Physiological and pathological cardiac hypertrophy induce different molecular phenotypes in the rat

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Iemitsu, Motoyuki, Takashi Miyauchi, Seiji Maeda, Satoshi Sakai, Tsutomu Kobayashi, Nobuharu Fujii, Hitoshi Miyazaki, Mitsuo Matsuda, and Iwao Yamaguchi. Physiological and pathological cardiac hypertrophy induce different molecular phenotypes in the rat. Am J Physiol Regulatory Integrative Comp Physiol 281: R2029–R2036, 2001.—Pressure overload, such as hypertension, to the heart causes pathological cardiac hypertrophy, whereas chronic exercise causes physiological cardiac hypertrophy, which is defined as athletic heart. There are differences in cardiac properties between these two types of hypertrophy. We investigated whether mRNA expression of various cardiovascular regulating factors differs in rat hearts that are physiologically and pathologically hypertrophied, because we hypothesized that these two types of cardiac hypertrophy induce different molecular phenotypes. We used the spontaneously hypertensive rat (SHR group; 19 wk old) as a model of pathological hypertrophy and swim-trained rats (trained group; 19 wk old, swim training for 15 wk) as a model of physiological hypertrophy. We also used sedentary Wistar-Kyoto rats as the control group (19 wk old). Left ventricular mass index for body weight was significantly higher in SHR and trained groups than in the control group. Expression of brain natriuretic peptide, angiotensin-converting enzyme, and endothelin-1 mRNA in the heart was significantly lower in the SHR group than in control and trained groups. Expression of adrenomedullin mRNA in the heart was significantly lower in the trained group than in control and SHR groups. Expression of b1-adrenergic receptor mRNA in the heart was significantly higher in SHR and trained groups than in the control group. Expression of b1-adrenergic receptor kinase mRNA, which inhibits b1-adrenergic receptor activity, in the heart was markedly higher in the SHR group than in control and trained groups. We demonstrated for the first time that the manner of mRNA expression of various cardiovascular regulating factors in the heart differs between physiological and pathological cardiac hypertrophy.

An induced beneficial adaptive response of the cardiovascular system, i.e., decreased resting and submaximal heart rates and increased filling time and venous return (1, 22, 28, 35). Together, these adaptations can help the myocardium satisfy the increased demands of exercise while maintaining or enhancing normal function (1, 22, 28, 35). Although it has been considered that exercise training-induced cardiac hypertrophy is partly caused by the increase in mechanical load by repeated bouts of exercise (28), the precise mechanisms are not known.

Hypertension and cardiac valvular disease induce pathological cardiac hypertrophy caused by pressure overload (24, 28). Pathological cardiac hypertrophy is a compensatory adaptation to an increase in workload of the heart (24). Pathological cardiac hypertrophy reduces cardiac function in the left ventricle (28). Furthermore, it has been reported that the progression of pathological cardiac hypertrophy results in heart failure (24, 27). Thus there are differences in cardiac properties between pathological and physiological cardiac hypertrophy (athletic heart).

Recently, it has been reported that some cardiovascular regulating factors participate in pathological cardiac hypertrophy (27). Recent in vivo studies have suggested that ANG II is a growth factor for pathological cardiac hypertrophy (16, 40). ANG II is converted from ANG I by angiotensin-converting enzyme (ACE). It has also been reported that ANG II plays an important role in the pathogenesis of heart failure (25). Furthermore, increased expression of ACE has been reported in the failing heart (25). Endothelin-1 (ET-1) also induces cardiac hypertrophy (11, 36). We previously reported that the tissue level of ET-1 is markedly increased in the failing heart of rats with congestive heart failure due to myocardial infarction (30, 31). Activation of the myocardial b1-adrenergic pathway also induces cardiac hypertrophy (27, 42). Furthermore, pressure overload hypertrophy and failing heart cause an increase in mRNA expression of brain natriuretic peptide; athletic heart; spontaneously hypertensive rat; swim training; hypertension

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uretic peptide (BNP) and a shift of isozyme from α- to β-myosin heavy chain (MHC) (10, 27, 29). It has been reported that adrenomedullin, which is produced in cardiac myocytes, inhibits hypertrophy of cardiac myocytes in vitro (5, 37). Therefore, it is considered that various cardiovascular regulating factors, such as ANG II, ET-1, BNP, adrenomedullin, β1-adrenergic pathway, and MHC, participate in the development of pathological cardiac hypertrophy. Although the athletic heart exhibits physiological cardiac hypertrophy, it is unknown whether the various cardiovascular regulating factors participate in the development of athletic heart induced by chronic exercise training.

Because there are differences in cardiac properties between pathological and physiological cardiac hypertrophy, we hypothesized that the manner of mRNA expression of various cardiovascular regulating factors in the rat heart differs between these two types of hypertrophy. Therefore, we investigated whether the mRNA expression of various cardiovascular regulating factors differs between physiological cardiac hypertrophy (athletic heart) and pathological cardiac hypertrophy. In the present study, we used the spontaneously hypertensive rat (SHR; 19 wk old) as a model of pathological hypertrophy and swim-trained rats (trained group; 19 wk old, swim training for 15 wk, 5 days/wk) as a model of physiological hypertrophy. We also determined whether hemodynamic features differ in the trained and SHR groups.

METHODS

Animals and protocol. Experimental protocols were approved by the Committee on Animal Research at the University of Tsukuba. Male 4-wk-old Wistar-Kyoto (WKY) rats and SHR were obtained from Charles River Japan (Yokohama, Japan) and cared for according to the Guiding Principles for the Care and Use of Animals, based on the Helsinki Declaration of 1964. The rats were maintained on a 12:12-h light-dark cycle and received food and water ad libitum. Eight WKY rats were exercised by swimming for 5 days/wk (trained group) in a tank of water at 30–32°C with a surface area of 1,960 cm² and a depth of 50 cm. The rats swam for 5 min/day for the first 2 days, and then the swim time was increased gradually over the 2-wk period from 5 to 75 min/day. Thereafter, the trained group continued swimming for 13 wk. Therefore, the trained group received 15 wk of swim training. Eight SHR (SHR group) and seven WKY rats (control group) remained confined to their cages but were handled daily. After swim training for 15 wk, the body weight and hemodynamic parameters of the animals were measured, and the heart was removed, weighed, and frozen in liquid nitrogen. Heart samples were stored at −80°C for determination of the expression levels of mRNA of various cardiovascular regulating factors by reverse transcription-polymerase chain reaction (RT-PCR) analysis. Control rats and SHR were killed at the same time point as the trained rats: all were 19 wk old.

Hemodynamic measurement and tissue sampling. On the day of the experiment, hemodynamic parameters were measured in anesthetized rats, as described previously (21, 29–31, 38, 39), with minor modifications. The rats were anesthetized with thiobutabarbital (50 mg/kg body wt ip). After the rats were fully sedated, arterial blood pressure and heart rate (HR) were measured via a cannula in the carotid artery with a pressure transducer (model SCK-590, Gould) connected to a polygraph system (amplifier: model AP-601G, Nihon Kohden, Tokyo, Japan; thermometer: model AT-601G, Nihon Kohden; thermal-pen recorder: model WT-687G, Nihon Kohden). Arterial blood pressure and HR were monitored and recorded continuously. Stroke volume (SV) was measured by the thermodilution technique using a Cardioglem 500 cardiac output computer (Columbus Instruments, OH) equipped with a small animal interface (3, 18). The thermodilutor microprobe catheter (Fr-1; Columbus Instruments) was inserted into the right carotid artery and advanced to the aortic arch. A catheter placed in the left jugular vein was advanced to the right ventricle for rapid bolus injection of 200 μl (plus catheter dead space) of cold saline. The saline solution was injected with a Hamilton constant-rate syringe to ensure rapid and repeatable injections of the saline indicator solution. The cardiac output measurement was repeated five times. Cardiac output was measured again when the aortic blood temperature of the rat was ≥36°C, and the aortic blood pressure returned to the basal value.

Catheter placement was verified by postmortem examination. Body temperature of the rat was maintained at 37°C by using a small animal warmer (model BWT-100, Bio Research Center, Nagoya, Japan). SV was determined by dividing cardiac output by the HR. After hemodynamic measurement, the whole heart was rapidly excised and washed thoroughly with cold saline to remove contaminating blood; then the left ventricle was separated from the right ventricle and atria. The left ventricle was weighed, frozen in liquid nitrogen, and stored at −80°C until extraction of total RNA.

Use of RT-PCR to determine levels of mRNA expression in heart. Expression of BNP mRNA, ACE mRNA, ET-1 mRNA, adrenomedullin mRNA, β1-adrenergic receptor mRNA, β1-adrenergic receptor kinase mRNA, muscarinic M2 receptor mRNA, and MHC mRNA in the left ventricle was analyzed by RT-PCR. Expression of β-actin mRNA was determined as an internal control. Semiquantitative RT-PCR was performed according to the method we described previously (9, 13, 20, 29, 38, 39).

Total tissue RNA was isolated by acid guanidinium thiocyanate-phenol-chloroform extraction with Isogen (Nippon Gene, Toyama, Japan) according to the method described by us previously (9, 13, 20, 29, 38, 39). Briefly, the tissue was homogenized in Isogen (100 mg tissue/ml Isogen) with a Polytron tissue homogenizer (model PT10/3K/35, Kinematica, Lucerne, Switzerland). The precipitated RNA was extracted with chloroform, precipitated with isopropanol, and washed with 75% (vol/vol) ethanol. The resulting RNA was resolved in diethyl pyrocarbonate-treated water, treated with DNase I (Takara, Shiga, Japan), and extracted again with Isogen to eliminate the genomic DNA. The RNA concentration was determined spectrophotometrically at 260 nm.

Total tissue RNA (10 μg) was primed with 0.05 μg of oligo[d(T)]18 and reverse transcribed by avian myeloblastosis virus RT using a first-strand cDNA synthesis kit (Life Sciences). The reaction was performed at 43°C for 60 min.

The cDNA was diluted in a 1:10 ratio, and 1 μl was used for PCR. Each PCR contained 10 mM Tris-HCl (pH 8.3), 50 mM KCl, 1.5 mM MgCl2, dNTP at 200 μM each, gene-specific primer at 0.5 μM each, and 0.025 U/μl Taq polymerase (Takara). The gene-specific primers were synthesized according to the published cDNA sequences for each of the following: BNP (15), ACE (14), ET-1 (33), adrenomedullin (32), β1-adrenergic receptor (19), β1-adrenergic receptor kinase (2), muscarinic M2 receptor (8), MHC (17), and β-actin (23). The sequences of the oligonucleotides were as follows: 5′-TA-
were scanned by CanoScan 600 (Canon, Tokyo, Japan), and quantification was performed by a computer with MacBAS software (Fuji Film, Tokyo, Japan) according to the method described previously (9, 13, 20, 29, 38, 39). The cDNAs for the verification of the semiquantitative PCR analysis were prepared from each gene PCR product of rat cDNA. Each PCR product was purified, quantified, and used as a positive-control cDNA. We performed semiquantitative PCR analysis to evaluate the expression levels of BNP mRNA, ACE mRNA, ET-1 mRNA, adrenomedullin mRNA, \( \beta_1 \)-adrenergic receptor mRNA, \( \beta_1 \)-adrenergic receptor kinase mRNA, MHC mRNA, and \( \beta \)-actin mRNA. To demonstrate that our semiquantitative PCR strategy was valid, serial dilutions of each positive-control cDNA were amplified by PCR and quantified by a scanner.

**Statistical analysis.** Values are means ± SE. Statistical analysis was carried out by analysis of variance followed by Scheffé’s F test for multiple comparisons. \( P < 0.05 \) was accepted as significant.

**RESULTS**

**Hemodynamic parameters in control, trained, and SHR groups.** Body weight was significantly lower in the trained group than in the control and SHR groups (Table 1). Left ventricular mass index for body weight was higher in the SHR and trained groups than in the control group (Table 1). Resting HR was lower in the trained group than in the control and SHR groups and significantly higher in the SHR group than in the control group (Table 1). Systolic and diastolic blood pressure were significantly higher in the SHR group than in the control and trained groups (Table 1). SV was lower in the SHR group than in the control and trained groups (Table 1). Pressure-rate product, which is an index of cardiac workload, was higher in the SHR group than in the control and trained groups (Table 1). These results suggest that the heart of trained rats exhibited physiological cardiac hypertrophy (athletic heart), and the heart of SHR exhibited pathological cardiac hypertrophy.

**mRNA expression of cardiovascular regulating factors in heart.** Expression of BNP mRNA, ACE mRNA, and ET-1 mRNA in the heart was significantly higher in the SHR group than in the control and trained groups (Fig. 1). There was no significant difference between the control and trained groups in expression of BNP mRNA, ACE mRNA, and ET-1 mRNA (Fig. 1). Expression of adrenomedullin mRNA in the heart was

**Table 1. Body weight, tissue weight, and hemodynamic parameters in SHR, trained, and control rats**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (n = 7)</th>
<th>SHR (n = 8)</th>
<th>Trained (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body wt, g</td>
<td>391.7 ± 5.8</td>
<td>379.0 ± 6.9</td>
<td>338.8 ± 4.4†</td>
</tr>
<tr>
<td>Left ventricle wt/body wt, mg/g</td>
<td>2.34 ± 0.19</td>
<td>2.76 ± 0.11*</td>
<td>2.63 ± 0.14*</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>354.5 ± 16.1</td>
<td>408.6 ± 7.8*</td>
<td>317.4 ± 4.2*</td>
</tr>
<tr>
<td>Blood pressure, mmHg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>130.8 ± 5.8</td>
<td>241.8 ± 2.0</td>
<td>129.8 ± 3.2†</td>
</tr>
<tr>
<td>Diastolic</td>
<td>102.8 ± 5.7</td>
<td>183.1 ± 1.8*</td>
<td>103.1 ± 2.5†</td>
</tr>
<tr>
<td>Stroke volume, µl</td>
<td>362.0 ± 15.5</td>
<td>281.6 ± 14.9*</td>
<td>414.5 ± 34.6†</td>
</tr>
<tr>
<td>Pressure-rate product, mmHg·beats·min⁻¹</td>
<td>43,391.2 ± 3,156.4</td>
<td>87,990.5 ± 2,060.7†</td>
<td>38,170.5 ± 1,201.2†</td>
</tr>
</tbody>
</table>

Values are means ± SE. SHR, spontaneously hypertensive rat; trained, swim-trained (15 wk) rat. *\( P < 0.05 \) vs. corresponding value in control rats. †\( P < 0.05 \) vs. corresponding value in SHR rats.

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significantly lower in the trained group than in the control and SHR groups (Fig. 2). Expression of $\beta_1$-adrenergic receptor mRNA in the heart was significantly higher in the SHR and trained groups than in the control group (Fig. 3A). There was no significant difference between the SHR and trained groups in expression of $\beta_1$-adrenergic receptor mRNA (Fig. 3A). Expression of $\beta_1$-adrenergic receptor kinase mRNA, which inhibits $\beta_1$-adrenergic receptor activity, in the heart was markedly higher in the SHR group than in the control and trained groups (Fig. 3B). There was no significant difference between the control and trained groups in expression of $\beta_1$-adrenergic receptor kinase (Fig. 3B). There were no significant differences among the three groups in expression of muscarinic $M_2$ receptor mRNA (Fig. 3C). Expression of $\alpha$-MHC mRNA in the heart was significantly higher in the trained group than in the SHR group (Fig. 4A). There were no significant differences among the three groups in expression of $\beta$-MHC mRNA (Fig. 4B).

**DISCUSSION**

We have demonstrated for the first time that the manner of mRNA expression of various cardiovascular regulating factors in the heart differed between physiological cardiac hypertrophy, which is induced by chronic exercise, and pathological cardiac hypertrophy, which is induced by hypertension. In the present study, the hearts of SHR and trained rats developed cardiac hypertrophy, as evidenced by an increase in left ventricular mass index for body weight. Trained rats received 15 wk of swim training, which caused enhancement of cardiac function, i.e., a decrease in resting HR and pressure-rate product and an increase in SV. SHR developed cardiac hypertrophy by hypertension and showed a decline in cardiac function, i.e., increase in resting HR and pressure-rate product and decrease in SV. Therefore, these results suggest that trained rats exhibited physiological cardiac hypertrophy (athletic heart) and SHR exhibited pathological cardiac hypertrophy.

The present study revealed that expression of BNP mRNA, ACE mRNA, and ET-1 mRNA in the heart was significantly higher in the SHR group than in the control and trained groups. It has been reported that BNP is involved in pathological cardiac hypertrophy (10). Furthermore, pathological cardiac hypertrophy is partly induced by humoral cardiovascular regulating factors such as ANG II (16, 40), which is converted from ANG I by ACE, and ET-1 (11, 36). These humoral cardiovascular regulating factors activate mitogen-activated protein kinase by the activation of GTP-binding (G$_\alpha$) protein (4, 41, 43), thereby resulting in cardiac myocyte hypertrophy (6, 27). Furthermore, cardiac hypertrophy and contractile dysfunction have been reported in G$_\alpha$-overexpressing mice (6). Therefore, it is
considered that G_q overactivation induces heart failure. In the present study, the mRNA expression of ACE and ET-1, which activate G_q protein, in the heart was increased in the SHR group. Taken together, the development of pathological cardiac hypertrophy in SHR in the present study may be partly caused by ANG II- and ET-1-induced activation of G_q protein. In the present study, the expression of ACE and ET-1 mRNA in the heart was not altered by 15 wk of swim training. Therefore, it is likely that activation of the G_q-signaling pathway by ANG II or ET-1 may not mainly participate in the development of physiological cardiac hypertrophy. Furthermore, the expression of BNP mRNA in the heart was not altered by exercise training. Therefore, it is possible that physiological cardiac hypertrophy (athletic heart) is induced by other mechanisms.

Cardiac myocytes, as well as vascular endothelial cells, produce adrenomedullin (5). It has been reported that adrenomedullin inhibits hypertrophy of cardiac myocytes in vitro (37). In the present study, the expression of adrenomedullin mRNA in the heart was significantly lower in the trained group than in the control and SHR groups. Therefore, the decrease in expression of adrenomedullin mRNA in the trained heart in this study may have accelerated the development of physiological cardiac hypertrophy in the trained rats. It is possible that a decrease in expression of myocardial adrenomedullin partly participates in development of the athletic heart.

The present study revealed that mRNA expression of β_1-adrenergic receptor, which is a receptor in the signal transduction pathway in sympathetic nerve stimulation, in the heart was significantly higher in the SHR and trained groups than in the control group. However, mRNA expression of β_1-adrenergic receptor kinase, which inhibits activation of the signal transduction system downstream of the β_1-adrenergic receptor, in the heart was markedly higher in the SHR group than in the control and trained groups. These findings suggest that in the heart of trained rats the signal transduction system downstream of the β_1-adrenergic receptor was activated, whereas in SHR the signal transduction system downstream of the β_1-adrenergic receptor was inactivated. Therefore, it is considered that the signal transduction system of the β_1-adrenergic receptor in the heart differs between the athletic heart (physiological cardiac hypertrophy) and pathological cardiac hypertrophy. Sympathetic nervous system activity has been implicated in development of cardiac hypertrophy (27). An in vivo study also indicated that stimulation of β-adrenergic receptors leads to development of myocardial hypertrophy independent of hemodynamic effects (42). Furthermore, Ji et al. (12) reported that β-adrenergic blockade prevented exercise training-induced cardiac hypertrophy. On the basis of results from past studies plus the present results, it is considered that β_1-adrenergic system activity participates in development of the athletic heart (physiological cardiac hypertrophy). In the present study, there were no significant differences among the three groups in mRNA expression of muscarinic M_2 receptor, which binds acetylcholine released from parasympathetic nerve endings.

In the present study, expression of α-MHC mRNA in the heart was significantly higher in the trained group than in the SHR group. We also demonstrated that expression of β-MHC mRNA in the heart was slightly increased in the SHR group. It has been reported that hypertension in rats results in a shift of myosin isoforms from the predominant V_1 to the V_3 pattern and that physical training by swimming in rats results in an increase in the percentage of V_1 myosin isozyme in cardiac myosin (34). These observations are consistent with our findings. Therefore, these results suggest that the myosin isoform differs between the athletic heart (physiological cardiac hypertrophy) and pathological cardiac hypertrophy. Furthermore, we suspect that Ca^{2+}-ATPase activity accelerates in the athletic heart and is attenuated in pathological cardiac hypertrophy, because the V_1 myosin isoform accelerates Ca^{2+}-ATPase activity, whereas the V_3 myosin isoform attenuates Ca^{2+}-ATPase activity.

The mechanism underlying the differences in the mRNAs measured between the athletic heart and pathological cardiac hypertrophy remains to be elucidated. However, the following mechanism is possible. Trained rats (athletic heart) induce tachycardia only
Fig. 3. Expression of β₁-adrenergic receptor mRNA (A), β₁-adrenergic receptor kinase mRNA (B), and muscarinic M₂ receptor mRNA (C) in the heart (left ventricle) of control rats (n = 7), SHR (n = 8), and trained rats (n = 8). Top: typical examples of RT-PCR analysis for levels of β₁-adrenergic receptor, β₁-adrenergic receptor kinase, and muscarinic M₂ receptor mRNA. Bottom: results of statistical analysis of expression of β₁-adrenergic receptor, β₁-adrenergic receptor kinase, and muscarinic M₂ receptor mRNA by a densitometer. Expression of β-actin mRNA was determined as an internal control. Photos of PCR products were scanned by a densitometer, and ratios of β₁-adrenergic receptor, β₁-adrenergic receptor kinase, and muscarinic M₂ receptor mRNA to β-actin mRNA were calculated. Thus expression of β₁-adrenergic receptor, β₁-adrenergic receptor kinase, and muscarinic M₂ receptor mRNA were normalized by expression of β-actin mRNA. Values are means ± SE. Expression of β₁-adrenergic receptor mRNA in the heart was significantly higher in SHR and trained groups than in the control group. Expression of β₁-adrenergic receptor kinase mRNA in the heart was markedly higher in the SHR group than in control and trained groups.

Fig. 4. Expression of α- and β-myosin heavy chain (α-MHC and β-MHC) mRNA in the heart (left ventricle) of control rats (n = 7), SHR (n = 8), and trained rats (n = 8). Top: typical examples of RT-PCR analysis for levels of α- and β-MHC mRNA. Bottom: results of statistical analysis of expression of α- and β-MHC mRNA by a densitometer. Expression of β-actin mRNA was determined as an internal control. Photos of PCR products were scanned by a densitometer, and ratios of α- and β-MHC mRNA to β-actin mRNA were calculated. Thus α- and β-MHC mRNA expression was normalized by β-actin mRNA expression. Values are means ± SE. α-MHC mRNA expression in the heart was significantly higher in the trained group than in the SHR group.
during exercise, whereas SHR (pathological cardiac hypertrophy) sustain tachycardia and hypertension at all times. The difference in periods of tachycardia and hypertension between the trained rats and SHR might cause a difference in workload on the heart. Therefore, it is possible that a difference in the persistence in the workload on the heart between the trained rats and SHR is one of the causal factors for the difference in mRNA expressions in these two types of hypertrophy.

In conclusion, we have demonstrated that the manner of mRNA expression of various cardiovascular regulating factors in the heart differs between pathological and physiological cardiac hypertrophy (athletic heart). The present study also demonstrated that hemodynamic features in the heart differed between pathological and physiological cardiac hypertrophy. We speculate that the different alterations in the molecular phenotypes between the athletic heart (physiological cardiac hypertrophy) and pathological cardiac hypertrophy are among the causal factors in the differences in hemodynamic features (e.g., SV and cardiac diastolic function) and the prognosis of cardiac hypertrophy (predisposition to heart disease or failure).

Perspectives

It is generally accepted that there are differences in cardiac function between physiological and pathological cardiac hypertrophy (24, 26, 28). The present study demonstrated a new molecular finding that the manner of mRNA expression of various cardiovascular regulating factors in the heart differed between physiological and pathological cardiac hypertrophy. These findings showed that a different molecular mechanism of formation of cardiac hypertrophy is possible between these two types of cardiac hypertrophy. Further studies to precisely reveal molecular features of physiological and pathological cardiac hypertrophy are needed, because these further studies will provide important findings on molecular and cellular mechanism of formation of physiological and pathological cardiac hypertrophy. In this regard, it is of great interest and of information of physiological and pathological cardiac hypertrophy. In this regard, it is of great interest and of findings on molecular and cellular mechanism of formation of physiological and pathological cardiac hypertrophy. We speculate that the different alterations in the molecular phenotypes between the heart (physiological cardiac hypertrophy) and pathological cardiac hypertrophy is possible between these two types of cardiac hypertrophy. Further studies to precisely reveal molecular features of physiological and pathological cardiac hypertrophy are needed, because these further studies will provide important findings on molecular and cellular mechanism of formation of physiological and pathological cardiac hypertrophy. In this regard, it is of great interest and of importance to study 1) whether the change in mRNA expression between physiological and pathological cardiac hypertrophy contributes to a change in expression of protein level or mature substance level in these hearts, 2) whether there is a difference in the signaling pathway mediated through these substances between these two types of cardiac hypertrophy, and 3) how the pharmacological action of these proteins or substances on the cardiac myocytes differently alters in these two types of cardiac hypertrophy. The present study demonstrated different molecular phenotypes between physiological and pathological cardiac hypertrophy. Therefore, the present study raised an important question, which should be solved by further studies: Is there a difference in the molecular mechanism of formation of cardiac hypertrophy between physiological and pathological cardiac hypertrophy?

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