Role of Sodium in Modulation of Myocardial Hypertrophy in Renal Hypertensive Rats

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SUMMARY To evaluate the role of dietary sodium and antihypertensive drugs in the modulation of myocardial structure, especially myosin isozymic pattern, renal hypertensive rats (two-kidney, one clip) were treated with a sodium-deficient diet (7 mEq/kg), captopril, or atenolol. Native myosin was extracted under nondissociating conditions and separated by polyacrylamide gel electrophoresis. The percentage of myosin isozyme V1 was significantly decreased from 71.5 ± 7.5 (Wistar controls) to 52.4 ± 1.7% (p<0.05) in renal hypertensive rats and was associated with an increase in V3 component from 12.7 ± 5.1 (Wistar controls) to 23.1 ± 1.4% (renal hypertensive rats; p<0.05). There was a dramatic change in the myosin isozyme distribution pattern after treatment with low sodium and captopril. Six weeks of low sodium therapy in renal hypertensive rats resulted in an increase in V1 from 52.4 ± 1.7 to 74.8 ± 4.8% and a reduction in V3 from 23.1 ± 1.4 to 9.5 ± 2.4%. Normal rats treated with low sodium showed similar results. The percentage distribution of isozymes after low sodium therapy in the captopril-treated rats was not different from that in normal Wistar controls. Captopril therapy also caused an increase in V1 and a decrease in V3. Atenolol therapy, on the other hand, caused a significant increase in V1 and decrease in V3 with no change in blood pressure or heart weight. These data suggest that dietary sodium may play an important role in the modulation of myocardial mass and may modulate signals for synthesis of V1 or V3 myosin phenotypes. (Hypertension 8: 918-924, 1986)

KEY WORDS myosin isozymes regression of hypertrophy sodium deficiency antihypertensive therapy

PERSISTENCE of myocardial hypertrophy has been shown to be associated with a gradual decline in the maximum velocity of cardiac muscle shortening that usually correlates with the decreased Ca2+-ATPase activity of myosin. It has also been demonstrated1 that during persistent cardiac hypertrophy, cardiac myosin isozymes shift from a faster migrating type V1 to type V3, a form that migrates more slowly.2-6 Furthermore, it has been determined that the changes in myosin isozymes express cellular regulation of myosin biosynthesis depending on two separate genes that code for two types of heavy chains. V1 and V3 are the two homodimer phenotypes of the genes,7,8 whereas V2 is the mixed heterodimer phenotype involving both genes.3-11 Most available information is based on hypertrophy induced by either thyroxine or aortic banding.2-6 Little work has been done to investigate the changes that occur during hypertrophy in hypertension (i.e., hypertrophy resulting from increased cardiac afterload). More important, it is not known whether the isozyme distribution pattern can be reversed or prevented by proper therapeutic means once it has been altered.

The present study describes the development of hypertrophy in renal hypertensive rats (two-kidney, one clip) with special reference to alterations in the myosin isozyme distribution pattern and the effects of antihypertensive therapy and dietary restriction of sodium on such a myosin isozyme distribution pattern.

Materials and Methods

Renal hypertensive rats were prepared by placing a 0.2-mm clip on the left renal artery of 8- to 9-week-old male Wistar rats (175-200 g). Food and water were provided ad libitum. Blood pressure was measured twice a week using the tail cuff method described previously.12 Blood pressure was determined by the same person at approximately the same time of day.

Four weeks after the development of hypertension (7 weeks after clipping, when the rats were 15 to 16 weeks of age), the rats were divided into three groups. Group 1 consisted of 11 untreated renal hypertensive controls that received a normal sodium intake (204
MYOSIN ISOZYMES IN RENAL HYPERTENSIVE RATS/Sen and Young

Preparation of Myosin and Gels

The rats were decapitated, and the heart was excised and rinsed in physiological saline. Myosin was then extracted by using the method described by Martin et al. Approximately 300 mg of the bottom of the left ventricle was removed and flash-frozen in liquid nitrogen. The tissue was minced with sharp small scissors and washed in phosphate-buffered saline (40 mM NaCl and 3 mM Na₂HPO₄, pH 7.0 at 2°C). The tissue was then homogenized in 7 ml of saline buffer using a Kontes ground glass tissue grinder (Kontes, Vineland, NJ, USA) for 90 seconds (three 30-second homogenization periods alternated with 30-second rest intervals). The homogenate was then centrifuged at 3000 rpm for 10 minutes in a Sorvall centrifuge (Model RC5B; Norwalk, CT, USA) at 2°C. The supernatant was discarded, and the pellet was rewashed with 7 ml of the phosphate-buffered saline and centrifuged at 3000 rpm for 10 minutes. The supernatant was again discarded. The pellet was next immersed in 3 ml of an SM-24 rotor for 2 hours at 2°C. The supernatant was again discarded. The pellet was next immersed in 3 ml of an SM-24 rotor for 2 hours at 2°C. The supernatant was again discarded. The pellet was next immersed in 3 ml of an extracting solution containing 100 mM Na₃P₂O₇, 5 mM ethylene glycol bis(β-aminoethyl ether)-N,N',N''-tetraacetic acid, and 5 mM dithiothreitol, pH 8.6. The homogenate was shaken in an ice bath in a walk-in cold room for 60 minutes, after which it was centrifuged at 20,000 rpm in a Sorvall model RC5B centrifuge using an SM-24 rotor for 2 hours at 2°C. The supernatant was collected, mixed with an equal volume of ice-cold glycerol, and stored at −20°C.

The polyacrylamide gels were prepared using the method of Hoh et al. Two polyacrylamide gels (4% gels; T = 4%, C = 3%, on the notation of HJ Hjerten, 1962) were prepared. Two gels consisted of 1 ml of an acrylamide stock solution (200 g/L acrylamide, 6.2 g/L of N,N'-methylene-bis-acrylamide), 3.1 ml of a pyrophosphate stock solution (27 mM Na₃P₂O₇, 13.4% vol/vol glycerol, pH 8.8), and 22 μl of N,N',N''-tetramethylethylene-diamine. Polymerization was initiated by adding 35 μl of freshly prepared ammonium persulfate solution (125 g/L). Gel tubes used were 9.5 cm long and had an internal diameter of 5 mm (the gels polymerized in 20 minutes and were left for a further 20 minutes before use).

Separation of Myosin Isozymes by Electrophoresis

Electrophoresis was carried out in a Pharmacia gel electrophoresis apparatus (Model GE2/4; Piscataway, NJ, USA) sufficient to accommodate 20 gel tubes. The electrophoresis buffer contained 20 mM Na₃P₂O₇ and 10% (vol/vol) glycerol, pH 8.8 at 2°C. The buffer was recirculated during the run by pumping it from the lower to the upper reservoir. This was done to neutralize the products of electrolysis formed during the run. The temperature of the electrophoresis buffer was maintained at 2°C by a refrigeration unit that circulated coolant through the coils of the electrophoresis apparatus. A 60-minute prerun was carried out before myosin was applied to the gel using a current of 2 mA per gel. Two microliters of myosin (2.65 ± 1.38 μg) in 50% (vol/vol) glycerol was loaded directly on top of the gel. The current of 2 mA per gel was maintained for 5 hours, and then the gels were run under constant voltage supplied by a constant power supply (Model 3-1500; Buchler, Fort Lee, NJ, USA).

Staining of the Gels

The gels were stained for protein in 10 ml of Coomassie brilliant blue R solution (0.3 g/L) for 2 hours at room temperature. The stain was first dissolved in 500 ml of methanol, then 100 ml of acetic acid was added, and the volume was brought up to 1 L with distilled water. These procedures ensured that the stain was completely dissolved. Gels were then destained in a 7% (vol/vol) acetic acid and 30% (vol/vol) methanol solution in a Bio-Rad gel electrophoresis diffusion destainer (Model 172A; Hoefer Scientific for Bio-Rad Laboratories, Richmond, CA, USA).

Quantitation of Myosin Isozymes and Statistical Analysis

The myosin isoforms were quantified by densitometric scanning of the gels using a quick scan R & D densitometer (Helena Laboratories, Beaumont, TX, USA). A typical separation pattern is shown in Figure 1. Statistical analysis was performed using Student’s t test and analysis of variance where appropriate.

Results

Blood Pressure and Ventricular Weight in Renal Hypertensive Rats

The blood pressures and heart weights in renal hypertensive rats are summarized in Table 1. There was a significant increase in blood pressure from 122 ± 6 to 194 ± 6 mm Hg (p < 0.001) that was associated with an increase in absolute ventricular weight (from 1.3 ± 0.03 to 1.6 ± 0.07 g; p < 0.05) and an increase in the ventricular weight/body weight ratio (from 2.4 ± 0.06 to 3.6 ± 0.12; p < 0.001).

Changes in Myosin Isozyme Distribution Pattern in Renal Hypertensive Rats

A typical separation pattern of myosin isoforms and their corresponding scanning densitometric pattern is shown in Figure 1. The effect of hypertension on myosin isozyme distribution pattern in hypertrophy is sum-
Figure 1. Typical separation pattern of myocardial myosin isozymes. Three distinct bands depict V₁, V₂, and V₃ types of myosin isozymes and their corresponding scanning densitometric pattern (see text for details).

Three renal hypertensive rats demonstrated symptoms of congestive heart failure such as sudden drop in blood pressure, lethargy, and weight gain. These rats were considered as a separate group, and when killed, a considerable amount of water was found in the chest cavity, especially around the myocardium. When the myosin isozyme distribution pattern was determined (see Figure 2), a further increase in V₃ and decrease in V₁ compared with that in the renal hypertensive group was found. This finding indicates that the myocardium is composed predominantly of V₃ myosin isozyme during heart failure.

Effect of Treatment on Blood Pressure, Ventricular Weight, and Myosin Isozyme Distribution Pattern

The effect of treatment on blood pressure and ventricular weight is summarized in Table 1. Dietary modification of sodium in the form of low sodium administration resulted in a trend but not a significant reduction in blood pressure (from 194 ± 6 to 173 ± 8 mm Hg) associated with a significant reduction in absolute ventricular weight (from 1.61 ± 0.07 to 1.3 ± 0.03 g; p < 0.05). Antihypertensive therapy with captopril normalized blood pressure (from 194 ± 6 to 125 ± 5.6 mm Hg; p < 0.05) and ventricular size (from 1.61 ± 0.07 to 1.13 ± 0.05 g; p < 0.05). Atenolol therapy, on the other hand, did not significantly alter blood pressure (from 194 ± 6 to 216 ± 15 mm Hg) or ventricular weight (1.61 ± 0.07 vs 1.43 ± 0.25 g). The amount of atenolol given was sufficient to significantly reduce the heart rate from 511 ± 12 to 378 ± 15 beats/min (see Table 1).

The effect of treatment on the distribution of myosin

### Table 1. Blood Pressure and Ventricular Weights in Renal Hypertensive and Wistar Rats Before and After Treatment

<table>
<thead>
<tr>
<th>Group</th>
<th>Body weight (g)</th>
<th>BP (mm Hg)</th>
<th>Heart rate (beats/min)</th>
<th>Ventricular weight (g)</th>
<th>Ventricular wt/body wt</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RHR (n = 11)</td>
<td>434 ± 28</td>
<td>194 ± 6*</td>
<td>511 ± 12</td>
<td>1.61 ± 0.07†</td>
<td>3.6 ± 0.12†</td>
</tr>
<tr>
<td>Wistar controls (n = 7)</td>
<td>502 ± 14</td>
<td>122 ± 2</td>
<td>442 ± 26</td>
<td>1.3 ± 0.03</td>
<td>2.4 ± 0.06</td>
</tr>
<tr>
<td><strong>RHR after treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Na (n = 18)</td>
<td>403 ± 12</td>
<td>173 ± 8</td>
<td>534 ± 11</td>
<td>1.33 ± 0.05†</td>
<td>3.3 ± 0.10†</td>
</tr>
<tr>
<td>Captopril (n = 7)</td>
<td>465 ± 19</td>
<td>125 ± 5.6*</td>
<td>493 ± 27</td>
<td>1.13 ± 0.05†</td>
<td>2.4 ± 0.12*</td>
</tr>
<tr>
<td>Atenolol (n = 3)</td>
<td>357 ± 53</td>
<td>216 ± 15</td>
<td>378 ± 15†</td>
<td>1.43 ± 0.25</td>
<td>3.9 ± 0.15</td>
</tr>
</tbody>
</table>

Values are means ± SEM. BP = blood pressure; RHR = renal hypertensive rats.

* p < 0.001, † p < 0.05, compared with untreated controls.
isoymes is summarized in Figures 3 and 4. The effect of the low sodium therapy was evidenced by a dramatic change in the myosin isozyme distribution pattern in renal hypertensive rats. Six weeks of dietary modification resulted in a significant increase in the distribution of V\(_1\) (from 49.2\(\pm\)1.3 to 72.6\(\pm\)1.7\%;\(p<0.05\)) that was associated with a significant decrease in V\(_3\) (from 25.3\(\pm\)1.1 to 10.0\(\pm\)0.91\%;\(p<0.05\)), demonstrating that exposure to low sodium significantly reduced the amount of V\(_3\) that was found in renal hypertensive rats and that these changes in the myosin isozyme distribution pattern (the increase in V\(_1\) and decrease in V\(_3\)) occurred despite the lack of change in blood pressure.

Treatment with captopril produced similar results. The distribution of V\(_1\) significantly increased (from 49.2\(\pm\)1.3 to 68.3\(\pm\)4.28\%;\(p<0.05\)) and was associated with a reduction in V\(_3\) (from 25.3\(\pm\)1.1 to 11.9\(\pm\)2.1\%;\(p<0.05\)). Alteration in the myosin isozyme distribution pattern with captopril therapy occurred with both normalization of blood pressure and heart weight (Table 2). Atenolol therapy, however, resulted in a significant decrease in V\(_1\) (from 49.2\(\pm\)1.3 to 29.9\(\pm\)10.48\%;\(p<0.05\)) and an increase in V\(_3\) (from 25.3\(\pm\)1.1 to 48.3\(\pm\)14.4\%;\(p<0.05\)). Although there was significant variability in the distribution pattern, the increase in V\(_1\) and decrease in V\(_3\) were very obvious, and the increase in V\(_1\) occurred without a change in either blood pressure or ventricular weight.

**Effect of Low Sodium on the Myosin Isozyme Distribution Pattern in Normal Rats**

The effect of low sodium therapy on blood pressure, ventricular weight, and myosin isozyme pattern in normal Wistar rats is summarized in Table 3. Six weeks of low sodium therapy had no effect on blood pressure, ventricular weight/body weight ratio, or absolute heart weight (see Table 3) but resulted in a dramatic increase
in the distribution of V₁ (from 70.4 ± 4.04 to 87.0 ± 1.82%) associated with a significant increase in the distribution of V₃ (from 12.8 to 4.9%; p < 0.005).

**Discussion**

We have demonstrated that the myosin isozyme distribution pattern alters (shifts from V₁ to V₃) during the development of hypertrophy and hypertension in the renal hypertensive rat model (two-kidney, one clip) as well as during heart failure. We have also demonstrated that the altered pattern can be normalized either by a low sodium diet or by captopril therapy. We have also shown that a dietary sodium restriction in normal rats resulted in a further reduction in the V₃ component and an increase in the V₁ component of myocardial myosin.

Myosin is an important structural component of the myocardium that has enzymatic properties related to cardiac energetics. The function of myosin as an enzyme is to convert chemical energy in the form of adenosine 5'-triphosphate (ATP) into the mechanical work of muscle contraction. In rats, the cardiac myosin isozyme profile has been demonstrated to be a biochemical marker for the enzymatic Ca²⁺-ATPase activity of myosin. Hoh et al. and others have shown that the faster form of V₁ is related to higher ATPase activity. It has been demonstrated that myosin isozyme enzymatic activity corresponds directly to the speed of myocyte shortening. The maximal speed of shortening of the isolated cardiac papillary muscle can be correlated to the ATPase activity. Schwartz et al. and Pagani and Julian have shown that the left ventricular myosin isozyme profile also correlates well with the ATPase activity in rats. It has been demonstrated that a decrease in the V₁ form associated with an increase in the V₃ form.

**Table 2. Relationship Between Blood Pressure, Heart Weight, and Myosin Isozyme During Development and Regression of Hypertrophy in Hypertension**

<table>
<thead>
<tr>
<th>Group</th>
<th>Blood pressure (mm Hg)</th>
<th>Heart weight (g)</th>
<th>Treatment-induced shifting of V₁ to V₃</th>
<th>Treatment-induced shifting of V₃ to V₁</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated RHR compared with normal rats</td>
<td>↑</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated SHR compared with normal rats</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>SHR + hydralazine*</td>
<td>↓</td>
<td>→</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHR + triple therapy*</td>
<td>↓</td>
<td>↓</td>
<td>→</td>
<td></td>
</tr>
<tr>
<td>RHR + captopril</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>RHR + atenolol</td>
<td>→</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RHR + low Na</td>
<td>↓ (†)</td>
<td>↓</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Triple therapy is a combination of reserpine, hydralazine, and hydrochlorothiazide.

RHR = renal hypertensive rats; SHR = spontaneously hypertensive rats; ↑ = increase; ↓ = decrease; → = no change.

*Spontaneously hypertensive rats also showed similar changes, as published previously.

**Table 3. Myosin Isozyme Distribution Pattern in Wistar Rats Receiving a Normal or a Low Sodium Diet**

<table>
<thead>
<tr>
<th>Diet</th>
<th>BP (mm Hg)</th>
<th>Ventricular wt/body wt</th>
<th>Heart rate (beats/min)</th>
<th>Percentage of distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Na, 204 mEq/kg</td>
<td>122±2</td>
<td>2.4±0.06</td>
<td>443±26</td>
<td>70.4±4.04</td>
</tr>
<tr>
<td>Low Na, 7 mEq/kg</td>
<td>121±5</td>
<td>2.4±0.06</td>
<td>485±16</td>
<td>87.0±1.82*</td>
</tr>
</tbody>
</table>

Values are means ± SEM.

* p < 0.005, compared with normal sodium diet values.
crease in $V_1$ form is accompanied by a decrease in the intrinsic contractility of the heart.\textsuperscript{18-21}

Numerous reports have focused on the alteration in the myosin isozyme distribution pattern induced by hormonal changes and age.\textsuperscript{2,7} It has been shown that an increase in cardiac afterload results in a change in the myosin isozyme distribution pattern.\textsuperscript{2,7} Thyroxine-induced hypertrophy was shown to be associated with an increase in the distribution of $V_1$, whereas hypertrophy caused by increased afterload was shown to be associated with an increase in $V_2$. Scheuer and Bhan\textsuperscript{1} have demonstrated that the increase in the $V_1$ form of cardiac myosin in experimental hypertension can be reversed by physical training without affecting either cardiac mass or systolic blood pressure in rats. This finding demonstrated that the alteration in the myosin isozyme can take place independently of blood pressure.

In the present study we have shown that in renal hypertensive rats (two-kidney, one clip) a significant increase in $V_2$ takes place that could be returned to normal with either low sodium therapy or captopril therapy independently of blood pressure control or myocardial mass. One of the most intriguing observations was the increase in $V_3$ in normotensive Wistar rats after treatment with low sodium. We, as well as others,\textsuperscript{2} have shown that the aging process in rats gradually increased the percentage of $V_3$ while it concomitantly reduced the percentage of $V_1$. In the present study, however, low sodium therapy in normal rats resulted in a significant increase in $V_3$ and a decrease in $V_1$, exactly the opposite of that found during aging. Whether the contractility of the heart also increased after low sodium therapy has yet to be determined.

A reversal of myocardial hypertrophy was achieved by a low sodium diet as well as by converting enzyme inhibitor therapy. This reversal of myocardial hypertrophy was associated with a reduction in blood pressure with administration of captopril, whereas the low sodium diet induced no change in blood pressure. Thus, the effect of hypertension or afterload was dissociated from the alteration of the myosin isozyme distribution pattern. Our previous finding in spontaneously hypertensive rats showed that triple therapy with a combination of reserpin, hydralazine, and hydrochlorothiazide resulted in a decrease in myocardial mass, and blood pressure reduction associated with no change in myosin isozyme distribution pattern further supports this observation.\textsuperscript{16} To our knowledge, the effect of low sodium on myocardial hypertrophy and its biochemical composition is the first evidence demonstrating a dissociation between the blood pressure and myocardial mass in renal hypertensive rats. Lindpaintner and Sen\textsuperscript{22} found a linear relationship between blood pressure and heart weight during the development of hypertrophy and little or no correlation during regression of hypertrophy with low sodium. Table 2 summarizes the effect of treatment on blood pressure and heart weight and its relationship to myosin isozyme pattern in spontaneously hypertensive and renal hypertensive rats.

The mechanism by which the myosin isozyme shifts from $V_1$ to $V_3$ is not clearly understood. Both converting enzyme inhibitor and low sodium stimulate plasma renin activity and thereby activate the renin-angiotensin system. Therefore, one logical explanation would be that angiotensin II has a direct effect on alteration in the shift of myosin isozyme from $V_1$ to $V_3$. When infusing angiotensin II directly to normal rats using an Alzet pump (Alza, Palo Alto, CA, USA) in a pilot experiment, we found no change in the distribution pattern of myosin isozyme patterns (unpublished observation) and therefore no evidence that a renin-angiotensin II-mediated mechanism converts $V_1$ to $V_3$. Another possible mechanism is the activation of the sympathetic outflow on alteration of protein synthesis. It has been suggested that high salt suppresses sympathetic outflow and low salt increases sympathetic outflow.\textsuperscript{23} Thus, if low salt therapy does indeed increase sympathetic outflow, perhaps one way to explain this shifting would be the stimulation of the sympathetic system through low sodium therapy. However, the converting enzyme inhibitor is not believed to increase sympathetic outflow.\textsuperscript{24}

The effect of atenolol on myocardial mass appears to be an adaptable change caused by a reduction in heart rate. Atenolol therapy significantly reduced heart rate; perhaps it can be assumed, therefore, that there was little demand for highly contractile protein. Still, the signal that stimulated $V_1$ synthesis remains unclear. An increase in $V_3$ has been implied to be associated with a reduction in cardiac hypertension of the heart. Our study confirms this observation. Atenolol therapy resulted in an increase in $V_3$, myosin isozyme, which should be associated with a reduction of contractility of the heart. Lauva and Tomanek\textsuperscript{25} recently demonstrated that chronic treatment of spontaneously hypertensive rats with atenolol results in a compromised function of the myocardium.

Our study demonstrated a shifting of the myosin isozyme pattern induced by sodium restriction and by therapeutic means that was independent of the degree of hypertension and myocardial mass. This study identified a definite biochemical defect that occurs during hypertrophy in renal hypertension and demonstrated that the defect can be prevented or corrected by proper therapy. However, the mechanism responsible for transmitting the signal at the gene level for selection of the type of protein to be synthesized remains to be studied.

Acknowledgment

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