Cardiac Hypertrophy-Related Pathways in Obesity

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Abstract

Obesity is often associated with the development of cardiac hypertrophy but the hypertrophy-related pathways in obesity remain unknown. The purpose of this study was to evaluate cardiac hypertrophy-related markers, atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), tumor necrosis factor-alpha (TNFα) and hypertrophy-related pathways, interleukin (IL)-6-STAT3, IL-6-MEK5-ERK5 and calcineurin-nuclear factor of activated T-cells (NFAT)3 in the excised hearts from obese rats. Twelve obese Zucker rats were studied at 5-6 months of age and twelve age-matched lean Zucker rats served as the control group. The cardiac characteristics, myocardial architecture, ANP, BNP, TNFα levels, IL-6, STAT3, p-STAT3, MEK5, ERK5, p-ERK5, calcineurin and NFAT3 in the left ventricle from the rats were measured by heart weight index, echocardiography, vertical cross section, histological analysis, reverse transcription polymerase chain reaction and Western blotting. Compared with the lean control, the whole heart weight, the left ventricle weight, the ratio of the whole heart weight to tibia length, echocardiographic interventricular septum, left ventricular posterior wall thickness, myocardial morphological changes and systolic blood pressure were found to increase in the obese rats. The protein levels of ANP, BNP, TNFα, IL-6, STAT3, p-STAT3, MEK5, ERK5, p-ERK5, calcineurin and NFAT3 were also significantly increased in the hearts of the obese rats. The results showed that the hypertrophy-related markers, ANP, BNP and TNFα, the hypertrophy-related pathways IL-6-STAT3 and IL-6-MEK5-ERK5, and the calcineurin-NFAT3 hypertrophy-related pathways
were more active in obese Zucker rats, which may provide possible hypertrophic mechanisms for developing cardiac hypertrophy and pathological changes in obesity.

Key Words: calcineurin, ERK5, heart, hypertrophy, IL-6, MEK5, NFAT3, signaling

Introduction

The obese Zucker rat, a genetic model of morbid obesity, presents many of the same cardiopulmonary deficits noted in obese humans including respiratory control dysfunction (24, 25, 27), chest wall limitations (12), upper airway narrowing (34), hypertension (2), myocardial hypertrophy (13), cardiac apoptosis (29, 30) and poor exercise capacity (26, 28). Severe obesity in human has long been recognized as causing a form of cardiomyopathy characterized by increased rates of hypertension, chronic volume overload, left ventricular hypertrophy and the development of heart failure (3, 8, 9, 31). However, the hypertrophy-related pathways of cardiac hypertrophy in severe obesity remain uncertain.

Cardiac hypertrophy, a cardiac adaptive response to stress, can exist in a state of compensation or progress to a decompensated state over time (10). It is well-recognized that atrial natriuretic peptide (ANP) and brain (B-type) natriuretic peptide (BNP) are markers of cardiac hypertrophy and are elevated in conditions of ventricular volume and pressure overload (16, 44). Accumulating evidences indicate that the pro-inflammatory cytokine, tumor necrosis factor alpha (TNFα), plays a pathogenic role in the myocardial remodeling process, inducing cardiac hypertrophy (18, 32, 36). Locally produced TNFα from the heart probably contributes to myocardial dysfunction via direct suppression of myocardial contractile function and the genesis of cardiac hypertrophy (32). TNFα was found to provoke a hypertrophic growth response in adult mammalian cardiac myocytes (45). In addition, overexpression of TNFα in the heart of mice leads to the transition from a hypertrophic to a dilated cardiac phenotype and adverse cardiac remodeling (11). However, the roles of cardiac TNFα in obese animals and humans are still unclear.

Cardiac hypertrophy, in which chamber volume enlarges without a relative increase, or even with a relative decrease, in wall thickness, is known to progress to dilated cardiomyopathy, heart failure and sudden death (37, 40). Interleukin (IL)-6, a ubiquitous cytokine, was found to have potent hypertrophic effects on cardiomyocytes (21). IL-6 could be involved in an autocrine and/or a paracrine network regulating myocardial hypertrophy (4). The IL-6 receptor (IL-6R) system consists of an IL-6-specific binding molecule, IL-6R, and a signal transducer, gp130. The multiple intracellular signaling pathways are evoked by the IL-6 and MAPK extracellular signal regulated kinase (ERK) pathways (18, 19, 38). The ERK5, also known as big MAPK 1 (BMK1), plays a critical role in post-natal hypertrophy of the heart (6, 37). ERK5 and its upstream MAPK-kinase 5 (MEK5) have a specific role in the transduction of the cytokine signals that regulate serial sarcomere assembly and in the induction of cardiac hypertrophy that progresses to dilated cardiomyopathy and sudden death (37).

Calcineurin has been reported to be a critical mediator for cardiac hypertrophy and cardiac myocyte apoptosis (23, 33, 42). Transgenic mice that express the activated forms of calcineurin in the heart develop cardiac hypertrophy and heart failure that mimic human heart diseases (33). It has been reported that the activation of Ca2+ induces the calcineurin-nuclear factor activation transcription (NFAT) pathway and in turn enhances hypertrophy (33, 46). Therefore, it is crucial to investigate the role of the cardiac hypertrophy markers, IL-6-STAT3, IL-6-MEK5-ERK5 and the calcineurin-NFAT pathway in obesity.

The role of cardiac hypertrophy in obesity is not well understood. In the current study, experimental procedures were undertaken to investigate whether cardiac hypertrophy in obesity was associated with hypertrophy-related markers or pathways. We hypothesized that cardiac abnormality in obesity might predispose the obese subjects to more activated ANP, BNP and TNFα hypertrophy-related markers as well as more activated IL-6-STAT3, IL-6-MEK5-ERK5 and calcineurin-NFAT3 hypertrophy-related pathways.

Materials and Methods

Animal Model

The studies were performed on 12 lean (Fa/Fa or Fa/fa) and 12 obese (fa/fa) age-matched 5-6-month old male Zucker rats. Animals were supplied by Zucker breeders purchased from Charles River Lab in France. One lean and one obese rat, obtained from the same breeder, were housed together. Ambient temperature was maintained at 25°C and the animals were kept on an artificial 12-h light-dark cycle, with the light period beginning at 7:00 am. Rats were provided with standard laboratory chow (Lab Diet 5001; PMI Nutrition International Inc., Brentwood, MO, USA) and water ad libitum. All protocols were approved by the Institutional Animal Care and Use Committee of China Medical University, Taichung, Taiwan, ROC.
Blood Pressure Measurements and Echocardiography

The animals were loosely restrained. Systolic, diastolic and mean arterial blood pressures were determined with an automated tail-cuff system (29SSP; IITC/Life Science Instruments, Woodland Hills, CA, USA) 16 h after the completion of all exposures to hypoxia. Transthoracic echocardiographic images of rats were performed using Philips M2424A ultrasound systems (Andover, MA, USA) under anesthesia with 1% isoflurane via a nose cone. M-mode echocardiographic examination was performed using a 6-15 MHz linear transducer (15-6L) via parasternal long axis approach. Left ventricular M-mode measurements at the level of the papillary muscles included left ventricular internal end-diastolic dimensions (LVIDd), left ventricular internal end-systolic dimensions (LVIDs), interventricular septum (IVS) and left ventricular posterior wall thicknesses (LVPW), and fractional shortening (FS). FS% was calculated according to the following equation:

\[
FS\% = \frac{[(LVIDd - LVIDs)/LVIDd] \times 100.}
\]

Cardiac Characteristics

The animals were loosely restrained. Systolic, diastolic and mean arterial blood pressures were determined with an automated tail-cuff system (29SSP; IITC/Life Science Instruments). All rats were weighed and decapitated. The hearts of eight lean and eight obese animals were excised and cleaned with ddH2O. The left and right atrium and ventricle were separated and weighed. The right tibias were also separated and the tibia length was measured by an electronic digital caliper (Mitutoyo Corporation, Tokyo, Japan) to correct for the whole heart weight. The ratios of the total heart weight to body weight, the left ventricle weight to whole-heart weight, and the whole-heart weight to tibial length were calculated.

Hematoxylin-Eosin Masson Trichrome Staining

After removal, the heart was soaked in 10% formalin and immersed in wax. Cross sections of the whole hearts were sliced. Slides were prepared by deparaffinization and dehydration. The slides were passed through a series of graded alcohols (100%, 95% and 75%) by immersion for 15 min in each solution. The slides were then stained with mayer hematoxylin for 5-10 min followed by washing with tap water for 10-20 min. Each slide was then soaked in warm water until it turned bright violet, followed by immersing in eosin solution for 3-5 min. After gently rinsing with water, each slide was soaked with 85% alcohol, 100% alcohol I and II for 15 min each. Finally, the slides were soaked twice with xylene. Photomicrographs were obtained using Zeiss Axioptot microscopes (Nikon, Japan).

Tissue Extraction

Cardiac tissue extracts were obtained by homogenizing left ventricle samples in a lysis buffer (20 mM Tris, 2 mM EDTA, 50 mM 2-mercaptoethanol, 10% glycerol, pH 7.4, proteinase inhibitor (Roche), phosphatase inhibitor cocktail (Sigma, St. Louis, MO USA) at a ratio of 100 mg tissue/ml buffer for 1 min. The homogenates were placed on ice for 10 min and then centrifuged twice at 12,000 g for 40 min. The supernatant was collected and stored at -70°C for further experiments.

Electrophoresis and Western Blots

The tissue extract samples were prepared as described by homogenizing with buffer. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis was performed in 10% polyacrylamide gels. The samples were electrophoresed at 140 V for 3.5 h and equilibrated for 15 min in 25 mM Tris-HCl, pH 8.3, containing 192 mM glycine and 20% (v/v) methanol. Electrophoresed proteins were transferred to polyvinylidene difluoride (PVDF) membrane (Millipore, Bedford, MA, 0.45 μm pore size) with a Bio-Rad Scientific Instruments Transphor Unit at 100 V for 2 h. PVDF membranes were incubated at room temperature for 1 h in a blocking buffer containing 100 mM Tris-HCl, pH 7.5, 0.9% (w/v) NaCl. Antibodies directed against ANP, BNP, TNFα, IL-6, STAT3, p-STAT3, ERK5, p-ERK5, calcineurin, NFAT3 and α-tubulin (Santa Cruz Biotechnology, Santa Cruz, CA, USA) and MEK-5 (BD, Franklin Lakes, NJ, USA) were diluted to 1:500 in an antibody binding buffer containing 100 mM Tris-HCl, pH 7.5, 0.9% (w/v) NaCl, 0.1% (v/v) Tween-20. Incubations were performed at 4°C overnight. The immunobLOTS were washed three times in TBS buffer (Tris-Base, NaCl, Tween-20, pH 7.4) for 10 min and then immersed in the second antibody solution containing goat anti-mouse IgG-HRP, goat anti-rabbit IgG-HRP, or donkey anti-goat IgG-HRP (Santa Cruz) for 1 h and diluted 500-fold in TBS buffer. The immunoblots were then washed three times for 10 min in the blotting buffer. The immunoblotted proteins were visualized by using an enhanced chemiluminescence ECL Western Blotting Luminal Reagent (Santa Cruz) and quantified using a Fujifilm LAS-3000 chemiluminescence detection system (Tokyo, Japan).

RNA Extraction

Total RNA was extracted by the Ultraspec RNA Isolation System (Biotex Laboratories, Inc., Houston,
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Table 1. Characteristics of the lean and obese rats

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Lean</th>
<th>Obese</th>
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<tbody>
<tr>
<td>Number</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Body weight (BW), g</td>
<td>393 ± 32</td>
<td>555 ± 61*</td>
</tr>
<tr>
<td>Whole-heart weight (WHW), g</td>
<td>0.89 ± 0.06</td>
<td>1.29 ± 0.13*</td>
</tr>
<tr>
<td>Left ventricular weight (LVW), g</td>
<td>0.57 ± 0.07</td>
<td>0.87 ± 0.11*</td>
</tr>
<tr>
<td>WHW/BW</td>
<td>22.7 ± 1.3 (x 10^4)</td>
<td>23.3 ± 1.9 (x 10^4)</td>
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<tr>
<td>WHW/Tibia length, g/m</td>
<td>22.0 ± 1.2</td>
<td>34.1 ± 3.6*</td>
</tr>
<tr>
<td>LVW/BW</td>
<td>14.6 ± 1.5 (x 10^4)</td>
<td>15.6 ± 1.3 (x 10^4)</td>
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<tr>
<td>LVW/WHW</td>
<td>0.64 ± 0.05</td>
<td>0.67 ± 0.05</td>
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**Blood Pressure**

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<tbody>
<tr>
<td>SBP, mmHg</td>
<td>117 ± 14</td>
<td>137 ± 12*</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>83 ± 15</td>
<td>92 ± 14</td>
</tr>
<tr>
<td>MBP, mmHg</td>
<td>94 ± 16</td>
<td>107 ± 13</td>
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**Blood Sampling**

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<tbody>
<tr>
<td>Fasting insulin, ng/ml</td>
<td>0.92 ± 0.06</td>
<td>4.93 ± 1.32*</td>
</tr>
<tr>
<td>Fasting glucose, mg/dl</td>
<td>102.4 ± 11.7</td>
<td>111.2 ± 19.5</td>
</tr>
<tr>
<td>Serum leptin, ng/l</td>
<td>3.4 ± 1.1</td>
<td>46.2 ± 4.2**</td>
</tr>
</tbody>
</table>

Values are means ± SD. *P < 0.05 and **P < 0.01 are significant differences between the lean and obese Zucker rats.

Reverse Transcription Polymerase Chain Reaction (RT-PCR)

Total RNA was reverse transcribed and then amplified by the polymerase chain reaction using the Super Script Preamplification System for first-strand cDNA Synthesis kit and Taq DNA polymerase (Life Technologies, Rockville, MD, USA). RT-PCR products (45 μl) were separated on a 1.25% agarose gel (Life Technologies). Amplifiers were synthesized based on cDNA sequences from the GenBank. The rat GAPDH was used as an internal standard. The primers used were: Rat TNFα forward primer: 5’-TCGAGTGACAAGCCC GTAG-3’; Rat TNFα reverse primer: 5’-CAGAGAATGACTCCAAAGTAGAC-3’; Rat GAPDH forward primer: 5’-GGGTGTGAACCAGGTCAGA-3’; Rat GAPDH reverse primer: 5’-CCACAGTCTTCTGAGTGGCA-3’ (MDBio Inc., Taipei, Taiwan, ROC).

Statistical Analysis

The data were compared between lean and obese groups using Student’s t-test for two independent samples. In all cases, a difference at P < 0.05 was considered statistically significant.

Results

Body Weight and Cardiac Characteristics

Obese rats weighed about 41% more than age-matched lean animals (555 ± 61 g versus 393 ± 32 g, P < 0.01). The absolute whole-heart weight (WHW), the left ventricular weight (LVW) and the ratio of whole-heart weight to tibia length were significantly increased in the obese group, compared with data of the lean group (Table 1). From blood sampling, serum leptin and fasting insulin levels in the obese rats were significantly higher than those in lean rats (Table 1). The averaged systolic blood pressure in the obese rats was significantly higher than that in the lean rats whereas DBP and MBP in the obese rats were not significantly increased. From echocardiographic observations, the IVS, the LVPW and the LVIDd were significantly increased. However, LVIDs in the obese group was significantly decreased compared with that of the lean group (Fig. 1). The ratio of average wall thickness to diameter of left ventricles in the obese group was significantly increased (P < 0.335 ± 0.032 versus 0.291 ± 0.012, n = 8) relative to the lean group.
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Cardiomyopathic Changes

The ventricular myocardium in the lean control group showed normal architecture with normal interstitial space. In contrast, a disarray of myocardial architecture, increased interstitial space and increased cardiac fibrosis were observed in the obese group (Fig. 2).

ANP and BNP

The ANP and BNP protein levels showed significant increases ($P < 0.01$) in the cardiac tissues excised from the obese rats as compared with the age-matched lean rats (Fig. 3).

TNFα

The mRNA expression and protein levels of TNFα were significantly increased ($P < 0.01$) in the cardiac tissues excised from the obese rats compared with age-matched lean rats (Fig. 4).
Fig. 4. Analysis of TNFα in lean and obese rats. The mRNA expression (A) and protein levels (B) of TNFα extracted from the left ventricles of the hearts of lean and obese rats were measured by RT-PCR and Western blotting analysis. (C) Relative quantification (n = 6 in each group) normalized to GAPDH and α-tubulin, respectively. **P < 0.01, significant difference between the lean and obese groups.

Fig. 5. Analysis of IL-6 and STAT3 in lean and obese rats. (A) The protein levels of IL-6, STAT3 and p-STAT3 extracted from the left ventricles of the hearts in three lean and three obese rats, as measured by Western blotting analysis. (B) Relative quantification normalized to α-tubulin (n = 6 in each group). **P < 0.01, significant difference between the lean and obese groups.
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IL-6-Related Pathway

The IL-6 protein levels showed significant ($P < 0.01$) increases in the cardiac tissues excised from the obese rats compared with the age-matched lean rats (Fig. 5). STAT3 and p-STAT3 protein levels were significantly increased ($P < 0.05$) in the obese rats compared with the lean rats (Fig. 5). MEK5, ERK5 and p-ERK5 protein levels were significantly increased ($P < 0.05$) in the cardiac tissues excised from the obese rats compared with the lean rats (Fig. 6). These findings suggest that the IL-6-STAT3 and IL-6-MEK5-ERK5 hypertrophy-related signaling pathways are activated in obese rats compared with those of the lean group.

Calcineurin-NFAT3 Hypertrophy-Related Pathway

The protein levels of calcineurin and NFAT3 also showed significant increases ($P < 0.01$) in the cardiac tissues excised from the obese rats compared with the lean rats (Fig. 7).

Discussion

Our main findings can be summarized as follows: [1] Increased systolic blood pressure, increased heart wall thickness, increased whole heart weight, increased ratio of whole-heart weight to tibia length, abnormal myocardial architecture, increased cardiac interstitial spaces and increased serum leptin levels were observed in the obese group compared with the lean group; [2] The ANP, BNP and TNFα hypertrophy-related markers in the cardiac tissues of the obese group were significantly increased; [3] Cardiac IL-6-STAT3 and IL-6-MEK5-ERK5 hypertrophy-related signaling pathways were more active in the hearts of the obese rats; [4] Cardiac calcineurin and NFAT3 hypertrophy-related signaling pathways were more active in the hearts of the obese rats.

Obesity is often associated with hemodynamic overload, ventricular remodeling and higher cardiac output due to an augmented stroke volume and an increase in the heart rate (1, 3). Obesity cardiomyopathy typically occurs in persons with severe and longstanding obesity, which may progressively develop left ventricular hypertrophy (3). In the current study, cardiac hypertrophy was found in 5-6-month old obese Zucker rats based on evidences from echography, heart weight index and myocardial architecture. We speculate that obese rats progressively develop dele-
terious cardiomyopathic changes through multiple internal or external factors. Various potential factors that enhance cardiac hypertrophy include hypertension, volume overload, hypoxia, oxidative stress and the unbalance of some hormones (5, 17, 35). Therefore, we have to add a note of caution that any effect on cardiomyopathic changes noted in the present investigation cannot be clearly attributed to any one specific factors. Furthermore, the ratio of whole-heart weight to tibia length, used for normalizing rodent skeletal sizes in the current study, was increased in obese rats whereas the ratio of whole-heart weight to whole-body weight, traditionally regarded as an index of cardiac hypertrophy, was unchanged due to proportionally increased body weight in obesity. In obesity, cardiac hypertrophic effects are underestimated if only the index of the ratio of whole-heart weight to the whole-body weight is used.

ANP and BNP are useful markers of preclinical cardiac disease in obese humans (14). Increased left ventricular ANP and a two-fold increase in cardiomyocyte volume were reported in diabetic Zucker fatty rats (13). The development of obesity and metabolic disturbance is strongly related to increased levels in pro-inflammatory cytokines IL-6 and TNFα, both of which are secreted by adipocytes; concentrations of these cytokines correlate with the percentage and distribution of fat tissue in the body (39). TNFα expression and peptide production are up-regulated in the adult heart in response to pressure overload and in response to myocardial infarction or ischemia (41). TNFα expression and peptide production are up-regulated in the adult heart in response to pressure overload and in response to myocardial infarction or ischemia (41). Over-expression of TNFα in the heart of mice leads to adverse cardiac remodeling (11). No other studies have directly observed TNFα in the hypertrophic hearts of obese animals or obese humans. Our findings demonstrate that the more active TNFα was found in the cardiac hypertrophy in the obese rats compared with the age-matched lean rats. This may imply that more active TNFα may partially enhance adverse cardiac remodeling.

IL-6, a typical cytokine, was found to have a potent hypertrophic effect on cardiomyocytes (21). The overexpressed IL-6 in the myocardium under hypoxia or other stressors appears to play an important role in the pathogenesis of cardiovascular diseases and cardiac hypertrophy (21, 22). Over-expression of IL-6 has also been confirmed in the injured myocardial...
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In the current study, the increased protein levels of IL-6 in the cardiac tissues were found in obese rat hearts, suggesting that IL-6 may be responsible for pathophysiologic challenges in obesity. No other study has directly observed IL-6 in the hypertrophic hearts in obese animals or in obese human cardiac tissues. Further studies clarifying the role of IL-6 in obese myocardial cells or obese humans are needed.

IL-6 is also involved in multiple intracellular signaling pathways including MEK5 and its downstream ERK5. The IL-6-MEK5-ERK5 pathway is believed to induce cardiac hypertrophy that progresses to pathophysiologic cardiomyopathy and sudden death (6, 37). However, the underlying mechanism of the cardiac remodeling in hypertrophy has not yet been well recognized. In addition, no other studies have observed the MEK5-ERK5 pathway in the heart of obese animals or obese humans. Therefore, no further information is available to compare with our findings. In the current study, more active IL-6, MEK5 and ERK5 levels were found in the dilated heart excised from obese group, compared with the lean group. We suggest here that cardiac hypertrophy in obesity may be partially mediated by the IL-6-associated MEK5-ERK5 hypertrophy-related pathway.

Previous studies have shown that cardiac hypertrophy is induced by the calcium-dependent phosphatase calcineurin, which dephosphorylates the transcription factor NFAT3 enabling it to translocate to the nucleus (46). Transgenic mice that express active forms of calcineurin or NFAT3 in the heart develop cardiac hypertrophy and heart failure that mimic human heart disease (33). Our findings showed that calcineurin and NFAT3 in obese heart tissues were more active, which may be related to one of the hypertrophy-related signal pathways to cause cardiac hypertrophy and heart failure in obesity (33).

The underlying mechanisms determining which pathways to be activated in cardiac remodeling of hypertrophy in obesity have not yet been recognized. Our current findings that indicate more active cardiac ANP, BNP, TNFα, IL-6-MEK5-ERK5 and calcineurin-NFAT3 pathway in obesity may provide possible mechanisms to explain the development of cardiac hypertrophy and heart failure in obesity. For therapeutic applications based on this work, we further propose that TNFα, IL-6-MEK5-ERK5 or the calcineurin-NFAT3 pathway should be de-activated in obesity to prevent the development of obesity-related cardiac abnormality or hypertrophy. In some previous studies, exercise has been found to have beneficial effects on cardiovascular health (15), such as reducing hypertension (7, 43) and cardiac apoptosis (20). Further studies, exercise therapy and other therapeutic approaches are required to clarify the possible mechanisms or treatments in obesity-related cardiac hypertrophy and abnormalities.

Acknowledgments

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References


42. Wilkins, B.J. and Molkentin, J.D. Calcineurin and cardiac hypertrophy: where have we been? Where are we going? *J. Physiol.* 541: 1-8, 2002.


