Role of Adrenergic Activity in Pressor Responses to Chronic Melanocortin Receptor Activation

Jay J. Kuo, Alexandre A. da Silva, Lakshmi S. Tallam, John E. Hall

Abstract—Acute studies have shown that MC3/4-R stimulation increases sympathetic activity, but the role of adrenergic activation in mediating the cardiovascular and renal responses to chronic melanocortin 3- and 4-receptor (MC3/4-R) activation is unknown. The present study tested whether chronic MC3/4-R activation raises blood pressure and whether these changes are attenuated by $\alpha_1+\beta$-adrenergic blockade. Rats were instrumented with an intracerebroventricular (ICV) cannula and arterial and venous catheters for measurements of mean arterial pressure (MAP) and heart rate (HR) 24 hours per day, and intravenous infusions. After control measurements, rats were intravenously infused with either saline vehicle (n=7) or $\alpha_1+\beta$-adrenergic antagonists (n=6, terazosin+propranolol, 10 mg/kg per day each) for 21 days. Five days after starting the vehicle or adrenergic blockade, the MC3/4-R agonist, MTII (10 ng/h), was infused ICV for 11 days followed by a 5-day recovery period. Another group of rats was infused with the adrenergic antagonists for 21 days but received the saline vehicle ICV for 11 days (n=7). MC3/4-R activation decreased food intake from 21±1 to 8±2 g/d by day 3 of MC3/4-R activation, and increased MAP and HR by an average of 8±2 mm Hg and 9±5 bpm, respectively. Adrenergic blockade did not alter the MC3/4-R-mediated decrease in food intake but abolished the increases in MAP and HR (1±2 mm Hg and −12±5 bpm, respectively, compared with control). ICV vehicle infusion during adrenergic blockade did not alter food intake or ICV. Glomerular filtration rate was unchanged in both the vehicle-infused and adrenergic blocked rats during MC3/4-R activation. These results indicate that the chronic actions of MC3/4-R activation on MAP and HR are mediated by adrenergic activation. (Hypertension. 2004;43[part 2]:370-375.)

Key Words: sympathetic nervous system ■ blood pressure ■ obesity

Numerous experimental and clinical studies have shown that activation of the sympathetic nervous system contributes to obesity-induced hypertension.1 Sympathetic activity is increased during obesity, and pharmacologic blockade of the sympathetic nervous system or renal denervation markedly attenuates the sodium retention and hypertension associated with a high-fat diet in experimental animals.2,3 Furthermore, blockade of adrenergic activity reduces blood pressure to a greater extent in obese than in lean hypertensive patients.4 However, the mechanisms by which obesity increases sympathetic activity are still unclear.

One potential mechanism for linking obesity with sympathetic activation is the hypothalamic proopiomelanocortin (POMC) pathway. Although the hypothalamic POMC pathway is recognized as an important regulator of energy balance and body weight,5 it has also been suggested to influence sympathetic and cardiovascular function.6-8 Acute studies have shown that injections of melanocortin 3- and 4-receptor (MC3/4-R) agonists stimulate brown adipose tissue, lumbar, and renal sympathetic activity.6,7 In addition, MC3/4-R blockade has been shown to prevent the acute renal sympathoexcitatory actions of leptin, indicating that the POMC pathway may mediate the effects of leptin on renal sympathetic activity.6 Recently, we demonstrated that chronic activation of the MC3/4-R modestly raises arterial pressure, whereas chronic MC3/4-R blockade prevents the increase in blood pressure normally associated with weight gain.8 However, whether the pressor actions of chronic MC3/4-R activation are mediated by sympathetic activation is unknown.

The primary goal of the present study is to determine the role of adrenergic activity in mediating the cardiovascular, renal, and metabolic responses to chronic central MC3/4-R activation. Our results indicate that adrenergic blockade completely prevents the chronic pressor effects of MC3/4-R activation, and provides further support for the concept that the hypothalamic melanocortin system may be a potential link among obesity, sympathetic activation, and increased arterial pressure.

Methods

Animal Surgeries

The experimental procedures and protocols of these studies conform to the National Institutes of Health Guide for the Care and Use of

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Intraarterial and Intravenous Catheterization
Male Sprague-Dawley (Harlan, Indianapolis, Ind) rats, 280 to 330 g, were anesthetized with 50 mg/kg sodium pentobarbital (Nembutal), and atropine sulfate (0.1 mg/kg) was administered to prevent excess airway secretions. The arterial and venous catheters were implanted according to procedures previously described. Briefly, using aseptic techniques, a laparotomy was performed and a sterile nonocclusive polyvinyl catheter was inserted into the abdominal aorta, distal to the renal arteries. Through a left femoral vein incision, a sterile catheter was placed in vena cava. Both catheters were exteriorized through a stainless steel button implanted subcutaneously.

Intracerebroventricular Cannulation
Immediately after arterial and venous catheter implantation, a stainless-steel cannula (26 G, 10 mm long) was implanted into the right lateral ventricle by using coordinates as previously described. The guide cannula was secured into place with 3 stainless steel machine screws, a metal cap, and dental acrylic, and a stylet was inserted to seal the cannula until use. During stereotaxic manipulation, anesthe-
sia was maintained with 0.5% isoflurane. Several days after recovery from surgery, accuracy of the cannula placement was tested by measuring the dopigeneic response (immediate drinking of at least 5 mL of water in 10 minutes) to an acute injection of 100 ng angiotensin II. After the experiment, the animals were killed, and the brains were removed and sectioned to confirm the placement of the cannula.

After recovery from surgery, the rats were housed in individual metabolic cages for determination of daily water and electrolyte balances. The arterial and venous catheters were connected to a dual-channel infusion swivel (Instech). The arterial catheter was connected to a pressure transducer (Maxxim) for continuous 24-hour measurement of mean arterial pressure (MAP) and heart rate (HR), using computerized methods as previously described. The venous catheter was connected to a syringe pump for continuous infusion of saline (0.45%, 40 mL/d). The rats received food and water ad libitum throughout the study. A normal sodium intake of approximately 3.4 mEq/d was calculated, assuming an average daily consumption of 20 g standard laboratory rat chow containing 0.4% or 0.17 mEq Na+ (0.006 mmol sodium/g food, Teklad). Intravenous solutions were infused through a sterile filter (0.22 μm, Millipore). The rats were allowed to recover for 7 to 10 days before control measurements were initiated.

Experimental Protocols
Twenty-four–hour MAP and HR, urine volume, urinary sodium and potassium excretion, and food and water intake were recorded daily. Blood samples (1.2 mL) were collected once during the control (day –2), adrenergic blockade pretreatment (day 4), experimental (day 13), and recovery (day R4) periods for measurements of glomerular filtration rate (GFR) and plasma insulin and glucose concentrations. The blood samples were replaced with 1.5 mL of 0.9% saline.

Chronic MC3/4-R Activation in Control Rats
After a 9-day control period, during which rats (n = 7) received an intravenous infusion of the vehicle (0.45% saline, 1.7 mL/h, n = 7), the MC3/4-R agonist, MTII (10 mg/kg, Polypeptide Laboratories) was infused intracerebroventricularly (ICV) via osmotic minipump for 11 days. The experimental period was followed by a 5-day recovery period during which the MTII infusion was terminated. The rate of MTII infusion chosen was based on acute studies showing effective suppression of appetite without side effects such as increased body temperature.

Chronic MC3/4-R Activation During Adrenergic Blockade
After 4 days of control measurements, the α1- and β-adrenergic receptor antagonists, terazosin and propranolol, respectively, were infused intravenously (10 mg/kg per day each, Sigma) for 21 days. After the first 5 days of adrenergic receptor blockade, the MC3/4-R agonist, MTII (10 ng/h), was infused ICV via osmotic minipump for 11 days. This experimental period was followed by a 5-day recovery period during which the MTII infusion was terminated, but adrenergic blockade was continued. In control and adrenergic blocked rats (n = 6), the effectiveness of α1- and β-adrenergic receptor blockade was tested before and during MTII infusion by analyzing the MAP responses to bolus intravenous injections of phenylephrine (4 μg) and isoproterenol (0.7 μg).

Central Vehicle Infusion During Adrenergic Blockade
To control for the effects of adrenergic blockade, a separate group of rats (n = 7) received the saline vehicle ICV during adrenergic blockade. After 4 days of control measurements, the α1- and β-adrenergic receptor antagonists were infused for 21 days. After the first 5 days of adrenergic receptor blockade, the saline vehicle (0.9%, 0.5 μL/h), was infused ICV via osmotic minipump for 11 days. The experimental period was followed by a 5-day recovery period, during which the ICV vehicle infusion was terminated, but adrenergic blockade continued.

Analitical Methods
Plasma insulin concentrations were determined by radioimmunoas-
say, and plasma glucose concentrations were determined using the glucose oxidation method (Beckman glucose analyzer 2). Urinary sodium and potassium concentrations were measured by using ion-sensitive electrodes (NOVA electrolyte analyzer 1+). GFR was calculated from clearances of [125I]-iothalamate after 24-hour infusions, as previously described.

Statistical Methods
The data are expressed as mean±SEM and analyzed by using 2-factor ANOVA with repeated measures. The Tukey-Kramer post-hoc test was used for comparisons between groups, and the Dunnett test was used for comparisons between control and experimental values within each group, when appropriate. Statistical significance was accepted at a level of P<0.05.

Results
Food Intake and Hormonal Responses to Melanocortin Activation and Adrenergic Blockade
Chronic ICV administration of the MC3/4-R agonist, MTII, transiently decreased food intake from 21±1 to 8±2 g/d on day 2 of infusion (Figure 1). Food intake gradually returned to control, averaging 19±1 g/d during the final 4 days of MTII infusion. Adrenergic blockade did not alter the effect of MTII to transiently decrease food intake, which averaged 12±2 g/d on day 2 of infusion compared with a control of 23±1 g/d. Food intake was unchanged in adrenergic blocked rats when infused ICV with the saline vehicle (Figure 1).

Fasting plasma insulin concentration decreased from a control of 27.2±1.8 to 21.8±2.0 μU/mL during MTII infusion. Adrenergic blockade did not alter the effect of MTII to decrease plasma insulin levels, which averaged 25.4±2.4 μU/mL compared with a control of 37.0±3.9 μU/mL (Table). Plasma glucose concentration decreased during MTII infusion from 125±5 to 114±5 mg/100 mL (Table). Adrenergic blockade did not alter the effect of MTII to decrease plasma glucose levels, which averaged 113±3 mg/100 mL compared with a control of 134±4 mg/100 mL.
Figure 1. Effect of ICV infusion of MTII on daily food intake in control rats intravenously infused with the vehicle (n=7) and in rats intravenously infused with the adrenergic receptor antagonists (n=6). Effect of ICV infusion of saline vehicle on daily food intake in rats intravenously infused with adrenergic receptor antagonists (n=7).

Hemodynamic Responses to Melanocortin Activation and Adrenergic Blockade
The 24-hour MAP increased from 93±3 mm Hg during control to an average of 101±3 mm Hg during MTII infusion. After termination of the MTII infusion, MAP returned to control values, averaging 90±2 mm Hg. During adrenergic blockade, MTII infusion did not alter MAP, which averaged 90±2 mm Hg compared with a control of 89±1 mm Hg (Figures 2 and 3). Infusion of the saline vehicle ICV during adrenergic blockade did not significantly alter MAP, which averaged 85±3 mm Hg during control and 88±3 mm Hg during ICV infusion. The effect of adrenergic blockade pretreatment on MAP before MTII or vehicle ICV infusion is similar to previous results.11

Chronic MTII infusion initially increased the 24-hour HR, from 390±7 to 410±9 bpm by day 2 of infusion, and HR averaged 399±7 bpm during the 11-day infusion. After terminating the MTII infusion, HR declined to an average of 382±7 bpm (Figures 2 and 3). Adrenergic blockade completely abolished the increase in HR during MTII infusion. In fact, MTII infusion during adrenergic blockade decreased HR by an average of -12±5 bpm (Figure 3). Infusion of the ICV

Effect of MTII or Vehicle (ICV) in Vehicle-Treated or Adrenergic Blocked Rats on Renal Function, Water Intake, and Circulating Hormones

<table>
<thead>
<tr>
<th>Group</th>
<th>GFR, mL/min</th>
<th>( U_{NaV}, ) mmol/d</th>
<th>( U_V, ) mmol/d</th>
<th>Urine Volume, mL/d</th>
<th>Water Drinking, mL/d</th>
<th>Plasma Insulin, ( \mu U/ML )</th>
<th>Plasma Glucose, mg/100 mL</th>
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<tr>
<td>MTII (ICV)+vehicle (IV)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Control</td>
<td>3.4±0.2</td>
<td>2.3±0.2</td>
<td>3.7±0.2</td>
<td>33±2</td>
<td>7±1</td>
<td>32.5±4.5</td>
<td>134±5</td>
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<td>Vehicle</td>
<td>3.3±0.1</td>
<td>2.5±0.1</td>
<td>3.7±0.1</td>
<td>35±1</td>
<td>7±1</td>
<td>27.2±1.8</td>
<td>125±5</td>
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<td>Vehicle+MTII</td>
<td>3.7±0.2</td>
<td>2.5±0.2</td>
<td>3.2±0.2*</td>
<td>40±3</td>
<td>10±2</td>
<td>21.8±2.0*</td>
<td>114*</td>
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<td>Vehicle</td>
<td>3.7±0.2</td>
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<td>35±2</td>
<td>10±3</td>
<td>48.3±5.0</td>
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<td>MTII (ICV)+adrenergic blockade (IV)</td>
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<tr>
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<td>6±3</td>
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<td>5±2</td>
<td>37.0±3.9</td>
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<td>25.4±2.4†</td>
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<td>3.6±0.2</td>
<td>34±2</td>
<td>5±2</td>
<td>30.3±5.7</td>
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<td>3±1</td>
<td>45.7±6.0†</td>
<td>115±6</td>
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<tr>
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<td>35±2</td>
<td>4±2</td>
<td>55.8±9.0</td>
<td>116±9</td>
</tr>
</tbody>
</table>

Values are mean±SEM. GFR indicates flomerular filtration rate; \( U_{NaV}, \) urinary sodium excretion; \( U_V, \) urinary potassium excretion. Urine volume and water drinking represent the average volumes for the 4-day control period, 5 days of IV vehicle or adrenergic blockade, 11 days of ICV MTII or vehicle during IV vehicle or adrenergic blockade, and 5 days of recovery. *P<0.05 vs vehicle; †P<0.05 vs adrenergic blockade.
vehicle during adrenergic blockade did not significantly decrease HR, which averaged 371 ± 6 bpm during control and 368 ± 11 bpm during ICV vehicle infusion.

Renal Function During Melanocortin Activation and Adrenergic Blockade

Chronic MTII infusion did not significantly alter GFR, which averaged 3.3 ± 0.1 mL/min during control and 3.7 ± 0.2 mL/min during MTII infusion (Table). In addition, the GFR was unchanged in adrenergic-blocked rats during MTII infusion, which averaged 3.3 ± 0.2 mL/min during control and 3.4 ± 0.2 mL/min during MTII infusion. ICV vehicle infusion during adrenergic blockade did not significantly change GFR, which averaged 3.5 ± 0.1 mL/min during control and 3.6 ± 0.2 during ICV vehicle infusion.

Urine volume and sodium excretion were not significantly altered during MTII infusion in both vehicle-infused and adrenergic blocked rats (Table). Infusion of the vehicle ICV after adrenergic blockade did not alter urine volume and sodium excretion. However, chronic MTII infusion significantly decreased potassium excretion (Table). During adrenergic blockade, MTII infusion did not significantly decrease potassium excretion. Infusion of the vehicle ICV during adrenergic blockade did not alter urinary potassium excretion.

Effectiveness of Adrenergic Blockade

To test the adequacy of adrenergic blockade, the blood pressure responses to the α1- and β-adrenergic receptor agonists, phenylephrine and isoproterenol, were determined by measuring the area under the curve (AUC) for the MAP. During adrenergic blockade, blood pressure responses to an acute intravenous injection of the agonists were markedly attenuated compared with that of control (Figure 4). In vehicle-infused rats, the blood pressure responses to phenylephrine and isoproterenol during MTII infusion were not altered. Adrenergic blockade continued to attenuate the blood pressure responses to the adrenergic agonists during MTII infusion.

Discussion

The importance of the POMC system and activation of the MC3/4-R in regulating energy balance and body weight is well known. The present study demonstrates that chronic activation of the MC3/4-R also has important effects on cardiovascular regulation, and that the increased arterial pressure during MC3/4-R activation is mediated by adrenergic activation.

Food Intake and Hormonal Responses to MC3/4-R Activation During Adrenergic Blockade

Although acute injections of MC3/4-R agonists have been shown to decrease food intake, chronic administration of a MC3/4-R agonist caused only a transient decrease in food intake for 5 to 6 days. Furthermore, the transient decrease in food intake during MC3/4-R activation was unaffected by adrenergic blockade. The mechanisms by which food intake returns to normal levels are not clear but may be caused by the compensatory activation of orexigenic pathways, such as neuropeptide Y (NPY), in response to decreased caloric intake. It is unlikely that higher doses of the MC3/4-R agonist would cause a sustained decrease in appetite because a...
transient decrease in food intake has been observed at higher doses of MTII than those used in the present study.\textsuperscript{12}

There is evidence that the POMC system may mediate a major part of the effects of leptin on appetite. Leptin stimulates melanocortinergic neurons in the hypothalamus,\textsuperscript{13} whereas leptin-deficient obese mice have reduced POMC mRNA that is normalized by leptin administration.\textsuperscript{14} The hypophagic response to leptin is abolished during MC3/4-R blockade.\textsuperscript{15} Furthermore, leptin administration fails to decrease appetite and body weight in mice lacking the MC4-R.\textsuperscript{16} These findings suggest that POMC activation may, at least partly, mediate the effects of leptin on satiety. However, chronic MC3/4-R activation caused only a transient decrease in appetite, whereas chronic leptin administration in previous studies demonstrated sustained hypophagia.\textsuperscript{9,17} This suggests that the hypophagic response to leptin cannot be solely due to POMC activation, and it is likely that other pathways, such as NPY inhibition, also participate in the effects of leptin on appetite.

Plasma insulin levels were decreased during chronic MC3/4-R activation in both vehicle-treated and adrenergic-blocked rats. The decreased plasma insulin levels during MC3/4-R activation occurred despite a decrease in plasma glucose concentrations, suggesting enhanced insulin sensitivity and glucose uptake. Furthermore, adrenergic blockade did not prevent the MC3/4-R-mediated decrease in plasma insulin and glucose concentrations, indicating that other mechanisms are responsible for their decline. Although the present study was not designed to investigate the mechanisms by which MC3/4-R activation alters plasma insulin and glucose levels, recent acute studies suggest that activation of the POMC pathway may markedly increase insulin sensitivity and glucose uptake.\textsuperscript{18,19}

**Cardiovascular Responses to MC3/4-R Activation: Role of Adrenergic Activation**

Acute studies have shown MC3/4-R agonists increase\textsuperscript{6,7,20} or decrease\textsuperscript{21} sympathetic activity, depending on the site of injection. However, the chronic effects of MC3/4-R agonists on sympathetic activity have not, to our knowledge, been investigated. In the present study, chronic MC3/4-R activation caused an increase in arterial pressure and HR that appeared to be mediated entirely by adrenergic activation because adrenergic blockade abolished these responses. These results support the concept that increased adrenergic activity mediates the blood pressure response to chronic MC3/4-R activation.

The hypothalamic melanocortin pathway may mediate at least part of the effects of leptin on sympathetic activity and blood pressure. Leptin has been shown to stimulate POMC expression, leading to increased production of \(\alpha\)-melanocyte stimulating hormone and to activation of the MC3/4-R. Acute studies have shown that MC3/4-R blockade abolishes the renal sympathoexcitatory effects of leptin without altering the increased sympathetic activity to brown adipose tissue.\textsuperscript{21} These results indicate that the sympathetic actions of leptin are heterogeneous and that MC3/4-R activation may mediate the renal sympathetic responses to leptin. However, whether POMC activation mediates the chronic cardiovascular effects of leptin is unclear and requires investigation.

Although the chronic blood pressure effects of leptin\textsuperscript{11} and MC3/4-R activation both appear to be mediated by increased adrenergic activity, there are some differences in their cardiovascular effects. For example, chronic leptin administration causes a slow gradual increase in arterial pressure and HR,\textsuperscript{9,11,17} whereas chronic MC3/4-R activation causes a rapid increase in arterial pressure with a slight increase in HR. One possible explanation is that leptin activates the POMC pathway and suppresses NPY expression, whereas chronic MC3/4-R activation may cause a compensatory increase in NPY expression, which tends to reduce MAP\textsuperscript{22} and HR.\textsuperscript{23} However, the importance of NPY in modulating the chronic actions of leptin and MC3/4-R is unknown.

**Renal Responses to Melanocortin Activation: Role of Adrenergic Blockade**

Chronic activation of the MC3/4-R in vehicle-infused and adrenergic-blocked rats did not alter urine volume, sodium excretion, or water intake. The changes in potassium excretion during MC3/4-R activation are likely owing to decreased food intake and, therefore, intake of potassium. However, these results should not be interpreted as evidence that chronic MC3/4-R activation has no effect on renal function. On the contrary, urinary sodium excretion remained normal despite increased arterial pressure during MC3/4-R activation. This suggests that the renal pressure/natriuresis relationship was shifted to higher pressures during chronic MC3/4-R activation. Because adrenergic blockade completely abolished the increase in arterial pressure, the effect of MC3/4-R activation to shift pressure/natriuresis appears to be mediated primarily by increased adrenergic activity.

The actions of MC3/4-R activation to shift the renal pressure/natriuresis do not appear to be owing to decreases in the GFR because GFR was unchanged during chronic MC3/4-R activation. Therefore, the precise mechanisms by which chronic MC3/4-R activation changes renal function are, as yet, still unclear.

**Perspectives**

Acute studies have shown that administration of MC3/4-R agonists increase renal sympathetic activity. Our results demonstrate that chronic activation of the MC3/4-R raises arterial pressure and HR, and these responses are mediated by adrenergic activation. Whether the renal sympathetic nerves mediate the chronic cardiovascular and renal effects of MC3/4-R activation and what are the mechanisms by which MC3/4-R activation increases adrenergic activity are still unclear. The chronic effects of hyperleptinemia to increase blood pressure and HR are also mediated by adrenergic activation, and the MC3/4-R has been suggested to mediate the acute sympathetic effects of leptin. Although further studies are needed to examine the role of the MC3/4-R in mediating the chronic sympathetic, renal, and cardiovascular responses to leptin, our observations are consistent with the hypothesis that the POMC pathway and chronic MC3/4-R activation may be a possible link between obesity, leptin, sympathetic activation, and increases in arterial pressure.
Acknowledgments
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