Ghrelin suppresses cardiac sympathetic activity and prevents early left ventricular remodeling in rats with myocardial infarction

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Soeki T, Kishimoto I, Schwenke DO, Tokudome T, Horio T, Yoshida M, Hosoda H, Kangawa K. Ghrelin suppresses cardiac sympathetic activity and prevents early left ventricular (LV) remodeling following myocardial infarction (MI) via the suppression of cardiac sympathetic activity. Ghrelin (100 μg/kg sc, twice daily, n = 15) or saline (n = 15) were administered for 2 wk from the day after MI operation in Sprague-Dawley rats. The effects of ghrelin on cardiac remodeling were evaluated by echocardiographic, hemodynamic, histopathological, and gene analysis. In addition, before and after ghrelin (100 μg/kg sc, n = 6) was administered in conscious rats with MI, the autonomic nervous function was investigated by power spectral analysis obtained by a telemetry system. In ghrelin-treated rats, LV enlargement induced by MI was significantly attenuated compared with saline-treated rats. In addition, there was a substantial decrease in LV end-diastolic pressure and increases in the peak rate of the rise and fall of LV pressure in ghrelin-treated MI rats compared with saline-treated MI rats. Furthermore, ghrelin attenuated an increase in morphometrical collagen volume fraction in the noninfarct region, which was accompanied by the suppression of collagen I and III mRNA levels. Importantly, a 2-wk administration of ghrelin dramatically suppressed the MI-induced increase in heart rate and plasma norepinephrine concentration to the similar levels as in sham-operated controls. Moreover, acute administration of ghrelin to MI rats decreased the ratio of the low-to-high frequency spectra of heart rate variability (P < 0.01). In conclusion, these data suggest the potential usefulness of ghrelin as a new cardioprotective hormone early after MI.

autonomic nervous function; infarction; peptide hormones

Ghrelin is a novel growth hormone (GH)-releasing peptide, originally isolated from the stomach, which has been identified as an endogenous ligand for the GH secretagogues receptor (GHS-R) (12). GHS-R mRNA is detected in not only the hypothalamus and pituitary but also the heart and blood vessels (9), and much evidence for a cardiovascular function of ghrelin has been reported. Previous studies revealed that chronic administration of ghrelin improved cardiac performance in rats with chronic heart failure, as indicated by increases in cardiac output and left ventricular (LV) fractional shortening (17) and that intravenous bolus infusion of human ghrelin significantly decreased mean arterial pressure in patients with chronic heart failure (16). However, the precise mechanism of ghrelin actions remains unclear.

On the other hand, LV remodeling after myocardial infarction (MI) is a major cause of subsequent heart failure and death. The sympathetic nervous system is thought to contribute to the post-MI cardiac dysfunction and remodeling, similar to the renin-angiotensin-aldosterone system (21). The β-adrenergic blockade, by the suppression of sympathetic activity, has been shown to attenuate the adverse ventricular remodeling seen in heart failure and to decrease mortality (21, 23). Since recent studies revealed that intracerebroventricular injection of ghrelin decreased renal sympathetic nerve activity in conscious rabbits (15) and suppressed sympathetic nerve activity in brown adipose tissue in rats (24), we hypothesized that ghrelin might decrease the cardiac sympathetic nerve activity and act against the progression of LV remodeling after MI. Therefore, in the present study, we investigated whether peripheral ghrelin administration attenuates LV dysfunction and remodeling after the early stage of MI and whether the underlying mechanisms are associated with the suppression of cardiac sympathetic activity.

MATERIALS AND METHODS

Model of MI. All experimental procedures were performed according to the National Institutes of Health guidelines for the use of experimental animals and the guidelines for animal experimentation of the National Cardiovascular Center. All animal protocols were approved by our Institutional Animal Care and Use Committee. Male Sprague-Dawley rats (Nihon SLC, Hamamatsu, Japan) weighing 180–220 g were anesthetized with pentobarbital sodium (30 mg/kg ip). After a left thoracotomy, the left coronary artery was ligated 2 to 3 mm from its origin using a 6-0 prolene suture. The chest was closed and the rats were allowed to recover. Sham-operated rats underwent the identical surgical procedure without coronary artery ligation.

Administration of ghrelin. From the day after the coronary ligation, the rats with MI were randomly divided into two groups: one to be administered with synthetic rat ghrelin (n = 15) and the other with saline as vehicle (n = 15). Ghrelin [100 μg/kg twice daily, the dose of which was shown to improve LV function in rats with chronic heart failure (17)] or saline was administered subcutaneously for 2 wk from the day after the MI operation. The duration of ghrelin administration was chosen based on the mean administration period of 3 wk, in patients with acute MI, in our center for future clinical application. The synthetic rat ghrelin was provided by Daiichi Asubio Pharma, (Tokyo, Japan).

Echocardiographic and hemodynamic studies. Echocardiographic studies were performed using an echocardiography system equipped with a 15-MHz phased-array transducer (SONOS 5500, Hewlett-Packard, Osaka, 565-8565, Japan (e-mail: kishimot@ri.ncvc.go.jp). The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

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Andover, MA) under anesthesia with pentobarbital sodium (30 mg/kg ip) 1 and 14 days after the experimental MI or sham operation.

After the administration of ghrelin or saline for 2 wk, hemodynamic studies were performed. After anesthesia, a polyethylene catheter (PE-50) was inserted into the aorta through the right carotid artery for the measurement of heart rate and mean arterial pressure, and the catheter was then advanced into the LV to measure LV pressure. These hemodynamic variables were measured with a pressure transducer connected to a physiological recorder (PowerLab system, AD Instruments, Mountain View, CA). After completion of hemodynamic measurements, blood sampling was performed, and the hearts were arrested by the injection of 30 mM potassium chloride through the carotid artery, excised, and weighed.

**Histological examination and Northern blot analysis.** The heart was divided from apex to base into four transverse sections (2.0 to 2.2 mm thick), identified as levels 1–4, respectively. Levels 1 and 3 were fixed with 4% paraformaldehyde and embedded in paraffin. Levels 2 and 4 were divided into infarcted (macroscopic connective tissue) and noninfarcted regions and immediately frozen for the measurement of gene expression. Paraffin sections (2 μm) were stained with Masson’s trichrome for measurement of infarct size and Sirius red F3BA for determination of collagen volume fraction. The infarct size was expressed as previously described (11). To measure collagen volume fraction, 16 fields in the noninfarcted LV walls per section were scanned and computerized with an Optima 6.5 digital image analyzer (Media Cybernetics, Silver Spring, MD) at a magnification of ×200. The collagen volume fraction was obtained by calculating the mean ratio of connective tissue to the total tissue area of all the measurements of the section. The collagen-positive areas from all sections were determined by a single investigator who was unaware of the experimental groups.

Total RNA (10 μg/lane) was extracted separately from the noninfarcted and infarcted regions of levels 2 and 4. Hybridization was carried out with cDNA probes for rat α1 (type I)-collagen, rat α1 (type III)-collagen, rat atrial natriuretic peptide, and rat glyceroldehyde-3-phosphate dehydrogenase. The band intensity was estimated by a radioimaging analyzer (BAS-5000, Fuji Film, Tokyo, Japan).

**Hormone assays.** Serum insulin-like growth factor I (IGF-I) was measured with an enzyme immunoassay kit (Active Rat IGF-I EIA, DSL, Webster, TX). Plasma concentrations of epinephrine, norepinephrine, and dopamine were measured by high-performance liquid chromatography (BML, Tokyo, Japan).

**Acute effect of ghrelin on the cardiac sympathetic and parasympathetic nervous activity.** In rats at 1 wk after MI or sham operation, the tip of the telemetry transmitter probe (TA11PA-C40, Data Science International, St. Paul, MN) was inserted into the femoral artery. Each rat cage was placed on a signal-receiving board (RLA1020, Data Science International) in the chamber. The pressure signal from conscious and unrestrained rats was continuously recorded by a pressure analyzing system (PowerLab system, AD Instruments). After we recorded the baseline for 0.5 h, ghrelin (100 μg/kg, the same as the one-shot dose of the antiremodeling study, n = 6) or saline (n = 6) was administered subcutaneously. The signals were recorded for 2.5 h thereafter. Acquisition of the pressure signal data was performed for 20 min before and every 1-h interval after the administration. The autonomic nervous function was investigated by a power spectral analysis of heart rate variability. The heart rate derived from pressure waves was used to generate a power spectral density curve by means of fast-Fourier transform. The range of the low-frequency (LF, 0.04–0.4 Hz) or high-frequency (HF, 0.4–1.5 Hz) component was chosen on the basis of our preliminary study.

**Statistical analysis.** All values are expressed as means ± SE. Differences among the groups were evaluated by one-way analysis of variance and two-way analysis of variance for repeated measurements, as appropriate. When a statistical difference was detected by analysis of variance, the Bonferroni method of adjusting for multiple pairwise comparisons was used. A value of P < 0.05 was considered statistically significant.

**RESULTS**

The effect of ghrelin on body weight, infarct size, and IGF-I. The body weights of the two MI groups were significantly lower than that of the sham-operated group. However, the decreases in body weights were significantly blunted in rats treated with ghrelin compared with those given the vehicle (Table 1). On the other hand, there was no difference of heart weight between ghrelin- and vehicle-treated MI rats. Therefore, the increase in the heart weight-to-body weight ratio after MI was significantly attenuated in rats treated with ghrelin. As shown in the Table 1, there was no difference of infarct size between the two MI groups.

Although GH is difficult to measure for its instability and the large diurnal change, serum IGF-I, which is secreted from liver in response to GH and more stable than GH in the serum, is readily quantified. Therefore, we measured serum IGF-I concentration instead of GH concentration. Serum IGF-I concentration was lower in the two MI groups than in the sham-operated group. However, there was no difference of IGF-I between the MI groups with the vehicle and ghrelin (Table 1).

The effect of ghrelin on echocardiographic and hemodynamic parameters. Significant thinning of the anterior wall and hypertrophy of the posterior wall were observed in the two MI groups compared with the sham-operated group after MI. There were no significant differences of these parameters between the vehicle and ghrelin groups even after treatment (Fig. 1A). Pretreatment, LV diastolic dimension was identical among the three groups, and LV fractional shortening was already smaller in MI rats with the vehicle than in sham-operated rats. In sham-operated rats, these parameters did not change after treatment. In MI rats with the vehicle, the LV enlargement and dysfunction deteriorated progressively during 2 wk. Posttreatment, LV diastolic dimension was significantly smaller in rats treated with ghrelin than in rats treated with the vehicle. Furthermore, LV fractional shortening was significantly greater in rats treated with ghrelin than in rats treated with the vehicle (Fig. 1B).

Table 2 shows hemodynamic assessments after the treatment. The important thing to note is that heart rate was increased in MI rats with the vehicle compared with sham-operated rats, but ghrelin significantly decreased heart rate to the same level as in the sham-operated group. LV systolic pressure was lower in the MI groups with the vehicle and ghrelin than in the sham-operated group, but there was no difference in this parameter between the two MI groups. LV end-diastolic pressure was higher in MI rats with the vehicle than in sham-operated rats. Ghrelin significantly decreased LV

| Table 1. Characterization of rats at 2 wk after MI |
|-----------------|-----------------|-----------------|
|                 | Sham            | MI + Vehicle    | MI + Grelin |
| n               | 14              | 15              | 15          |
| Body weight, g  | 302±24          | 260±3*          | 272±4*‡    |
| Heart weight, g | 0.09±0.02       | 1.08±0.02*      | 1.04±0.02  |
| Heart weight/body weight | 3.31±0.08 | 4.16±0.10* | 3.82±0.07§ § |
| Infarct size, % | 45.5±0.7        | 44.1±0.9        |             |
| IGF-I, ng/ml    | 577±23          | 473±15*         | 500±20*    |

Values are means ± SE; n, number of rats; MI, myocardial infarction. *P < 0.01 and †P < 0.05 compared with the sham-operated group; ‡P < 0.05 and §P < 0.01 compared with the MI + vehicle group.
end-diastolic pressure. The peak rate of the rise and fall of LV pressure (dP/dt_{max/min}) was lower in MI rats with the vehicle than in sham-operated rats. The MI-induced systolic and diastolic LV dysfunction was significantly improved by ghrelin.

The effect of ghrelin on cardiac collagen volume and gene expression. To clarify the mechanism of improved cardiac performance caused by ghrelin, we examined the effects of ghrelin treatment on collagen volume in the noninfarcted LV region. Ghrelin markedly attenuated an increase in morphometrical collagen volume fraction in the noninfarcted region in rats with MI (Fig. 2). To confirm the effects of ghrelin on cardiac remodeling, we examined the expression of several mRNAs associated with heart failure and fibrosis in the noninfarcted LV region. As shown in Fig. 3, the increased mRNA expressions of atrial natriuretic peptide and collagen type I and III in MI rats were significantly suppressed by treatment with ghrelin.

The effect of ghrelin on plasma catecholamine concentrations. To further clarify the mechanism of improved cardiac performance caused by ghrelin, we examined the effects of ghrelin on plasma catecholamine concentrations, which reflect sympathetic activation and spillover from nerve endings into circulation. Figure 4 shows the effects of ghrelin on plasma concentrations of catecholamines. Plasma norepinephrine concentration was significantly increased in MI rats with the vehicle compared with sham-operated rats. Importantly, ghrelin markedly decreased plasma concentration of norepinephrine to the same level as in the sham-operated group. Although there were no significant differences of epinephrine and dopamine concentrations between the three groups, ghrelin tended to decrease these hormone levels.

Acute response of heart rate variability to ghrelin. As shown in Fig. 5, we next examined the acute effect of ghrelin on the heart rate variability, which has been used to investigate the cardiac autonomic activity separately for the sympathetic and parasympathetic nerves in human and rats. In conscious rats, 7 days after MI, heart rate, the LF power, and the LF power-HF ratio (LF/HF) were higher and mean arterial pressure was lower than that in sham-operated rats. On the other hand, there was no difference of the HF power between rats with MI and sham operation.

Acute administration of ghrelin significantly decreased heart rate in rats with MI, whereas ghrelin did not affect the heart rate in sham-operated rats. Ghrelin also tended to decrease mean arterial pressure in rats with and without MI. In conscious rats after MI, an acute administration of ghrelin decreased the LF power and tended to increase HF power obtained by a telemetry system. Therefore, ghrelin significantly decreased the LF/HF ratio (i.e., cardiac sympathetic activity) in MI rats (Fig. 5). In sham-operated rats, ghrelin had no substantial effect on heart rate variability. Administration of saline (vehicle) instead of ghrelin did not affect the heart rate variability in rats with MI.

Table 2. Hemodynamic parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sham</th>
<th>MI + Vehicle</th>
<th>MI + Ghrelin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>427±7</td>
<td>449±8†</td>
<td>422±9‡</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>122±4</td>
<td>108±2*</td>
<td>108±3*</td>
</tr>
<tr>
<td>LVSP, mmHg</td>
<td>140±4</td>
<td>121±3*</td>
<td>123±3*</td>
</tr>
<tr>
<td>LVEDP, mmHg</td>
<td>7±1</td>
<td>21±2*</td>
<td>15±2*‡</td>
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<tr>
<td>LV dP/dt_{max}, mmHg/s</td>
<td>7.544±238</td>
<td>5.391±282*</td>
<td>6.274±304‡</td>
</tr>
<tr>
<td>LV dP/dt_{min}, mmHg/s</td>
<td>5.664±182</td>
<td>-4.108±184*</td>
<td>-4.902±255‡</td>
</tr>
</tbody>
</table>

Values are means ± SE. MAP, mean arterial pressure; LVSP, left ventricular (LV) systolic pressure; LVEDP, LV end-diastolic pressure; LV dP/dt_{max} or LV dP/dt_{min}, peak rate of LV pressure rise or fall, respectively. †P < 0.01 and 

DISCUSSION

The main novel findings of the present study are that a continuous administration of ghrelin improved LV dysfunc-
tion and attenuated early cardiac remodeling after acute MI. The beneficial effects of ghrelin were accompanied by the suppression of MI-induced increase of heart rate and plasma norepinephrine concentration. In addition, in conscious rats after MI, an acute administration of ghrelin decreased the cardiac sympathetic nerve activity, which was examined by heart rate variability using a telemetry system. Taken together, the cardioprotective effects of ghrelin could be mediated by the suppression of cardiac sympathetic nerve activity.

Fig. 2. Effects of ghrelin treatment on collagen volume in the noninfarcted LV region. After the administration of ghrelin for 2 wk in rats with MI, the LV sections were stained with Sirius red. Representative photomicrographs of collagen volume (top) and quantitative morphometric analysis (bottom) were shown. Ghrelin markedly attenuated an increase in morphometrical collagen volume fraction in the noninfarcted LV region in rats with MI. **P < 0.01 and *P < 0.05 compared with sham-operated group; ###P < 0.01 compared with MI + vehicle group.

Fig. 3. Expression of genes associated with heart failure and fibrosis in noninfarcted LV region. After the administration of ghrelin for 2 wk in rats with MI, RNAs were extracted from the noninfarcted portion of LV. As shown, the increased mRNA expressions of atrial natriuretic peptide (ANP) and collagen type I and III in MI rats were significantly suppressed by treatment with ghrelin. Each mRNA expression was corrected by the expression of glyceraldehyde-3-phosphate dehydrogenase (GAPDH). **P < 0.01 compared with sham-operated group; ###P < 0.01 and #P < 0.05 compared with MI + vehicle group.
In the present study, LV enlargement induced by MI was significantly attenuated by ghrelin treatment. Moreover, there was a substantial decrease in LV end-diastolic pressure, and there were increases in $dP/dt_{max/min}$ in ghrelin-treated MI rats compared with saline-treated MI rats. We have previously reported that subcutaneous administration of ghrelin improves LV dysfunction and attenuates the development of LV remodeling in rats with chronic heart failure (17). In the study, ghrelin apparently stimulates the GH/IGF-I axis, which could induce myocardial growth (1), and, therefore, the beneficial effects of ghrelin could be mediated by the activation of the GH/IGF-I pathway. In the present study, serum IGF-I concentration did not increase in MI rats treated with ghrelin, and there was no difference of heart weight between MI rats with and without ghrelin. The discrepancy between the present study and the previous study using same daily dose of ghrelin might be due to the different study period (acute phase and chronic phase) after MI. In the early phase of MI, serum IGF-I levels were shown to decrease (5), which is compatible with our results that serum IGF-I concentration was lower in the two MI groups than in the sham-operated group. The neurohumoral changes following MI, which include elevated interleukin-1 and tumor necrosis factor-$\alpha$ or reduced IGF-binding proteins, might contribute to the sustained decrease in IGF-I (7, 8). The suppressive effects of these factors on IGF-I might be stronger than the stimulatory effect of exogenous ghrelin on the GH/IGF-I axis. Furthermore, several previous studies suggested that ghrelin has cardioprotective and vasodilatory effects not mediated by GH, because the synthetic GHS-R ligand hexarelin prevented cardiac damage after ischemia-reperfusion even in hypophysectomized rats (14), and vasodilatory effects of ghrelin were not affected by GH release inhibitors (19). Taken together, we suggest that ghrelin has...

### Fig. 4. Effect of ghrelin on plasma concentrations of catecholamines.
After the administration of ghrelin for 2 wk in rats with MI, plasma catecholamines were measured. Plasma norepinephrine concentration was significantly increased in vehicle-treated MI rats compared with sham-operated rats. Ghrelin markedly decreased plasma norepinephrine level almost to the same level as seen in sham-operated group. There was a tendency that ghrelin decreases epinephrine and dopamine levels compared with vehicle, although it did not reach statistical significance. $^*P < 0.05$ compared with sham-operated group; $^\#P < 0.05$ compared with MI + vehicle group.

### Fig. 5. Effect of ghrelin on heart rate (HR) variability.
At 1 wk after MI (○) or sham operation (●), the autonomic nervous function was investigated by power spectral analysis of HR variability, before (Pre), and 1 to 2 h after ghrelin (100 μg/kg) or saline subcutaneous injection. In conscious rats, after MI, acute administration of ghrelin decreased the low-frequency power (LF) and tended to increase high-frequency power (HF), which was accompanied by the significant decrease in HR. In sham-operated rats, ghrelin had no substantial effect on LF or HF. Ghrelin did not have a significant effect on mean arterial pressure (MAP) in rats with or without MI. Administration of saline (vehicle) instead of ghrelin did not affect the HR variability in rats with MI. $^{**}P < 0.01$ and $^*P < 0.05$ compared with pretreatment values.
beneficial effects on early cardiac remodeling and dysfunction after acute MI through a GH/IGF-I-independent mechanism.

As shown in results, ghrelin decreased heart rate to the same level as in the sham-operated group without affecting the arterial pressure in MI rats. In accordance with this result, a chronic administration of ghrelin markedly decreased the plasma norepinephrine level to the similar level as in the sham-operated group. In addition, in the present study, we found that chronic ghrelin administration significantly attenuated an increase in morphometrical collagen volume fraction in the noninfarcted LV and that the mRNA levels of collagen type I and III in the noninfarcted LV were suppressed by treatment with ghrelin. It may be due in part to the suppression of sympathetic nerve activity by ghrelin, because it has been suggested that norepinephrine regulates synthesis of myocardial type I collagen via an indirect effect (3). Since these results suggest the suppression of the sympathetic nervous system in ghrelin-treated MI animals, we next examined the effect of ghrelin on the autonomic nerve activity by the heart rate variability spectra using the telemetry system. In the present study, we have shown for the first time that in conscious rats after MI, an acute administration of ghrelin decreased the activated LF and LF/HF ratio, reflecting sympathetic activity. In contrast, in sham-operated rats, the LF, LF/HF ratio, and heart rate were substantially not affected by ghrelin administration. Thus ghrelin may have stronger effect on the activated sympathetic nervous system than on the nonactivated system. This hypothesis is supported by our preliminary study that, in sham-operated rats, ghrelin had no significant effects on the body weight, heart weight, and serum IGF-I concentration (sham + ghrelin: body weight, 305 ± 4 g; heart weight, 1.04 ± 0.02 g, heart weight/body weight, 3.42 ± 0.08, and IGF-I, 602 ± 17 mg/ml). Since a previous study reported that higher LF and total power were associated with the subsequent LV dilatation in patients with first MI (18), the suppressive effect of ghrelin on the sympathetic activity could lead to the attenuated LV remodeling in rats with MI.

The nucleus of the solitary tract, where baroreceptor and chemoreceptor afferent terminate, is one of the most important brain regions to regulate blood pressure and the sympathetic nervous system (20). A previous study demonstrated that microinjection of ghrelin into the nucleus of the solitary tract elicited dose-related decreases in heart rate and mean arterial pressure and that the GHS-R were predominantly present in the nucleus of the solitary tract (13). A recent study suggested that effects of ghrelin on renal sympathetic nerve activity and blood pressure might be caused via the histaminergic system connecting to the brain stem, including the nucleus of the solitary tract (22). In addition, it has been shown that ghrelin produced in the stomach stimulates the gastric vagal afferent nerve and influenced the neuronal activity in the nucleus of the solitary tract (6), resulting in an increase in feeding behavior. Taken together, the present study suggests that peripheral ghrelin might act on the cardiac vagal afferent nerve, which sends projection to the nucleus of the solitary tract, resulting in a decrease in sympathetic activity and heart rate in rats with MI.

Another possibility is that ghrelin has a direct effect on cardiomyocytes not through GH or autonomic nervous system. Some in vitro studies support the direct action of ghrelin on cardiomyocytes. Ghrelin was shown to reduce the doxorubicin-induced mortality of H9c2 cardiomyocytes and endothelial cells (2) and the Ara C-induced mortality of HL-1 cardiomyocytes (10). In addition, a recent ex vivo study has shown that the administration of ghrelin during ischemia-reperfusion protects against myocardial injury, and this effect involves binding to cardiovascular receptors, a process that is upregulated during ischemia-reperfusion (4). Unfortunately, we could not exclude these possible mechanisms of the action of ghrelin in the present study. Further studies are necessary to establish the precise mechanism of ghrelin on the in vivo cardiovascular system.

In conclusion, the present study demonstrated that subcutaneous administration of ghrelin improved LV dysfunction and attenuated early cardiac remodeling after MI. These beneficial effects of ghrelin might be mediated by the suppression of cardiac sympathetic nerve activity. These data suggest the potential usefulness of ghrelin as a new therapeutic agent after MI.

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GRANTS

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