + a_2.
\]

Solution of the above equation, based on our experimental data and as shown in Figure 6, gave a regression line with the intercept of 160 (a2) and a slope of 259, therefore \(a_1 = 419\). The correlation coefficient was 0.85 (n = 19). Thus the calculated values for the Ca\(^{2+}\)-activated myosin ATPase activity of rabbit R-V1 and R-V3 are 419 nmol P\(_i\)/mg protein/min and 160 nmol P\(_i\)/mg protein per min, respectively, based on myofibrillar protein content.

**Figure 5** Comparison of rabbit and rat ventricular myosin isoenzymes. Rabbit ventricular myosin isoenzymes are labeled R-V1, R-V2, and R-V3. Rat ventricular myosin isoenzymes are labeled V1, V2, and V3. Myosin preparations of rabbit and rat hearts were co-electrophoresed on 4% gels. Panel A = densitometric gel profiles for a mixture of normal rat and rabbit myosins. Panel B = densitometric gel profiles for a mixture of normal rat and thyrotoxic rabbit myosins. Panel C = pyrophosphate gels corresponding to the densitometric profiles shown in Panels A, a and B, b.
We have performed a similar analysis of the myosin isoenzyme population and the Ca\(^{2+}\)-activated myosin ATPase activity of normal and hypophysectomized rat ventricle. The values we obtained for the Ca\(^{2+}\)-activated myosin ATPase activity of rat V\(_1\) and V\(_3\) by this procedure were 846 nmol Pi/mg myofibrillar protein/min and 193 nmol Pi/mg myofibrillar protein/min, respectively. The correlation coefficient was 0.98 (n = 14). These values for the rat ventricular myosin isoenzymes V\(_1\) and V\(_3\) and their relative enzymatic activity are consistent with previously published values (Yazaki and Raben, 1975; Pope et al., 1980). There was no significant difference between the value for rabbit R-V\(_3\) (160) and rat V\(_3\) (193) (Student’s t-test; 0.5 > P > 0.1). However, the Ca\(^{2+}\)-activated myosin ATPase activity of rat V\(_1\) was twice that of rabbit R-V\(_1\).

**Discussion**

The dynamics of contraction of the heart are greatly affected by thyroid state, and these altered dynamics show a close association with the Ca\(^{2+}\)-stimulated ATPase activity of myosin (Morkin, 1979; Alpert et al., 1979). Data presented here clearly show that this altered Ca\(^{2+}\)-ATPase activity is correlated with a redistribution of myosin isoenzymes in the rabbit heart. It appears, therefore, that thyroxine preferentially stimulates the synthesis of a preexisting myosin isoenzyme rather than initiating the synthesis of a new myosin. Moreover, this effect of thyroid hormone on the primary structure of myosin is most likely the major factor giving rise to the altered activity of rabbit heart myofibrils. Phosphorylation of myosin light chains is the same in euthyroid and hyperthyroid rabbit hearts (Litten et al., 1981), and there do not appear to be alterations in the thin filament regulatory proteins. Litten et al. (1981) have shown that phosphorylation of troponin I is the same in myofibrils prepared from euthyroid and hyperthyroid rabbit hearts and that the free Ca\(^{2+}\) giving half maximum activation of myofibrillar ATPase and the shape of curves relating free Ca\(^{2+}\) to normalized ATPase are the same in both preparations. The redistribution of myosin isoenzymes is also likely to be the major reason for the altered dynamics of intact hearts (Taylor et al., 1969) that occur with various thyroid states. Yet, the changes in the contraction-relaxation cycle of hearts in different thyroid states may also be related to changes in other enzymes regulating contractility such as the sarcoplasmic reticulum Ca\(^{2+}\)-ATPase (Suko, 1973).

Although thyroxine administration causes the preferential synthesis of R-V\(_1\), it is not clear if the synthesis of R-V\(_3\) is completely suppressed. We attempted to evaluate this possibility by analyzing the myosin isoenzyme profile in the easily released filament fraction described by Huxley (1963), and suggested by Etlinger et al. (1975) to be a precursor pool in the assembly of the total myofibrillar population. We could detect no differences in the myosin isoenzyme population between the easily released filament fraction and the residual myofibrils after 3 or 5 days of thyroxine treatment. However, these results do not definitively preclude the synthesis of a single myosin species in response to thyroxine administration because of the possibility of rapid mixing between the residual myofibrils and the easily released filament fraction (Sims et al., 1978). Differential accumulation and coordinate synthesis of two myosin heavy chain isoenzymes have been demonstrated by Garcia et al. (1978) in nematode muscle during development, and both R-V\(_3\) and R-V\(_1\) are present in normal rabbit heart. In rat ventricle, the synthesis of V\(_1\) appears to be dependent on the presence of thyroid hormone since only the V\(_3\) isoenzyme is detectable in hypophysectomized rats (Hoh et al., 1977). There are plausible ideas on how alterations in thyroid state induce a change in myosin isoenzyme population of the heart, but the actual mechanism is not known. Flink et al. (1979) postulated that the changes in myosin isoenzyme population in response to thyroxine administration result from a direct effect of the hormone on gene transcription comparable to its effect on the transcription of...
growth hormone mRNA (Martial et al., 1977). Yet the alterations in functional demands on the heart associated with sustained pressure overload also result in a change in the ventricular myosin isoenzyme population (Lompre et al., 1979). Moreover, chronic exercise increases cardiac myosin ATPase activity, and this may be associated with a change in the myosin isoenzyme population (Pagani and Solaro, unpublished observations). If thyroid state is the single variable operative in these conditions, the implication is that chronic pressure overload or exercise alters serum levels of thyroid hormone. It has been shown that thyroid administration prevents the decrease of rat cardiac myosin ATPase caused by constriction of the aorta (Afflito et al., 1979) and, presumably, the alteration of isoenzyme population. This observation suggests that both thyroxine and mechanically produced pressure overload alter the myosin isoenzyme population by a common mechanism. It is also possible that the common factor initiating changes in myosin isoenzyme distribution is the altered functional demands on the heart. This appears to be the mechanism by which skeletal muscle adapts to different functional requirements. In experiments using long-term stimulation, Salmons and Sreter (1976) showed that cross-reinnervation of slow and fast muscles had no requirements. In experiments using long-term stimulation, Salmons and Sreter (1976) showed that cross-reinnervation of slow and fast muscles had no effect on the biochemical and mechanical properties of the tissue unless there was an actual change in the pattern of impulse activity. In the heart, the correlate of this kind of pattern of electrical stimulation is the heart rate. Administration of thyroid hormone increases the heart rate, and there is evidence that the magnitude of the effects of thyroid hormone administration on the mechanical and biochemical properties of heart muscle in different species is an inverse of the basal heart rate (Korecky and Beznak, 1971; Yazaki and Raben, 1975). Since redistribution of the myosin isoenzyme population seems to occur in response to different initiating signals, it may be that the mechanism of this response to stress is more complex than a simple change in thyroid hormone levels or heart rate. Yet the possibility of a common mechanism remains an attractive hypothesis.

Acknowledgments

We would like to acknowledge the excellent technical assistance of David C. Robinson.

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Thyroxine-induced redistribution of isoenzymes of rabbit ventricular myosin.
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Circ Res. 1982;50:117-124
doi: 10.1161/01.RES.50.1.117

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