Significance of Myocardial α- and β-Adrenoceptors in Catecholamine-Induced Cardiac Hypertrophy

W. Zierhut and H.-G. Zimmer

The role of α- and β-adrenoceptors in the development of catecholamine-induced cardiac hypertrophy in vivo was investigated. Rats received a constant intravenous infusion of norepinephrine or sodium chloride (control) for 3 days. The norepinephrine infusion was combined with the α-blocker prazosin, the β-blocker metoprolol, or both blockers. For modulation of the work load of the heart, the calcium channel blocker verapamil was added to the norepinephrine infusion. A further group of animals was treated with the α-adrenergic stimulator norfenephrine, which also was combined with prazosin or verapamil. Norepinephrine induced significant increases in mean aortic pressure, left ventricular dP/dt\text{\max}, heart rate, and total peripheral resistance. The left ventricular weight/body weight ratio was significantly elevated and was accompanied by an increase in the RNA concentration and the RNA/DNA ratio. Prazosin as well as metoprolol partially antagonized the increase in left ventricular weight and RNA concentration, whereas simultaneous prazosin and metoprolol treatment prevented the norepinephrine-induced alterations. Although combination of norepinephrine with verapamil resulted in considerable reduction of all functional parameters, the development of cardiac hypertrophy and the elevated RNA/DNA ratio were not significantly influenced. Stimulation of α-receptors with norfenephrine elicited an increase in total peripheral resistance and in left ventricular weight, which was abolished by prazosin. Verapamil did not affect the norfenephrine-induced cardiac hypertrophy, although it normalized essentially all functional parameters. Thus, the rapid development of cardiac hypertrophy in the norepinephrine model seems to be directly mediated by stimulation of myocardial α- and β-adrenoceptors rather than by hemodynamic changes. (Circulation Research 1989;65:1417-1425)

In spite of intensive investigations, the signal linking increased work load of the heart with the development of cardiac hypertrophy is still a subject of controversy. Many authors consider the catecholamine norepinephrine (NE) to play an important role in this context. In a number of pathophysiological conditions leading to cardiac hypertrophy, the activity of the sympathetic nervous system is enhanced, resulting in increased release of NE from the sympathetic nerve endings within the myocardium.1 Furthermore, administration of catecholamines can induce cardiac hypertrophy,2-4 and, in addition, exercise-induced cardiac hypertrophy can be prevented by chemical sympathectomy.5 However, in other studies using different models, hypertrophy occurred independently of the adrenergic system.6-10 Thus, the significance of catecholamines seems to be dependent on the model used for initiation of cardiac hypertrophy.

The stimulus responsible for mediation of cardiac hypertrophy by NE may be via activation of α- and β-adrenoceptors. α_1-, β_1-, and β_2-adrenoceptors have been shown to exist on the mammalian myocyte.11-14 Furthermore, it is well established that activation of myocardial β-receptors induces cardiac hypertrophy in vivo.15-18 More recently, the hypertrophic response of cultured neonatal myocytes was related to an α_1-adrenergic effect, while β-stimulation did not result in cellular hypertrophy.19,20 Whether α-receptors are important mediators of cardiac hypertrophy in vivo is difficult to assess, since α-stimulation in the intact animal leads to an increase in work load of the heart due to an increase in peripheral resistance, which per se could induce cardiac hypertrophy. The present study was undertaken to clarify the role of myocardial α- and
β-receptors in the catecholamine-induced hypertrophy in vivo as compared with the peripheral circulatory alterations evoked by NE. Therefore, we developed a model in which cardiac hypertrophy was induced after 3 days of intravenous infusion of NE. The short time period made possible administration of NE and specific antagonists as constant intravenous infusion, which provided an excellent control of the dose.

Our experimental model shows that direct stimulation of α₁- and β-adrenoceptors leads to the development of cardiac hypertrophy and that the concomitant hemodynamic changes seem to play a minor role.

Materials and Methods

The experiments were done on female Sprague-Dawley rats (200–250 g body wt) fed a control rat chow diet (Altromin C 1000 Altromin GmbH, Lade, FRG) with free access to water. All substances were given as constant, intravenous infusions for 3 days via a catheter (Vygon, Aachen, FRG) positioned in the left jugular vein. The catheter was connected to a 20-ml syringe placed in an infusion pump (Infors AG, Basel, Switzerland). The infusion rate was 4 ml/kg/hr. The animals could move around freely in their cages during the infusions. NE was administered in a dose of 0.2 mg/kg/hr; sodium chloride-infused animals served as controls. NE was combined with the α₁-blocker prazosin (0.1 mg/kg/hr), the β₁-blocker metoprolol (1 mg/kg/hr), both prazosin and metoprolol, or the calcium-channel blocker verapamil (1 mg/kg/hr). In addition, a further group of animals received the α-adrenergic stimulator norfenephrine (2 mg/kg/hr), which was also combined with prazosin or verapamil. Thus, the animals were divided into nine groups: 1) control (sodium chloride), 2) NE, 3) NE+prazosin, 4) NE+metoprolol, 5) NE+prazosin+metoprolol, 6) NE+verapamil, 7) norfenephrine, 8) norfenephrine+prazosin, and 9) norfenephrine+verapamil. Although the affinity of metoprolol to the β₁-receptor is considerably higher than to the β₂-receptor, the dose of 1 mg/kg/hr should be sufficient to block both β₁- and β₂-adrenoceptors. To test this assumption, a further group of animals was treated with NE in combination with the nonselective blocker propranolol (1 mg/kg/hr). For estimation of DNA, the sediments were suspended three times with 0.3N PCA. The lipids were extracted by use of 10% potassium acetate in 50% ethanol, followed by methanol, chloroform and methanol (2:1), benzene, and diethyl ether. For hydrolysis of RNA, the samples were incubated in 0.5N KOH for 14 hours at room temperature. After addition of 0.5 ml of 6N PCA, the samples were kept in an ice bath for 1 hour. The precipitate (containing DNA) was separated by centrifugation, and the supernatant (containing RNA) was decanted. For estimation of DNA, the sediments were suspended in 2 ml of 1N PCA and incubated in a water bath at 70°C for 1 hour. Then the supernatant was separated by centrifugation. For elimination of errors arising from the release of proteins, mainly in the RNA fraction, during the alkaline digestion in 0.5N...
TABLE 1. Changes in Functional and Metabolic Parameters After 3 Days of Continuous Intravenous Infusion of Prazosin (0.1 mg/kg/hr), Metoprolol, or Verapamil (each 1 mg/kg/hr)

<table>
<thead>
<tr>
<th></th>
<th>Control (n=23)</th>
<th>Prazosin (n=7)</th>
<th>Metoprolol (n=6)</th>
<th>Verapamil (n=6)</th>
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<tbody>
<tr>
<td>HR (beats/min)</td>
<td>328±6</td>
<td>373±12*</td>
<td>243±21*</td>
<td>373±17</td>
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<tr>
<td>LVdP/dt(\max) (mm Hg/sec)</td>
<td>9,740±309</td>
<td>14,257±981*</td>
<td>6,233±681*</td>
<td>7,500±901</td>
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<tr>
<td>MAP (mm Hg)</td>
<td>123±2</td>
<td>113±3</td>
<td>108±8</td>
<td>105±6*</td>
</tr>
<tr>
<td>CO (ml/kg/min)</td>
<td>353±7</td>
<td>443±24*</td>
<td>303±21</td>
<td>391±20</td>
</tr>
<tr>
<td>TPR (mm Hg/kg/min/ml)</td>
<td>0.35±0.01</td>
<td>0.26±0.02*</td>
<td>0.37±0.04</td>
<td>0.27±0.01*</td>
</tr>
<tr>
<td>RNA (mg/gDNA)</td>
<td>1.83±0.03</td>
<td>1.95±0.07</td>
<td>1.79±0.04</td>
<td>1.93±0.03</td>
</tr>
<tr>
<td>LVW (mg/BW)</td>
<td>2.35±0.02</td>
<td>2.35±0.06</td>
<td>2.43±0.05</td>
<td>2.44±0.05</td>
</tr>
</tbody>
</table>

Values are mean±SEM; number of experiments in parentheses. HR, heart rate; LVdP/dt\(\max\), left ventricular rate of change of pressure; MAP, mean aortic pressure; CO, cardiac output; TPR, total peripheral resistance; LVW/BW, left ventricular weight/body weight.

*p<0.05 vs. control.

KOH, the supernatants were measured at two wavelengths (RNA, 260 and 286 nm; DNA, 268 and 284 nm).23 The reliability of this method was tested by determination of the RNA and DNA concentrations of myocardial tissue enriched with calf thymus DNA (Sigma Chemical) and calf liver RNA (Sigma Chemical). The result was that the RNA concentration was slightly overestimated while the DNA concentration was measured correctly. The overestimation was less than 10% and of a comparable extent in all determinations so that comparison of the different experimental groups was possible.

Statistical Analysis
Each value is expressed as a mean±SEM. The data were first compared by analysis of variance (ANOVA). In case of significant differences, multiple r testing was done by use of the Bonferroni modification. A value of p<0.05 was considered significant. The significance of correlations was evaluated by calculation of the correlation coefficient r. In this investigation, the r values were calculated using the Spearman rank correlation coefficient.

Results
All substances were well tolerated by the animals. None showed signs of cardiac decompensation such as pleural or abdominal effusion. The left ventricular end-diastolic pressure did not differ significantly among the groups; it did not exceed 7 mm Hg. The end-diastolic pressure did not differ significantly among the groups; it did not exceed 7 mm Hg. The end-diastolic pressure did not differ significantly among the groups; it did not exceed 7 mm Hg. The end-diastolic pressure did not differ significantly among the groups; it did not exceed 7 mm Hg. The end-diastolic pressure did not differ significantly among the groups; it did not exceed 7 mm Hg. The end-diastolic pressure did not differ significantly among the groups; it did not exceed 7 mm Hg. The end-diastolic pressure did not differ significantly among the groups; it did not exceed 7 mm Hg. The end-diastolic pressure did not differ significantly among the groups; it did not exceed 7 mm Hg. The end-diastolic pressure did not differ significantly among the groups; it did not exceed 7 mm Hg. The end-diastolic pressure did not differ significantly among the groups; it did not exceed 7 mm Hg. The end-diastolic pressure did not differ significantly among the groups; it did not exceed 7 mm Hg. The end-diastolic pressure did not differ significantly among the groups; it did not exceed 7 mm Hg. The end-diastolic pressure did not differ significantly among the groups; it did not exceed 7 mm Hg. The end-diastolic pressure did not differ significantly among the groups; it did not exceed 7 mm Hg. The end-diastolic pressure did not differ significantly among the groups; it did not exceed 7 mm Hg. The end-diastolic pressure did not differ significantly among the groups; it did not exceed 7 mm Hg. The end-diastolic pressure did not differ significantly among the groups; it di

Effect of Norepinephrine
Intravenous infusion of NE led to an enhancement of nearly all functional parameters. HR and LVdP/dt\(\max\) were elevated, while the LVSP was only slightly increased (Table 2, Figure 1A). MAP was significantly higher compared with the control value, CO was slightly diminished, and TPR was higher. These functional changes were accompanied by an increase in the myocardial RNA concentration and in the RNA/DNA ratio, indicating the development of left ventricular hypertrophy (Table 3, Figure 1A). These changes in RNA metabolism were associated with an elevation in the LV weight/body weight ratio (Table 3, Figure 1A).

Effect of Concomitant \(\alpha\)- and \(\beta\)-Adrenergic Blockade on Norepinephrine-Induced Alterations
Simultaneous administration of prazosin antagonized the NE-induced elevation in MAP, but hardly influenced the increase in HR and LVdP/dt\(\max\) (Table 2, Figure 1B). CO was elevated, and TPR fell below the control level. Metoprolol attenuated the increase in HR and LVdP/dt\(\max\). In contrast with \(\alpha\)-blockade, \(\beta\)-blockade reduced the CO and elevated TPR (Table 2, Figure 1C). Prazosin as well as metoprolol significantly attenuated the left ventricular RNA concentration and the RNA/DNA ratio to the same extent (Table 3). Likewise, the LV weight/body weight ratio was partially antagonized by either \(\alpha\)-or \(\beta\)-blockade (Table 3). Simultaneous administration of both prazosin and metoprolol attenuated the NE-induced increase in the RNA/DNA ratio and abolished the elevation of the LV weight/body weight ratio (Table 3, Figures 1A and 1D). The functional parameters were different from the control values but in the opposite direction compared with the influence of NE alone (Table 2, Figures 1A and 1D). Combination of NE with propranolol instead of metoprolol revealed no differences in the functional and metabolic parameters between these two groups (data not shown).
TABLE 2. Changes in Functional Parameters After 3 Days of Continuous Intravenous Infusion of Norepinephrine (200 μg/kg/hr) Norfenephrine (2 mg/kg/hr) Alone or in Combination With Prazosin (0.1 mg/kg/hr), Metoprolol, or Verapamil (each 1 mg/kg/hr)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (n=23)</th>
<th>NE (n=13)</th>
<th>NE+P (n=8)</th>
<th>NE+M (n=8)</th>
<th>NE+P+M (n=10)</th>
<th>NE+V (n=8)</th>
<th>NORF (n=8)</th>
<th>NORF+P (n=8)</th>
<th>NORF+V (n=8)</th>
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<tr>
<td>HR (beats/min)</td>
<td>328±6</td>
<td>448±8*</td>
<td>411±5*</td>
<td>316±12†</td>
<td>290±8†</td>
<td>382±18*†</td>
<td>435±10*</td>
<td>386±14*</td>
<td>337±7</td>
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<td>LVSP (mm Hg)</td>
<td>142±2</td>
<td>152±4</td>
<td>130±6†</td>
<td>136±7</td>
<td>134±3†</td>
<td>136±4</td>
<td>144±3</td>
<td>121±2*</td>
<td>126±3</td>
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<td>LVPd/dtmax (mm Hg/sec)</td>
<td>9740±309</td>
<td>21,338±882*</td>
<td>19,900±845*</td>
<td>12,038±756*†</td>
<td>11,290±304†</td>
<td>17,687±430*</td>
<td>17,638±1324*</td>
<td>12,713±923*</td>
<td>12,275±801*</td>
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<tr>
<td>MAP (mm Hg)</td>
<td>123±2</td>
<td>137±4*</td>
<td>116±7</td>
<td>120±7</td>
<td>113±2†</td>
<td>116±41</td>
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<td>CO (ml/kg/min)</td>
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<td>330±15</td>
<td>466±24*†</td>
<td>261±11†</td>
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<td>345±20</td>
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<td>459±26*</td>
<td>337±8</td>
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<tr>
<td>TPR (mm Hg-kg-min)</td>
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<td>0.47±0.03*</td>
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<td>0.45±0.01*</td>
<td>0.23±0.01*</td>
<td>0.35±0.01</td>
</tr>
</tbody>
</table>

Values are mean±SEM; number of experiments in parentheses. HR, heart rate; LVSP, left ventricular systolic pressure; LVPd/dtmax, left ventricular rate of change of pressure; MAP, mean aortic pressure; CO, cardiac output; TPR, total peripheral resistance; NE, norepinephrine; P, prazosin; M, metoprolol; V, verapamil; NORF, norfenephrine.

*p<0.05 vs. control.
†p<0.05 vs. NE.

(Table 2, Figure 1E). The myocardial RNA/DNA and LV weight/body weight ratios were still elevated and were not significantly different from those in the NE group (Table 3, Figures 1A and 1E).

Effects of Norfenephrine Without and With Concomitant Infusion of Prazosin or Verapamil

Norfenephrine did not evoke significant changes in LVSP and MAP (Table 2). However, CO was depressed and TPR was higher than the control values (Table 2, Figure 2A). These norfenephrine effects were more pronounced than in the NE experiments. HR and LVPd/dtmax were increased (Table 2, Figure 2A) and the RNA/DNA and LV weight/body weight ratios were enhanced (Table 3, Figure 2A).

Concomitant administration of prazosin lowered MAP and TPR below the control level (Table 2, Figure 2B). There was still a moderate elevation of HR and LVPd/dtmax, and CO was increased. The increases in RNA concentration and in LV weight/body weight ratio were abolished; however, there remained a slight elevation of the RNA/DNA ratio (Table 3, Figure 2B).

The results of the norfenephrine + verapamil group correspond well with those of the NE + verapamil group. Although functional parameters except for LVPd/dtmax were essentially normal (Table 2, Figure 2C), the hypertrophy elicited by norfenephrine was not influenced. The RNA concentration was diminished when compared with norfenephrine alone; however, the RNA/DNA ratio was elevated by about the same extent (Table 3, Figures 2A and 2C).

Relation Between Total Peripheral Resistance and Myocardial DNA Concentration

A significant correlation was found between increases in TPR and DNA concentration (Figure DNA concentration tended to be higher in gro with elevated TPR (Tables 2 and 3). β-Block; (NE+metoprolol group) did not reduce the DI concentration when compared with the NE gro However, the significantly elevated DNA concent tion in the norfenephrine group was antagonized concomitant prazosin or verapamil treatment.

Discussion

In this in vivo study it has been shown that stimulation of myocardial β- and α-adrenergic receptors either alone or in combination can result in the development of hypertrophy of the rat heart. Card hypertrophy resulting from β-adrenergic stimulation has been studied extensively in the isoproteren model in vivo. However, the hypertrophy response to NE in cultured cardiac myocytes shown to be related only to stimulation of the adrenergic receptor. This raised the question whether the β-receptor-mediated hypertrophy in vivo could be the result of facilitation of NE release from sympathetic nerve endings induced by stimulation presynaptic β2-receptors and, consequently, could depend on postsynaptic α1-adrenoceptor stimulation. If this mechanism were responsible for the receptor-mediated hypertrophy in vivo, β-adrenergic stimulation in the presence of α-blockade should cause hypertrophy. In our study, however, NE in
sion in the presence of α-blockade caused left ventricular hypertrophy as assessed by a significant increase in the LV weight/body weight and RNA/DNA ratios (Figure 1B). Thus, this hypertrophy model was not likely to be mediated by postsynaptic α1-receptors. It may be argued that simultaneous prazosin administration caused an increase in CO, which might serve as a trigger for cardiac hypertrophy independent of the β-receptor. This possibility could be excluded in our experiments by infusion of prazosin alone, which induced a similar increase in CO but did not evoke an elevation in the LV weight/body weight and RNA/DNA ratios (Table 1). Moreover, additional infusion of metoprolol to the NE+prazosin group entirely prevented the development of cardiac hypertrophy (Figure 1D). Thus, cardiac hypertrophy observed after NE infusion seems to be partially mediated by β-adrenergic stimulation.

Recently, findings were presented that link increased mechanical contractions to an increase in myosin synthesis in association with cell growth. Therefore, it is possible that mechanical alterations such as the enhancement of LVDp/dt max could play an important role in the development of hypertrophy. In the present study, no close correlation between LVDp/dt max and hypertrophy could be detected. Despite significant elevations in LVDp/dt max, the groups treated with prazosin alone and norfenephrine+prazosin did not show left ventricular hypertrophy. Furthermore, groups with similar LVDp/dt max values (NE and NE+prazosin; NE+verapamil and norfenephrine; norfenephrine+prazosin and norfenephrine+verapamil) exhibited significantly different degrees of hypertrophy. Thus, in this model LVDp/dt max seems not to play a major role.

Apart from the involvement of cardiac β-adrenergic receptors, more recently the interest has been focused on cardiac α-receptors. In our present study the effect of α-adrenergic stimulation was tested by addition of the β-blocker metoprolol to the NE infusion. The dose of metoprolol was sufficient to block both β1- and β2-receptors despite the β-selective properties of the drug. This finding is supported by the data obtained in the NE+propran-
TABLE 3. Effects of 3 Days' Infusion of Norepinephrine (200 μg/kg/hr) or Norfenephrine (2 mg/kg/hr) Alone or in Combination With Prazosin (0.1 mg/kg/hr), Metoprolol, or Verapamil (each 1 mg/kg/hr) on the Development of Left Ventricular Hypertrophy as Assessed by Changes in RNA Concentration, DNA Concentration, RNA/DNA Ratio, and Left Ventricular Weight/Body Weight Ratio

<table>
<thead>
<tr>
<th></th>
<th>RNA (mg/g)</th>
<th>DNA (mg/g)</th>
<th>RNA/DNA</th>
<th>LVW(mg)/BW(g)</th>
<th>BW (g)</th>
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<tbody>
<tr>
<td>Control (n = 23)</td>
<td>4.07±0.06</td>
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<td>1.83±0.03</td>
<td>2.35±0.02</td>
<td>232±2</td>
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<tr>
<td>NE (n = 13)</td>
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<td>2.66±0.07*</td>
<td>3.26±0.09</td>
<td>217±4</td>
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<td>NE+P (n = 8)</td>
<td>5.08±0.13*</td>
<td>2.23±0.06</td>
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<td>NE+M (n = 8)</td>
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<td>NE+P+M (n = 10)</td>
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<td>NORF (n = 8)</td>
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<td>NORF+V (n = 8)</td>
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<td>2.69±0.03</td>
<td>226±5</td>
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Values are mean±SEM; number of experiments in parentheses. LVW/BW, left ventricular weight/body weight; BW, mean body weight; NE, norepinephrine; P, prazosin; M, metoprolol; V, verapamil; NORF, norfenephrine.

*p<0.05 vs. control.
†p<0.05 vs. NE.
‡p<0.05 vs. norfenephrine.

olol group, which were in close correlation with the NE+metoprolol group. During β-blockade, the LV weight/body weight ratio turned out to be elevated to the same extent as in the NE+prazosin group. However, the NE+metoprolol group was characterized by an increase in TPR, most probably due to activation of vascular α-receptors. One may argue that this alteration in TPR could have served as a trigger for the remaining hypertrophy. In this context the results of the NE+verapamil group are important. Verapamil did reduce TPR and MAP to values slightly below the control level. HR was also reduced but remained elevated (Table 2, Figure 1E). Despite these reductions, the LV weight/body weight and RNA/DNA ratios were not significantly affected as compared with the NE group. In con-

![Figure 2](http://circres.ahajournals.org/)

**FIGURE 2.** Percentage changes in functional parameters (HR, MAP, CO, TPR) and in RNA/DNA and LVW/BW ratios in norfenephrine experiments as compared with control (C) values (C=100%) (see Tables 2 and 3). Panel 2A, norfenephrine (NORF); 2B, norfenephrine+prazosin (NORF/P); 2C, norfenephrine+verapamil (NORF/V). HR, heart rate; MAP, mean aortic pressure; CO, cardiac output; TPR, total peripheral resistance; LVW/BW, left ventricular weight/body weight. Significant changes are indicated by asterisks (p<0.05 vs. control).
Norfenephrine and prazosin; O, norfenephrine; •, fenephrine; •, norfenephrine–prazosin; △, norfenephrine; •, fenephrine; •, norfenephrine–prazosin; △, norfenephrine–verapamil.

Figure 3. Correlation between DNA tissue concentrations and total peripheral resistance (TPR). Alterations in TPR were significantly correlated (correlation coefficient $r_S=0.71$) with changes in DNA concentration. ●, control; ○, norepinephrine; ●, NE+metoprolol; ○, NE+prazosin; △, NE+prazosin+metoprolol; △, NE+verapamil; ●, norfenephrine; •, norfenephrine+prazosin; △, norfenephrine+verapamil.

This concept is confirmed by the results of our norfenephrine experiments. Similar to the NE+metoprolol group, norfenephrine evoked an elevation of the LV weight/body weight and RNA/DNA ratios (Table 3). Likewise, TPR was increased (Table 2). The norfenephrine-induced hypertrophy was abolished by prazosin; however, a slight increase of the RNA/DNA ratio remained (Table 3). This increase and the small enhancement of HR and $LVdP/dt_{max}$ may be related to a mild $\beta$-adrenergic stimulation by norfenephrine. In contrast with prazosin, verapamil did not affect the development of hypertrophy, although it normalized MAP, HR, and TPR and substantially reduced $LVdP/dt_{max}$. Thus, this hypertrophy model is due to stimulation of myocardial $\alpha$-receptors and seems not to be the response of the myocardium to the circulatory changes.

$\alpha_1$-Receptors have been shown to exist on cardiac myocytes$^{1,12}$; their biological relevance, however, is still a matter of debate. The putative second messenger system linked to myocardial $\alpha_1$-receptors is the hydrolysis of phosphatidylinositol 4,5-bisphosphate, leading to formation of inositol trisphosphate (IP3) and diacylglycerol.$^{26-29}$ Both reaction products are probably involved in the generation of the positive inotropic effect seen after activation of $\alpha_1$-receptors.$^{30}$ However, this $\alpha_1$-receptor–mediated increase in contraction force is relatively small compared with the effect mediated by stimulation of $\beta$-receptors.$^{11}$ The anabolic effect of $\alpha_1$-receptor stimulation in cultured myocytes is possibly mediated by activation of protein kinase C by diacylglycerol, since direct activation of protein kinase C by tumor-promoting phorbol esters also results in cellular hypertrophy.$^{31}$

Recently, findings were presented that support a role of myocardial $\alpha_1$-receptors in the development of cardiac hypertrophy due to aortic banding in guinea pigs.$^{32}$ These results suggest that pressure overload elicits an increase of $\alpha_1$-adrenergic binding sites already in the prehypertrophic period.$^{33}$ Blockade attenuated the hypertrophic response.

In conclusion, our data show that in the model of NE-induced hypertrophy myocardial $\alpha_1$- and $\beta$-receptors may primarily contribute to the development of cardiac hypertrophy in vivo. However, we want to emphasize that this mechanism probably is limited to pathophysiological circumstances with...
increased levels of catecholamines, since in other models cardiac hypertrophy seems to occur independent of adrenergic mechanisms. Moreover, our model is limited to a relatively short period. If the model were expanded to longer time intervals, other mechanisms may replace the mediation by adrenoceptors and continue to serve as a trigger for hypertrophy. This could help to explain the difference in the results of several reports on the role of adrenergic mechanisms in the development of cardiac hypertrophy. Given these limitations, our results demonstrate that direct activation of myocardial α- or β-adrenoceptors may elicit cardiac hypertrophy in vivo. The weight gain of the left ventricle is at least additive when both receptors are stimulated. Furthermore, the changes in peripheral circulation caused by NE seem not to play a major role within the observed period of 3 days.

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References

43. Starksen NF, Simpson PC, Bisphoric N, Coughlin SR, Lee WMF, Escobedo JA, Williams LT: Cardiac myocyte hypertrophy is associated with c-myc protooncogene expression. Proc Natl Acad Sci USA 1986;83:8348–8350
37. Zak R: Development and proliferative capacity of cardiac muscle cells. Circ Res 1974;34 and 35(suppl II):II-17-II-26
38. Zak R, Rabinowitch M: Molecular aspects of cardiac hypertrophy. Annu Rev Physiol 1979;41:539–552

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