Ghrelin Modulates Sympathetic Nervous System Activity and Stress Response in Lean and Overweight Men

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Abstract—Ghrelin is a growth hormone-releasing peptide secreted by the stomach with potent effects on appetite. Experimental and clinical studies indicate that ghrelin also influences cardiovascular regulation and metabolic function and mediates behavioral responses to stress. We investigated the effects of ghrelin on blood pressure (BP), sympathetic nervous system activity, and mental stress responses in lean (n=13) and overweight or obese (n=13) individuals. Subjects received an intravenous infusion of human ghrelin (5 pmol/kg per minute for 1 hour) and saline in a randomized fashion. Ghrelin decreased systolic (−6 and −11 mm Hg) and diastolic BP (−8 mm Hg for both), increased muscle sympathetic nervous system activity (18±2 to 28±3 bursts per min, P<0.05 and from 21±2 to 32±3 bursts per min, P<0.001) in lean and overweight or obese subjects, respectively, without a significant change in heart rate, calf blood flow, or vascular resistance. Ghrelin induced a rise in plasma glucose concentration in lean individuals (P<0.05) and increased cortisol levels in both groups (P<0.05). Stress induced a significant change in mean BP (+22 and +27 mm Hg), heart rate (+36 and +29 bpm), and muscle sympathetic nervous system activity (+6.1±1.6 and +6.8±2.7 bursts per min) during saline infusion in lean and overweight or obese subjects, respectively. During ghrelin infusion, the changes in BP and muscle sympathetic nerve activity in response to stress were significantly reduced in both groups (P<0.05). In conclusion, ghrelin exerts unique effects in that it reduces BP and increases muscle sympathetic nervous system activity and blunts cardiovascular responses to mental stress. These responses may represent a combination of peripheral (baroreflex-mediated) and central effects of ghrelin. (Hypertension. 2011;58:43-50.)

Key Words: ghrelin ■ obesity ■ stress ■ blood pressure ■ sympathetic nervous system

Since its discovery in 1999, ghrelin has attracted much attention, because this growth hormone (GH)–releasing peptide modulates multiple biological functions, including food intake, glucose, and lipid metabolism, as well as influencing cardiovascular function. Ghrelin’s ability to beneficially influence the cardiovascular system has been described in several clinical studies. Of particular interest are results indicating that ghrelin has the ability to improve cardiac function in chronic heart failure and endothelial function in patients with the metabolic syndrome. Against this background, the fact that circulating plasma levels of ghrelin are decreased in obesity suggests that low ghrelin levels might play a role in the etiology of obesity and the associated cardiovascular risk that accompanies obesity. Indeed, ghrelin levels have been shown to be lower in obese individuals and to rise after weight loss.

Emerging data from animal experiments indicate that ghrelin may also be linked to stress reactivity and to anxiety and depression, conditions known to be linked with increased cardiovascular risk and possibly with metabolic dysfunction. Experimental and clinical studies have shown that acute psychological stress induced a rise in plasma ghrelin concentration. Consequently, it has been suggested that ghrelin may be a mediator of both behaviors linked to food intake and body weight, as well as those associated with psychological stress; however, few data are available to support such a hypothesis. Activation of ghrelin signaling pathways in response to chronic stress has been suggested as a potential homeostatic adaptation that helps an individual to cope with stress. How ghrelin may influence the cardiovascular system and stress responses is not known, but there is some evidence to suggest that ghrelin may act centrally to decrease sympathetic nervous system (SNS) activity and blood pressure (BP), as well as the behavioral responses to stress. To date, the effects of ghrelin administration on SNS activity and stress reactivity have not been investigated in humans. We hypothesized that acute administration of ghrelin would inhibit sympathetic activity and...
alter the cardiovascular response to stress and that the responses may differ between lean and overweight subjects.

Methods

Subjects

Twenty-six healthy male volunteers were recruited through 2 major universities in the Melbourne metropolitan area. Thirteen lean (body mass index: <$25 kg/m²) and 13 overweight (Ob) subjects (body mass index: >$25 kg/m²) participated in the study. Subjects were aged between 19 and 25 years. They were nonsmokers and not on any medications. None of the participants had a history of metabolic, cardiovascular, or cerebrovascular disease. Physical examination and ECG were all normal. Subjects attended at 8:00 AM, having fasted for 12 hours. The study protocol was approved by the Alfred Hospital Ethics Committee, and all of the subjects gave written informed consent before participating in the study.

Study Protocol

Participants were studied in the supine position over one morning. They were instrumented for muscle sympathetic nerve activity (MSNA), heart rate (HR), BP recordings, and calf blood flow (CBF) measurements. A venous catheter was placed in an antecubital vein in each arm. One was used for drug infusion and the other for venous blood sampling. All of the subjects underwent an identical testing session. After a recovery period of 15 to 20 minutes, they received either acylated ghrelin (Bachem) or saline for a period of 1 hour in randomized order separated by a recovery period of ≥1 hour. The recovery period was based on previous data showing that the half-life of plasma ghrelin is very short, because it is degraded/eliminated with a half-life of 10 minutes. Ghrelin was given at a dose of 5 pmol/kg per minute. Infusion rates were 20 mL/h for both ghrelin and saline. The dose of ghrelin was chosen because it has been shown previously to induce a 2- to 3-fold increase in plasma ghrelin concentration, which reached steady state within 45 to 60 minutes. At 55 minutes postdrug infusion, mental stress (forced mental arithmetic) was performed for a period of 5 minutes. At the end of each stress test, subject-perceived stress levels were evaluated using a 5-point scale of 0 (not stressful), 1 (somewhat stressful), 2 (stressful), 3 (very stressful), and 4 (very very stressful), as described by Callister et al. Blood samples were taken for measurements of glucose, insulin, ghrelin, cortisol, and adrenaline. A first blood sample (10 mL) was taken just before the infusion of each drug, and subsequent blood samples (10 mL) were taken at 55 minutes after infusion (before stress) and at 60 minutes after infusion (after stress). The participants were not made aware of the order of saline or ghrelin administration.

Anxiety levels were examined immediately before the commencement of the investigation. The Spielberger State-Trait Anxiety Inventories were used to assess the anxiety proneness (trait anxiety) and the situational anxiety (state anxiety) of each subject.

MSNA, BP, and HR Recording

A tungsten microelectrode (FHC, Bowdoinham, ME) was inserted directly into the right peroneal nerve at the fibular head. A subcutaneous reference electrode was positioned 2 to 3 cm away from the recording site. The nerve signal was amplified (×50 000), filtered (bandpass, 700 to 2000 Hz), and integrated. Beat-to-beat BP was measured to the digit using a Finometer device, and brachial BP was assessed every 5 minutes (Dinapam). Brachial BP was used to assess the effect of the drugs over time, and the Finometer was used to determine changes in arterial BP occurring during mental stress. HR was derived from continuous lead III ECG recordings.

Finometer BP, ECG, and MSNA were digitized with a sampling frequency of 1000 Hz (PowerLab recording system, model ML 785/SBP, ADI Instruments, Bella Vista, New South Wales, Australia). MSNA was analyzed over a period of 3 to 5 minutes before drug infusion and at 10 to 15 minutes, 30 to 35 minutes, and 50 to 55 minutes after infusion. During mental stress, MSNA was averaged over the 5-minute duration of the test. The MSNA was expressed as burst incidence (bursts per 100 heartbeats).

CBF and Vascular Resistance

Calf arterial blood flow was measured in the left leg using automated venous occlusion plethysmography equipment (D.E. Hokansen, Bellevue, WA). During measurements, an arterial occlusion cuff was attached around the ankle to exclude the circulation of the foot, and a venous occlusion cuff was placed around the thigh. Ankle cuffs were inflated ≥60 seconds before measurements of flow to allow CBF to stabilize. Strain gauges were attached around the thickest part of the calf. Throughout the experiment, the leg was supported 10 cm above heart level to empty the venous system. CBF (in mL·100 mL⁻¹·min⁻¹) was calculated as the average of 12 measurements before infusion and at times 12 to 15, 30 to 35, and 50 to 55 minutes. Calf vascular resistance, expressed in arbitrary units, was calculated as mean BP/CBF.

Biochemical Analysis

Plasma concentration of adrenaline was measured by high-performance liquid chromatography with electrochemical detection. Insulin was measured by radioimmunoassay (Linco Research Inc). The plasma concentration of cortisol was assayed using an extracted radioimmunoassay, which was developed for fetal sheep plasma using hydrocortisone (H4001, Sigma) as standard. The mean recovery of [1,2,6,7 3H]cortisol (Perkin Elmer) from human plasma using a dichloromethane extraction procedure was 82.68%. The assay sensitivity was 0.33 ng/mL. The concentration of total ghrelin in plasma was measured using a Ghrelin ELISA kit (Phoenix Pharmaceuticals, Inc, Burlingame, CA) following the manufacturer’s instructions.

Statistics

For each group of subjects the effects of the infusions (saline and ghrelin) on brachial BP, HR, MSNA, and CBF and biochemical measurements were analyzed using a 2-way repeated-measures ANOVA (time × drug). The responses to stress for Finometer BP, HR, MSNA, ghrelin, cortisol, and adrenaline were first compared in each group of subjects using a 2-way repeated-measures ANOVA for infusion (saline versus ghrelin) and stress (prestress versus stress). Then, to compare possible differences in stress response between lean and OW/Ob subjects, absolute changes (Δ) in cardiovascular parameters were tested using a 2-way repeated-measures ANOVA for the group comparison (lean versus OW or Ob) and infusion effect (saline versus ghrelin). All of the post hoc comparisons were performed by the Tukey test. The effects of saline and ghrelin on plasma cortisol, adrenaline, and total ghrelin during stress were assessed for all of the subjects combined by using a 1-way repeated ANOVA. Means were considered significantly different when P<0.05.

Results

Complete sets of data were obtained in 11 lean subjects and 11 OW/Ob subjects. For 3 participants, the study was stopped prematurely because of technical difficulties, and for 1 subject the study was stopped because the participant felt unwell while receiving the ghrelin infusion (sensation of flushes). The ghrelin infusion was overall well tolerated but unwell while receiving the ghrelin infusion (sensation of flushes). The ghrelin infusion was overall well tolerated but was associated with marked perspiration in 6 subjects. Table 1 presents the characteristics of the participants. OW/Ob individuals had higher plasma levels of low-density lipoprotein cholesterol, triglycerides, and human C-reactive protein and also presented with higher trait anxiety.

Effects of Saline and Ghrelin on BP, HR, MSNA, CBF, and Calf Vascular Resistance

Figure 1 represents the BP and HR responses to both saline and ghrelin infusions in lean and OW/Ob individuals. In both
groups, saline had no effect on BP, whereas ghrelin induced a gradual reduction in BP. In lean subjects, ghrelin induced a slight but not significant decrease in systolic BP compared with that observed during saline infusion. Diastolic BP (DBP) was significantly decreased during ghrelin compared with saline infusion (ANOVA drug effect \( P=0.008 \)), with the changes significant between saline and ghrelin from 20 minutes postinfusion. At 55 minutes after ghrelin infusion, DBP was 61±2 mm Hg compared with 67±2 mm Hg before infusion \( (P<0.05) \).

In OW/Ob subjects, systolic BP was significantly decreased during ghrelin compared with the saline infusion (ANOVA drug effect \( P=0.031 \)), with the changes significant from 25 minutes after infusion. At 55 minutes after ghrelin infusion, systolic BP was 112±1 mm Hg compared with 123±3 mm Hg before infusion \( (P<0.05) \). DBP also decreased significantly during ghrelin compared with saline infusion (ANOVA drug effect \( P=0<0.001 \)), with the changes significant between the 2 drugs from 20 minutes after infusion. At 55 minutes after ghrelin infusion, DBP was 60±1 mm Hg compared with 68±2 mm Hg before infusion \( (P<0.05) \). Ghrelin or saline infusion did not affect the HR in either of the subject groups.

Figure 2 shows the effects of saline and ghrelin infusions in lean and OW/Ob individuals on MSNA expressed in bursts per minute. In lean participants, MSNA increased from 18±2 to 28±3 bursts per min (55 minutes; \( P<0.001 \)), whereas MSNA remained stable during saline infusion \( (19±2 \text{ to } 17±2 \text{ bursts per minute}; \text{P value not significant}) \). The changes in MSNA were significantly different between saline and ghrelin (ANOVA, drug effect \( P=0.012 \)), and the difference in infusions became significant from 12 minutes after infusion. In OW/Ob participants, MSNA increased from 21±2 to 32±3 bursts per minute (55 minutes, \( P<0.001 \)). Saline did not influence MSNA \( (22±2 \text{ to } 20±2 \text{ bursts per minute}; \text{P value not significant}) \). The changes in MSNA were significantly different between saline and ghrelin (ANOVA, drug effect \( P=0.002 \)), and the difference became significant from 30 minutes after infusion.

CBF recordings were performed in 7 subjects in each group. As presented in Figure 3, in both lean and OW/Ob individuals, CBF and calf vascular resistance remained stable during the infusion of either saline or ghrelin.

![Figure 1](http://hyper.ahajournals.org/)

**Figure 1.** Systolic and diastolic blood pressures (BP) and heart rate (HR) during the infusion of saline and ghrelin in lean (left) and overweight/obese (OW/Ob; right) individuals. \( *P<0.05 \), ANOVA drug effect.
Effects of Anginine on BP, HR, and MSNA
Given the fall in BP elicited by ghrelin, we examined in 6 additional subjects the MSNA response to BP reduction elicited by the vasodilator anginine (sublingual, 600 µg). In this group following anginine, systolic BP and DBP decreased by 7 and 6 mm Hg, respectively, within 15 to 20 minutes. This was associated with a rise in HR of 4 bpm and an increase in MSNA by 13 bursts per minute (*P*<0.05, ANOVA drug effect).

Effects of Saline and Ghrelin on Plasma Ghrelin, Glucose, Insulin, Cortisol, and Adrenaline
Ghrelin infusion induced a rise in total plasma ghrelin in both groups. Ghrelin induced glucose to rise significantly in lean subjects (Tables 2 and 3). The same trend was observed in OW/Ob but it did not reach significance (*P*=0.11). Plasma cortisol and adrenaline concentrations were increased during ghrelin infusion (*P*<0.001) when all of the subjects were combined (Table 3). Saline was without any effect on any of these parameters.

Effects of Stress on BP, HR, and MSNA
Figure 4 presents the mean BP, HR, and MSNA changes observed under mental stress during saline and ghrelin infusion for both lean and OW/Ob subjects. During saline infusion, mental stress induced a significant elevation in mean BP and HR and MSNA (*P*<0.05 versus prestress for all). During ghrelin infusion, the maximum BP and MSNA rises observed during mental stress were significantly altered compared with that observed during the saline infusion in both groups (ANOVA, drug effect *P*<0.001). The HR responses to stress observed under ghrelin infusion were similar to those during saline infusion.

Effects of Saline and Ghrelin on Plasma Cortisol, Adrenaline, and Total Ghrelin During Stress
Given that plasma levels of adrenaline, cortisol, and total ghrelin were similar between lean and OW/Ob subjects at rest and before stress, changes in these parameters during stress...
Table 3. Effects of Mental Stress on Plasma, Adrenaline, Cortisol, and Ghrelin Concentrations in All of the Subjects Combined During Either Saline or Ghrelin Infusion

<table>
<thead>
<tr>
<th>Drug</th>
<th>Saline Infusion</th>
<th>Ghrelin Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before Stress</td>
<td>After Stress</td>
</tr>
<tr>
<td>Adrenaline, pmol/L</td>
<td>11.6 ± 1.7</td>
<td>30.6 ± 6.9*</td>
</tr>
<tr>
<td>Cortisol, ng/mL</td>
<td>161 ± 16</td>
<td>159 ± 16</td>
</tr>
<tr>
<td>Ghrelin, nmol/L</td>
<td>3.87 ± 0.20</td>
<td>4.04 ± 0.18</td>
</tr>
</tbody>
</table>

*P < 0.05 after vs before stress.
†P < 0.05 ghrelin vs saline, before stress.
‡P < 0.05 ghrelin vs saline, after stress.

Note that plasma sample for glucose determination before infusion was only performed before the first preinfusion. OW indicates overweight; Ob, obese; NA, not applicable.

Discussion

This study is the first to document the effects of ghrelin administration in humans on resting SNS activity and cardiovascular response to mental stress. Our results indicate that ghrelin did the following: (1) reduced BP; (2) increased sympathetic nerve activity; and (3) blunted the sympathetic and BP responses to mental stress without any effect on HR. The responses to ghrelin do not differ between lean and OW/Ob individuals.

In line with previous studies in humans, we report that ghrelin induces a slight drop in BP. This decrease in BP has been suggested previously to involve either a direct peripheral arterial vasodilatation or a direct central inhibition of the SNS. Contrary to expectation, our data clearly indicate that MSNA is increased after peripheral ghrelin administration. Whether sympathetic activation is triggered by arterial baroreflex unloading is unsure. The drop in BP was not accompanied by any change in HR or significant changes in CBF or calf vascular resistance, suggesting the absence of significant vasodilatation. Although ghrelin has been shown previously to induce significant vasodilatation in vitro, in patients, much higher doses of ghrelin than the one used in the present study are required to observe vasodilatation. Likewise, it was found that when administered at doses closer to the one used in the present study, ghrelin exerts no vasodilatation in the radial artery and is without any effect on forearm blood flow. Nevertheless, anginine, which was associated with a similar BP reduction to that observed after ghrelin, elicited a similar degree of sympathetic activation. Given that vasodilatation was only investigated in the calf, we cannot rule out the possibility that dilation occurred in other vascular beds and that baroreflex mechanisms may have contributed to the sympathoexcitation. Other alternatives include deactivation of low-pressure receptors caused by a possible decrease in central venous pressure through GH receptor action or a direct central effect. This last alternative is based on the knowledge that ghrelin and ghrelin receptors have been identified in many brain areas and that peripherally injected ghrelin can activate neurons within the hypothalamus and may, in turn, modulate resting BP and SNS activity in our subjects.

The present study is the first to demonstrate that ghrelin blunts both BP and sympathetic activation associated with mental stress in both lean and OW/Ob individuals. The fact that baseline BP was decreased and MSNA augmented is unlikely to affect the stress response, because isosorbide dinitrate, a vasodilator that induced similar changes in these parameters, has been shown not to alter sympathetic and BP responses to mental stress. Ghrelin may possibly affect stress response through a central effect. Peripheral or intraperitoneal administration of ghrelin induces c-fos expression in the paraventricular nucleus of rats, an area involved in a neural network mediating the autonomic, neuroendocrine, and skeletal-motor responses of fear and anxiety, which may be a prime area for mediating the effects of ghrelin on the cardiovascular response to stress. Moreover, it is possible that ghrelin acts to reduce the BP response to stress by a peripheral mechanism, vasodilatation is known to occur during mental stress, and circulating adrenaline has been shown to contribute to forearm vasodilatation during mental stress. Because ghrelin induced a rise in circulating adrenaline levels, this may boost the vasodilatory effect during stress and, hence, restrain the BP rise.
All of the cardiovascular effects of ghrelin observed during rest and stress were very similar between the lean and OW/Ob individuals, suggesting that ghrelin responses are unlikely to be affected by weight. In agreement with Espelund et al., plasma ghrelin concentrations were identical between lean and OW/Ob subjects, which is in contrast with previous studies. However, the body mass index of our OW/Ob cohort was lower than in this study (29 compared with 38 kg/m²), which may explain the discrepancy.

Interestingly, although we observed that, during ghrelin administration, BP and sympathetic response to stress were blunted, perception of stress was not different. A previous study provided evidence that MSNA is not primarily governed by the perception of stress, suggesting that perceived stress does not modulate the autonomic responses to stress and that there is a dissociation of MSNA and BP during mental stress. The fact that ghrelin influences the cardiovascular responses to stress without affecting the stress perception indicates that ghrelin may act differently to modulate the complex cardiovascular and emotional responses induced by psychological stress. The effects of ghrelin administration on cardiovascular response to stress have, to our knowledge, never been studied in either animals or humans. Only anxiety-like behaviors have been examined in rodents, and these have yielded conflicting results with ghrelin inducing either anxiogenic or antianxiogenic effects.

Overweight subjects presented with increased trait anxiety but similar stress perception and cardiovascular responses to the mental stress test compared with the lean individuals. Some experimental and clinical studies have shown a link between ghrelin response to stress and anxiety state; in rats, acute stress induced a rise in plasma ghrelin, with the rise being higher in animals who displayed more anxiety in behavioral tests than other rat strains. Similarly, in humans, plasma ghrelin increased during psychological stress, and this rise was associated with a rise in cortisol but not in BP. In the present study, although mental stress induced a rise in plasma adrenaline concentrations, we found no effects on plasma ghrelin or cortisol concentrations. The reason for this lack of effect is not known but may involve differences in the type of stress, its intensity, and length used compared with the study from Rouach et al. As described previously, plasma cortisol and adrenaline increased during ghrelin administration, indicating that ghrelin is able to modulate the hypothalamic-pituitary-adrenal axis stress pathway. The increase in cortisol and adrenaline was suggested previously to be because of ghrelin’s adrenocorticotropic hormone–releasing property after activation of neuropeptide Y neurons in the paraventricular nucleus. Adrenaline-releasing effect of ghrelin may also involve the direct effect on the adrenal, because GH-binding sites are present.

In agreement with others, we found that ghrelin administration induced a significant increase in plasma glucose levels in lean subjects. The change observed in our study is comparable to that seen in the study from Vestergaard et al at a similar time point with the same dose. This hyperglycemic effect has been shown to be GH and cortisol independent. The mechanism of glucose release, in the present study, is also not related, at least in the first hour, to any decrease in insulin levels. However, it has been reported that glucose is increased via a reduction in basal- and insulin-stimulated disposal rate, and ghrelin was shown recently to suppress glucose-stimulated insulin secretion; hence, insulin resistance is a likely candidate for the hyperglycemic effect of ghrelin. The findings of this study offer a new hypothesis into ghrelin’s hyperglycemic actions: SNS activation in a fasting state accelerates hepatic gluconeogenesis and in a fed state promotes glycogenolysis. Our observation of an increase in MSNA could, therefore, be another mechanism by which glucose is released into the circulation during ghrelin infusion.

**Limitations**

Possible limitations of our study include the use of 1 short-term dose of ghrelin and 1 type of stress, as well as reliance on measurement of sympathetic activity in the muscle vascular bed. The dose of ghrelin was chosen to elicit minimal BP drop. Nagaya et al reported that a single injection of ghrelin at a dose 10 times higher than ours elicited an increase in plasma ghrelin by ~61-fold and a drop in BP by 12 mm Hg. The dose that we used, however, was more in the physiological range, because it only doubled the plasma ghrelin concentration and moderately decreased BP by 7 mm Hg. Ghrelin was constantly infused for a limited period of 1 hour and may have triggered some acute responses that may not have occurred if the peptide was infused over a longer period of time. Effects of longer-term administration of the peptide would need to be addressed, because chronic effects may result in different cardiovascular effects. Mental stress resulted in a marked increase in BP and HR but a modest rise in MSNA. Muscle sympathetic response to mental stress has
been reported previously to present large individual differences and preferentially activates cardiac sympathetic activity. However, it consistently increases BP and HR, and Callister et al demonstrated that other types of stress, such as the stroop color word test, induced qualitatively similar responses.

**Perspectives**

Given the potential orexigenic and adipogenic properties of ghrelin, treatment with an antagonist would seem logical in obesity; however, the numerous actions of ghrelin need to be clarified before it can be envisaged as to whether ghrelin antagonists could be used for treating obesity and related metabolic disorders. The findings of the present study provide the first direct evidence in humans that ghrelin is able to modulate resting sympathetic activity and the cardiovascular response to mental stress. We and others have previously demonstrated abnormal MSNA in obesity and metabolic disorders, as well as the deleterious impact of sympathetic activation on cardiovascular health. Unraveling the mechanisms by which ghrelin affects both metabolic and cardiovascular functions may pose a challenge.

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**Disclosures**


**References**


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