Cardiovascular, Renal, and Metabolic Responses to Chronic Central Administration of Agouti-Related Peptide

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

Abstract—Although excess hypothalamic agouti-related peptide (AGRP), an endogenous antagonist of the melanocortin 3/4 receptor, causes hyperphagia and obesity, its role in regulating cardiovascular function is unclear. This study examined control of mean arterial pressure (MAP), heart rate (HR), and metabolism during chronic central administration of AGRP in rats. A cannula was placed in the lateral ventricle for intracerebroventricular infusion, and arterial and venous catheters were implanted for monitoring MAP and HR 24 hours per day, as well as intravenous infusions. After a 5-day control period, rats received AGRP (n=6; 0.02 nmol per hour ICV) or artificial cerebrospinal fluid (aCSF; n=9; 0.02 nmol per hour ICV) for 12 days, followed by a 5-day recovery period. A third group was infused intracerebroventricularly with AGRP and pair-fed to match food intake of control rats (n=7). AGRP produced a peak decrease in MAP and HR of −7±2 mm Hg and −68±7 bpm, respectively, despite increased food intake (from 23±0.5 to 36±3 g per day) and weight gain (from 350±8 to 454±5 g). AGRP also increased glomerular filtration rate, plasma insulin, glucose, and leptin. AGRP infusion in pair-fed rats produced a peak decrease in HR of −70±8 bpm but did not alter MAP or other variables. The metabolic effects of AGRP may be secondary to hyperphagia because they were abolished in pair-fed rats. aCSF infusion did not change any of the variables studied. These results demonstrate that increased central nervous system AGRP levels produce chronic reductions in MAP and HR despite marked increases in food intake and weight gain that normally tend to raise arterial pressure. (Hypertension. 2004;44:853-858.)

Key Words: hypertension, obesity ■ neuropeptides ■ body weight ■ blood pressure ■ heart rate

A
gouti-related peptide (AGRP) is a 132-aa protein that is coexpressed with neuropeptide Y exclusively in the hypothalamic arcuate nucleus neurons and is known for its potent orexigenic actions.1 A single bolus intracerebroventricular AGRP injection increases food intake for several days, and transgenic AGRP overexpression results in pronounced hyperphagia and severe obesity.2,3 On the basis of pharmacological studies, the most accepted mechanism action for AGRP is competitive antagonism of α-melanocyte-stimulating hormone (α-MSH), a cleavage by-product of pro-opiomelanocortin (POMC) that binds the melanocortin 3/4 receptor (MC3/4R) to induce satiety.4 However, recent studies suggest that at least part of the long-term actions of AGRP may be independent of competitive antagonism of MC3/4R and may involve additional mechanisms such as prolonged downstream signaling changes initiated by MC3/4R antagonism, inverse agonism of MC3/4R, or interaction with an unknown receptor.2,5–7 AGRP may also function downstream of leptin, the adipocyte-derived hormone known for potent satiety-inducing actions. Leptin appears to increase activity of MC3/4R by decreasing AGRP expression while simultaneously increasing α-MSH expression.8,9 Several studies suggest that the POMC pathway may mediate some of the effects of leptin on cardiovascular regulation. Chronic leptin infusion raises mean arterial pressure (MAP) and heart rate (HR) as a result of adrenergic activation, and these effects were abolished by central blockade of MC3/4R, suggesting a role for MC3/4R in the cardiovascular actions of leptin.10–13 We have shown previously that chronic central activation of MC3/4R using melanotan-II (MT-II), a synthetic agonist, raises MAP and HR, whereas central blockade of MC3/4R using SHU9119, a synthetic antagonist, causes obesity but prevents the increases in arterial pressure normally associated with excess weight gain.14 Although considerable evidence suggests that the hypothalamic melanocortin receptors may regulate cardiovascular function and mediate the cardiovascular actions of leptin, there have been no studies, to our knowledge, that have evaluated the chronic cardiovascular and renal actions of AGRP, the only endogenous peptide known to act as an MC3/4R antagonist. Therefore, the present study was designed to examine the chronic cardiovascular, renal, metabolic, and dietary responses to chronically elevated AGRP levels in the central nervous system (CNS) of normal Sprague-Dawley rats.

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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Laboratory Animals and were approved by the institutional animal care and use committee of the University of Mississippi Medical Center.

Intraarterial and Intravenous Catheterization
Male Sprague-Dawley rats (Harlan), weighing 300 to 360 g, were anesthetized with 50 mg/kg sodium pentobarbital (Nembutal) and administered atropine sulfate (0.1 mg/kg) to prevent excessive secretions. Arterial and venous catheters were implanted using procedures described previously. 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 introduced into the vena cava. Both catheters were exteriorized through a stainless-steel button implanted subcutaneously.

Intracerebroventricular Cannulation
Immediately after arterial and venous catheter implantation, rats were placed in a stereotaxic apparatus and maintained under anesthesia using 0.5% isoflurane. A stainless-steel cannula (26-gauge, 10-mm long) was placed into the right lateral ventricle using coordinates as described previously and secured into place with 3 stainless-steel machine screws, a metal cap, and dental acrylic. A stylet was inserted into the cannula to seal it until use. Several days after recovery from surgery, accuracy of cannula placement was tested by measuring the dipsogenic response (immediate drinking of ≥5 mL of water in 10 minutes) to an acute injection of 100 ng of angiotensin II. At the end of the experiment, animals were killed and their brains removed and sectioned to confirm cannula placement.

After recovery from surgery, 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 MAP and HR using computerized methods as described previously. The venous catheter was connected through a sterile filter (0.22 μm; Millipore) to a syringe pump for continuous infusion of saline (0.45%; 40 mL per day). Rats received food and water ad libitum throughout the study. A normal sodium intake of 3.2 meq per day was maintained constant via the continuous saline infusion. Rats received food and water ad libitum during a 5-day recovery period.

Experimental Design
Three groups of rats were used in this study. After a 4-day control period, rats received an intracerebroventricular infusion of the vehicle (artificial cerebrospinal fluid; 0.5 μL per hour; n=8) or AGRP(83-132)-NH₂ (0.02 nmol per hour; n=6) for 12 days through an osmotic minipump. AGRP(83-132)-NH₂ was used because it was the lowest dose that yielded a peak hyperphagic response. To control for the expected increase in food intake and weight gain with AGRP, rats in a separate group were administered AGRP (0.02 nmol per hour ICV) for 12 days and were pair-fed to match the food intake of vehicle-treated rats (n=7). At the end of the 12-day experimental period, the intracerebroventricular infusion was terminated and rats were monitored during a 5-day recovery period.

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 1), AGRP infusion (day 11), and recovery (day 5) periods for measurements of glomerular filtration rate (GFR), plasma renin activity (PRA), plasma insulin, glucose, and leptin concentrations. Blood samples were replaced with 1.5 mL of 0.9% saline.

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

Statistical Methods
Data are expressed as mean±SEM. All data obtained were analyzed using 1-way ANOVA with repeated measures, followed by the Dunnett post hoc test for comparison between control and experimental values within each group. Comparisons between groups were made using 2-way ANOVA with repeated measures, followed by the Bonferroni post hoc test when appropriate. Statistical significance was accepted at a level of P<0.05.

Results
Food Intake, Body Weight, and Hormones
Chronic central infusion of AGRP significantly increased food intake by >50%, from an average value of 23±0.5 g per day in the control period to 36±1 g per day, whereas vehicle infusion did not alter food intake significantly (Figure 1). Associated with the increase in food intake, AGRP infusion in the ad libitum–fed rats also increased body weight 30% by the end of the experimental period compared with an 6% increase in body weight in the vehicle-infused or pair-fed rats (Table).

Plasma leptin levels in rats treated with AGRP and fed ad libitum increased 14-fold during the experimental period and returned toward basal levels during the recovery period, parallel to the changes in body weight (Table). In contrast, plasma leptin levels were not significantly altered in the vehicle-infused and pair-fed AGRP-treated rats. AGRP treatment increased plasma insulin levels significantly from 42±7 to 234±49 μU/mL in ad libitum–fed rats, whereas no significant changes were observed in the vehicle-infused or pair-fed AGRP-treated rats (Table). AGRP infusion also significantly increased plasma glucose levels in the ad libitum–fed rats but did not change plasma glucose concentration in pair-fed rats (Table). The absence of changes in plasma insulin, leptin, and glucose with AGRP in the pair-fed group suggests that the alterations observed with AGRP in the ad libitum–fed group were related to increases in food intake. PRA was not significantly altered in any of the groups.

Hemodynamics
Chronic central AGRP infusion for 12 days in ad libitum–fed rats tended to decrease MAP (average of −4±1 and peak of −7±2 mm Hg) and produced a pronounced fall in HR (average of −45±7 and a nadir of −68±10 bpm) despite a 30% increase in body weight. AGRP infusion in the pair-fed group also caused a decrease in HR (average of −42±1 and a nadir of −70±8 bpm) but did not alter MAP. There were no significant changes in MAP or HR in the vehicle-infused rats. With termination of AGRP infusion, MAP and HR increased in ad libitum–fed rats (by 4±1 mm Hg and 34±7 bpm, compared with control values) and pair-fed rats (6±2 mm Hg and 42±6 bpm) by the third day of the recovery period (Figures 1 and 2).
Renal Function
Urine volume, sodium excretion, and cumulative sodium balance were not significantly altered by vehicle or AGRP infusion (Table). AGRP infusion in ad libitum–fed rats significantly increased potassium excretion from 3.2/1000 to 5.2/1000 mmol per day, paralleling the increase in food intake, and produced an increase in cumulative potassium balance of 4.8/1000 meq. There were no significant changes in potassium balance in the vehicle-infused and pair-fed rats. AGRP infusion also increased GFR by 28%. There were no changes in GFR in vehicle-infused or pair-fed AGRP-infused rats.

Discussion
A new finding of this study is that AGRP acts in the CNS to produce chronic reductions in MAP and HR despite marked increases in food intake and weight gain, which normally tend to raise arterial pressure. Although the mechanisms by which AGRP influences cardiovascular function are still unclear, they may be related to antagonism of the hypothalamic MC3/4R because AGRP is a potent antagonist of MC3/4R.

Metabolic and Hormonal Responses to AGRP
Chronic central infusion of AGRP for 12 days markedly increased food intake and caused substantial weight gain. Although AGRP has been proposed to decrease metabolic rate, weight gain associated with central AGRP infusion in the present study appears to be primarily a result of increased food intake because pair-fed rats infused with AGRP had similar weight gain to control rats. Moreover, the increase in food intake and weight gain during AGRP infusion occurred despite a 14-fold increase in the plasma concentrations of leptin, which is known to decrease food intake. These observations suggest that the appetite suppressant actions of leptin were masked, possibly by the ability of AGRP to antagonize MC3/4R, which may mediate most of the actions of leptin on food intake. The sharp fall in food intake after termination of AGRP infusion in ad libitum–fed rats could be related to the elevated plasma concentrations of leptin because terminating AGRP suddenly increased the availability of MC3/4R, thus unmasking the hypophagic actions of leptin.

Administration of AGRP in pair-fed rats for 3 to 7 days has been reported to impair insulin sensitivity and cause hyperinsulinemia independent of the hyperphagic actions of AGRP. However, in the present study, increases in fasting plasma insulin and glucose levels caused by a 12-day infusion of AGRP closely paralleled the increases in food intake in the ad libitum–fed rats and were abolished in the pair-fed rats infused with AGRP. These observations suggest that the chronic effects of AGRP on plasma insulin and glucose may be secondary to increases in food intake rather than by direct effects of AGRP as reported previously at higher doses of AGRP. However, it is possible that AGRP may have some acute metabolic actions that are independent of hyperphagia and that were compensated during chronic exposure to increased AGRP.

Hemodynamic Responses to AGRP
Chronic intracerebroventricular infusion of AGRP in the ad libitum–fed rats decreased MAP and HR despite an increase in food intake, body weight, and a 14-fold increase in plasma leptin, all of which would tend to raise MAP and HR. However, AGRP also antagonizes MC3/4R, which may mediate most of the effects of leptin on renal sympathetic activity and blood pressure. Thus, the absence of hypertension despite obesity and hyperleptinemia may be attributable to antagonism of MC3/4R by AGRP. Termination of AGRP resulted in an increase in MAP to a level above control values. Although pronounced increases in plasma leptin could account for the pressure changes observed after termination of AGRP infusion because of sudden increased availability of the hypothalamic MC3/4R in ad libitum–fed rats, this would
Effect of Chronic Central Infusion of AGRP on Body Weight, Renal Function, and Circulating Hormones

<table>
<thead>
<tr>
<th>Groups</th>
<th>Body Weight, g</th>
<th>Glucose, mmol/L</th>
<th>Insulin, μU/mL</th>
<th>Leptin, ng/mL</th>
<th>GFR, mL/minute</th>
<th>PRA, ng Al/mL per hour</th>
<th>UV, mL/day</th>
<th>U_aNaV, mmol/day</th>
<th>U_aK, mmol/day</th>
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<tr>
<td>aCSF vehicle</td>
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<tr>
<td>Control day 3</td>
<td>338±10</td>
<td>7.4±0.3</td>
<td>38.7±2.8</td>
<td>1.9±0.4</td>
<td>3.3±0.2</td>
<td>3.3±0.5</td>
<td>36±2</td>
<td>2.6±0.1</td>
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<td>359±12</td>
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<td>Recovery day 5</td>
<td>360±13*</td>
<td>7.3±0.4</td>
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<td>3.2±0.1</td>
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<td>Experimental day 11</td>
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<td>Recovery day 5</td>
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<tr>
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<td>7.6±0.2</td>
<td>42.7±3.9</td>
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</tr>
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</table>

U_aNaV indicates average urinary sodium excretion during each period; U_aK, average urinary potassium excretion during each period; UV, average urine volume during each period.

*P<0.05 compared with control values; †P<0.05 compared with corresponding values in vehicle-infused and AGRP-infused pair-fed group.

not explain the results in pair-fed rats, in which there were only minor increases in plasma leptin. Previous studies report that central administration of AGRP over a 7-day period in pair-fed rats increased the ratio of hypothalamic POMC/AGRP mRNA expression, which is consistent with increased melanocortin signaling that could participate in increasing arterial pressure. Failure of AGRP infusion to decrease MAP in pair-fed animals may be related to stress induced by increased hunger with pair feeding.

The cardiovascular effects of AGRP may be related to inhibition of sympathetic activity. Supporting this view, Yasuda et al showed recently that an acute bolus injection of AGRP in the third cerebral ventricle decreased brown adipose tissue sympathetic activity and body temperature. In addition, we demonstrated that combined α-adrenergic/β-adrenergic receptor blockade abolished the pressor and tachycardiac actions induced by chronic central MC3/4R activation, suggesting that the cardiovascular responses to MC3/4R activation were mediated by adrenergic activation. Because AGRP antagonizes MC3/4R, it is likely that the chronic depressor and bradycardiac actions of AGRP were through inhibition of the sympathetic nervous system.

The results obtained with AGRP in the present study resemble those obtained with chronic central administration of the synthetic MC3/4R antagonist SHU9119 in our previous studies and are consistent with the possibility that the actions of AGRP are attributable mainly to MC3/4R blockade. Furthermore, blockade of MC4R rather than MC3R may be more important in mediating the actions of AGRP because MC4R but not MC3R appears to regulate sympathetic nervous system activity, as suggested by absence of increases in renal sympathetic activity in homozygous MC4R-deficient mice during MC3/4R stimulation with the agonist MT-II.

Another peptide that is highly homologous to AGRP that is also capable of acting as an antagonist of MC4R is agouti peptide. Mice overexpressing agouti peptide ubiquitously are hyperphagic and obese, presumably because of hypothalamic MC4R blockade but surprisingly have elevated rather than reduced arterial pressures. Using telemetry in conscious mice, Williams et al measured arterial pressure 24 hours per day and confirmed the results reported previously by Mark et al.

Figure 2. Change in MAP (ΔMAP) and HR (ΔHR) with chronic intracerebroventricular infusion of vehicle (n=8), AGRP (0.02 nmol per hour; n=6), or AGRP (0.02 nmol per hour) with pair-feeding (n=7) in conscious Sprague-Dawley rats. *P<0.05 compared with control values of the same group.
and Aizawa et al that agouti obese mice exhibit elevated MAP compared with wild-type control mice.23–25 These observations suggest that in the agouti mouse, there may be additional factors that oppose the depressor actions of MC4R blockade and raise arterial pressure. For instance, agouti peptide has been reported to directly increase intracellular Ca++ concentration in many tissues, including vascular smooth muscle, that could contribute to increased vascular resistance in the agouti mouse.26 Although homozygous MC4R-deficient mice fail to exhibit any increases in renal sympathetic activity during leptin infusion, agouti mice are not resistant to these sympathoexcitatory actions of leptin.22,27 Therefore, sympathetic activation caused by hyperleptinemia may be another mechanism that could raise arterial pressure in agouti mice.

Consistent with this view, agouti mice were shown to have increased urinary catecholamine secretion.25 The mechanisms for maintaining leptin sensitivity in obese agouti mice is unclear. In agouti mice, leptin may mediate its actions by MC4R-independent pathways such as the hypothalamic cocaine–amphetamine-regulated transcript pathway, which has been shown to be upregulated in agouti mice and to have some pressor actions.28–29 It is also possible that agouti mice have only partial antagonism of MC4R, as evidenced by the ability of MT-II (MC3/4R agonist) to suppress food intake in agouti mice and the inability of MC3R to mediate appetite suppression.30 Irrespective of the mechanisms involved in increasing blood pressure in agouti mice, our study suggests that the chronic cardiovascular actions of AGRP may be different from those of agouti peptide despite similar metabolic actions that have been attributed to MC4R blockade.

Previous studies demonstrate that hypothalamic arcuate nucleus neurons coexpress AGRP and the leptin receptor.31 Moreover, whereas conditions such as fasting, leptin deficiency, or leptin receptor deficiency are associated with increased hypothalamic AGRP mRNA expression, leptin administration decreases hypothalamic AGRP expression, suggesting AGRP may constitute a significant component of the satiety actions of leptin.8,31 Whether hypothalamic AGRP also participates in the cardiovascular actions of leptin remains to be investigated.

Alterations in AGRP expression have been observed in chronic conditions of positive or negative energy balance. Huang et al reported that 22 weeks of high-fat diet significantly reduced hypothalamic arcuate nucleus AGRP mRNA expression and increased MC4R expression,32 changes that could enhance the actions of leptin in obesity. Similarly, Tritos et al reported suppressed hypothalamic arcuate nucleus AGRP mRNA in obese mice with brown adipose tissue deficiency.33 These observations are consistent with the hypothesis that in obesity, suppressed AGRP formation relieves MC3/4R blockade and may enhance sympathoexcitatory and pressor actions of leptin, thereby contributing to increased blood pressure. In conditions associated with negative energy balance, hypothalamic AGRP expression is increased, which could act to inhibit MC3/4R and stimulate appetite while decreasing sympathetic activity and thermogenesis. Consequently, this decrease in sympathetic activity may contribute to decreases in arterial pressure and HR during states of negative energy balance.34–36

Renal Responses to AGRP

AGRP caused a significant increase in GFR in ad libitum–fed rats but not in pair-fed rats, suggesting that the increased GFR may be attributable to increased body weight. In the present study, despite reductions in arterial pressure with AGRP infusion, there were no changes in urine volume or urinary sodium excretion. This suggests that AGRP shifted the renal-pressure natriuresis relationship to lower pressures. AGRP caused significant increases in potassium excretion only in ad libitum–fed rats, suggesting that increased urinary potassium excretion was directly related to the increase in dietary potassium intake.

Perspectives

Our results demonstrate that AGRP can act in the CNS to produce chronic reductions in arterial pressure and HR despite causing dramatic increases in body weight that normally tend to raise arterial pressure. However, the role of endogenous AGRP in regulating cardiovascular function and appetite is not yet clear, and future studies should be directed toward interfering with endogenous AGRP expression, possibly by using genetic techniques because there are currently no specific AGRP antagonists. Whether AGRP functions downstream of leptin and other neuroendocrine factors that act through MC3/4R to regulate appetite and cardiovascular function and whether these interactions are altered in obesity are also unclear and remain to be investigated.

Acknowledgments

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References


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