Chronic Central Nervous System MC3/4R Blockade Attenuates Hypertension Induced by Nitric Oxide Synthase Inhibition but not by Angiotensin II Infusion

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Abstract—We examined whether central melanocortin 3 and 4 receptor (MC3/4R) blockade attenuates the blood pressure (BP) responses to chronic L-NAME or angiotensin II (Ang II) infusion in Sprague–Dawley rats implanted with telemetry transmitters, venous catheters, and intracerebroventricular cannula into the lateral ventricle. After 5 days of control measurements, L-NAME (10 μg/kg/min IV, groups 1 and 2) or Ang II (10 ng/kg/min IV, groups 3 and 4) were infused for 24 days, and starting on day 7 of L-NAME or Ang II infusion, the MC3/4R antagonist SHU-9119 (24 nmol/d, n=6/group; groups 1 and 3) or vehicle (saline 0.5 μL/h, n=6/group; groups 2 and 4) was infused intracerebroventricularly for 10 days. A control normotensive group also received SHU-9119 for 10 days (n=5). L-NAME and Ang II increased BP by 40±3 and 56±5 mm Hg, respectively, although heart rate was slightly reduced. MC3/4R blockade doubled food intake and reduced heart rate (≈40 to ≈50 bpm) in all groups. MC3/4R blockade caused only a small reduction in BP in normotensive group (4 mm Hg) and no change in rats receiving Ang II, although markedly reducing BP by 21±4 mm Hg in L-NAME–treated rats. After SHU-9119 infusion was stopped, food intake, heart rate, and BP gradually returned to values observed before L-NAME–induced hypertension was started. Ganglionic blockade at the end of L-NAME or Ang II infusion caused similar BP reduction in both groups. These results suggest that the brain MC3/4R contributes, at least in part, to the hypertension induced by chronic L-NAME infusion but not by Ang II. (Hypertension. 2014;65:00-00.)

Key Words: blood pressure ■ CNS ■ food intake ■ heart rate

One of the most important regulators of energy balance and body weight homeostasis is the central nervous system (CNS) melanocortin system. Activation of pro-opiomelanocortin neurons leads to production and release of α-melanocyte stimulating hormone which, in turn, activates melanocortin 3 and 4 receptors (MC3/4R), leading to suppressed appetite and increased energy expenditure, the latter promoted by increased sympathetic nerve activity (SNA) to thermogenic tissues, such as brown adipose tissue.1–3 Dysfunction of the melanocortin system in humans or rodents, caused either by mutations of the MC4R or pro-opiomelanocortin deficiency, is associated with marked hyperphagia, reduced energy expenditure, and severe early onset obesity that is accompanied by many characteristics of the metabolic syndrome, including hyperglycemia, insulin resistance, and hyperleptinemia.4–6 Some studies suggest that a defective melanocortin system may account for as much as 5% to 6% of early onset, morbid obesity in humans.7–9

In addition to its role in regulating appetite and energy balance, acute and chronic MC3/4R activation stimulate SNA to tissues that regulate cardiovascular function, including the heart, the blood vessels, and the kidneys, causing increased blood pressure (BP) and heart rate (HR).10–12 Studies in experimental animals and in humans suggest that a functional MC3/4R may be necessary for obesity to cause hypertension. For example, blood pressure of MC4R-deficient mice is not elevated, despite severe obesity, insulin resistance, hyperinsulinemia, and other features of the metabolic syndrome.13,14 Likewise, humans with dysfunctional MC4R exhibit severe obesity and metabolic syndrome but are not hypertensive and actually have lower BP, reduced SNA, and lower prevalence of hypertension than control obese subjects.15 These observations support the concept that MC3/4R activation (in particular, MC4R activation) is required for excess weight gain to increase BP.

In addition to its importance in linking obesity with increased SNA and elevations in BP and HR in obesity, the brain melanocortin system may play a more fundamental role in regulation of blood pressure beyond obesity-induced hypertension. For instance, we showed that chronic MC3/4R blockade in lean spontaneous hypertensive rats (SHR), a model of hypertension associated with high sympathetic tone, markedly reduced their hypertension to a similar degree achieved by adrenergic receptor blockade.16 This observation is consistent with the hypothesis that the brain MC3/4R is a key regulator...
of SNA and may be important in the development and maintenance of elevated BP in other commonly used experimental models of hypertension. Moreover, other factors, including reduced nitric oxide (NO) availability, seem to augment the effect of MC3/4R activation on cardiovascular function.17

Therefore, to test the hypothesis that MC3/4R is an important modulator of SNA and may play a fundamental role in BP control, we examined the effect of chronic MC3/4R antagonism on 2 distinct and widely used models of hypertension caused by (1) reduced peripheral NO availability, a common feature in human obesity, by blocking oxide nitric synthase with No-nitro-L-arginine methyl ester hydrochloride (L-NNAME) and (2) increased circulating angiotensin II (Ang II) levels by chronic infusion of Ang II. We found that chronic MC3/4R blockade doubled food intake and promoted weight gain while causing significant reductions in HR in both models of hypertension. However, despite a similar effect on appetite and HR, MC3/4R antagonism markedly attenuated the hypertension induced by chronic L-NNAME infusion, but failed to significantly buffer the increase in BP during chronic Ang II infusion.

Methods

All experimental procedures conformed to the National Institute of Health Guide for the Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee of the University of Mississippi Medical Center.

Animal Surgery

Male Sprague–Dawley rats weighing between 300 and 350 g (Harlan Sprague–Dawley, Inc, Indianapolis, IN) were anesthetized with sodium pentobarbital (50 mg/kg), and atropine sulfate (0.37 mg/kg) was administered to prevent excessive airway secretion. A telemetry blood pressure transmitter (Model T111PAC40, Data Sciences International, MN) were implanted in the abdominal aorta distal to the kidneys under sterile conditions as previously described.16 A femoral vein catheter was implanted, and the tip of the catheter was advanced into the inferior vena cava. The catheter was exteriorized through a stainless steel button implanted subcutaneously in the scapular region. A stainless steel cannula (26 gauge, 10 mm long) was also implanted into the brain right lateral ventricle using coordinates previously described.16 Ten days after recovery from surgery, accuracy of the cannula was examined by determining the dipsogenic response to an acute injection of 100 ng of Ang II. After recovery from surgery, the rats were housed individually in metabolic cages. The venous catheter was connected to a swivel and a continuous infusion of saline was maintained throughout the study. All rats received water and food ad libitum, and total daily sodium intake was maintained constant at ≈3.2 mEq/d by continuous infusion of 20 mL/d of 0.9% saline combined with a sodium-deficient rat chow (0.006 mmol sodium/g of food, Harlan Teklad, Madison, WI).

Experimental Protocols

Experiment 1: Responses to Chronic MC3/4R Blockade During L-NNAME–Induced Hypertension

Two groups of rats were used in these experiments. After a 5-day control period, rats received intravenous (IV) L-NNAME (10 μg/kg/min; Sigma, St. Louis, MO) infusion for 24 consecutive days. Beginning on day 7 of L-NNAME treatment, the rats also received either an intracerebroventricular (ICV) infusion of the vehicle (0.9% saline, 0.5 μL/h, n=6) or the MC3/4R antagonist, SHU-9119 (24 nmol/d, n=6; Polypeptide Laboratories, Torrance, CA), for 10 days via an osmotic minipump (Alzet model 2002, Cupertino, CA) implanted subcutaneously in the scapular region and connected to the ICV cannula via tygon tubing. At the end of the 10-day SHU-9119 infusion, the tygon tubing was severed but the animals continued to be infused with L-NNAME for additional 7 days. After this additional 7-day period of L-NNAME infusion alone, L-NNAME treatment was stopped, and the animals were followed for a 5-day recovery period.

Experiment 2: Responses to Chronic MC3/4R blockade During Ang II–Induced Hypertension

Two groups of rats were also used in these experiments, and the protocol was similar to experiment 1. After a 5-day control period, Ang II (10 ng/kg/min; Sigma, St. Louis, MO) was infused intravenously for 24 consecutive days. Beginning on day 7 of Ang II treatment, the rats also received either an ICV infusion of the saline vehicle or SHU-9119. At the end of the 10-day SHU-9119 infusion, the tygon tubing was severed, but the animals continued to be infused with Ang II for additional 7 days. After this additional 7-day period of Ang II infusion alone, Ang II treatment was stopped and the animals followed a 5-day recovery period.

A control group of normotensive rats infused with SHU-9119 was also included in the protocol to account for the effects of MC3/4R antagonism in normotensive rats. This control group was only infused with saline intravenously for the duration of the experiment, and SHU-9119 was infused ICV for 10 days as described earlier.

Cardiac Sympathetic-Vagal Balance

To evaluate changes in sympathetic and parasympathetic tone to the heart L-NNAME or Ang II hypertension and to chronic MC3/4R antagonism, we performed cardiac sympathetic-vagal balance measurements in separate groups of rats (n=4/group) under resting conditions by measuring the chronotropic effects of full-blocking doses of propranolol (4 mg/kg), a β-adrenergic receptor antagonist, and atropine (2 mg/kg), a muscarinic receptor blocker, at a volume per injection of ≤0.2 mL. Propranolol and atropine injections were performed at the end of the control period, 7 days after starting L-NNAME or Ang II infusion, and again on day 10 of SHU-9119 treatment. After resting, BP and HR were recorded for 30 to 60 minutes, propranolol was injected first, and atropine was injected 15 minutes later.

Acute Ganglionic Blockade

To determine the overall contribution of autonomic tone to the maintenance of BP in L-NNAME– and Ang II–treated groups, we injected a bolus dose of the ganglionic blocker hexamethonium (20 mg/kg IV) at the end of the 3rd week of treatment. The volume per injection was ≤0.2 mL followed by 0.4 mL of saline to flush the catheter.

Statistical Methods

The results are expressed as means±SEM. The data were analyzed by 1-way analysis of variance with repeated measures followed by Dunnett’s post hoc test for comparisons between control and experimental values within each group when appropriate. Comparisons between different groups were made by 2-way analysis of variance followed by Dunnett’s post hoc test when appropriate. Statistical significance was accepted at a level of P<0.05.

Results

Chronic MC3/4R Antagonism Markedly Increased Food Intake in L-NNAME– and Vehicle-Treated Rats

As shown in Figure 1A, chronic central MC3/4R blockade with SHU-9119 caused a significant increase in appetite, leading to doubling of food intake during the last 5 to 6 days of SHU-9119 infusion in hypertensive L-NNAME–treated rats and in normotensive intravenously saline–treated rats. After stopping SHU-9119 infusion, food intake remained elevated for an additional 3 to 4 days when it gradually fell toward control baseline values on day 7 post SHU-9119 infusion. L-NNAME treatment had no effect on food intake.
Chronic MC3/4R Antagonism Attenuated Hypertension Induced by Chronic L-NAME Infusion and Reduced HR in Control and L-NAME–Treated Groups

As expected, chronic peripheral inhibition of NO formation by L-NAME raised mean arterial pressure (MAP) in ICV vehicle-treated group by ≈30 mmHg during the first week of treatment (Figure 1B). BP continued to increase during the course of the 24-day L-NAME treatment period, reaching its peak (+60 mmHg) at the last 4 days of treatment (Figure 1B). After termination of L-NAME infusion, MAP rapidly returned toward control values during the 5-day recovery period.

In the group treated with the MC3/4R antagonist, MAP also increased to a similar degree during the first week of L-NAME treatment; however, when SHU-9119 began to be infused, MAP dropped by ≈27 mmHg during the first 5 to 6 days of ICV SHU-9119 infusion after which MAP gradually increased during the remaining days of L-NAME treatment, but to a much lesser degree (varying from −15 to −25 mmHg) compared with ICV saline vehicle even after SHU-9119 infusion was terminated (Figure 1B). This suggests that MC3/4R antagonism not only attenuates hypertension induced by L-NAME but also exerts a long-lasting effect to buffer the increase in BP caused by reduced peripheral NO availability.

As we have previously demonstrated in normotensive SD rats, SHU-9119 caused a small reduction in MAP (≈5 mmHg), but this reduction in BP was only a fraction of the effect observed in L-NAME–treated hypertensive rats (Figure 1B).

L-NAME treatment caused a small reduction in HR (≈20 bpm) during the first 17 to 19 days, which was caused mainly by an increase in cardiac parasympathetic tone, whereas cardiac sympathetic tone remained unaffected (±1), after which HR markedly increased in parallel with the increase in MAP during the last week of L-NAME treatment (Figure 1C). Chronic MC3/4R antagonism markedly reduced HR in both hypertensive and normotensive groups by 40 to 50 bpm (Figure 1C). This resulted in a difference in HR between the 2 L-NAME–treated groups of 35 to 40 bpm (Figure 1C). The reduction in HR during MC3/4R antagonism was associated with increased parasympathetic tone to the heart in combination with a reduction in cardiac sympathetic tone (Table 1).

Chronic MC3/4R Antagonism Markedly Increased Food Intake in Ang II–Treated Rats

Chronic MC3/4R blockade also markedly increased food intake in rats chronically infused with Ang II, although the
magnitude of the increase was slightly less pronounced when compared with control normotensive rats (Figure 2A). It is important to note that although the hyperphagia caused by SHU-9119 was attenuated by ≈10% in the Ang II group, food intake still almost doubled compared with the days immediately before SHU-9119 infusion was initiated (from 20±1 to 39±2 g/d; Figure 2A). As observed in normotensive control and L-NAME–treated groups, food intake also gradually returned to baseline levels after stopping SHU-9119 infusion in Ang II–treated rats.

Chronic MC3/4R Antagonism Failed to Attenuate Hypertension Induced by Chronic Ang II Infusion but Reduced HR in Control and Ang II–Treated Groups

Similar to L-NAME treatment, chronic intravenous Ang II infusion in SD rats raised MAP by ≈40 mm Hg (Figure 2B). Chronic central MC3/4R antagonism, however, did not significantly affect the hypertension induced by Ang II, and BP levels in this group was similar to those observed in Ang II–treated rats that received vehicle ICV infusion (Figure 2B). This suggests that, contrary to the hypertension induced by L-NAME, the elevation in BP caused by chronic Ang II is not modulated by the brain melanocortin system. After cessation of Ang II infusion, MAP returned to normotensive baseline levels (Figure 2B).

Chronic Ang II infusion in ICV vehicle-treated rats was also associated with an initial phase of bradycardia lasting 6 to 7 days, after which HR gradually increased past its initial baseline levels (Figure 2C). The effects of MC3/4R antagonism on HR during Ang II–induced hypertension, however, were more complex when compared with the effects of MC3/4R on HR regulation in L-NAME–treated rats described earlier. For example, SHU-9119 treatment did not cause a significant decrease in HR, but prevented HR from increasing to levels observed in Ang II+vehicle group, leading to a 30 to 35 bpm lower HR in Ang II+SHU9119 group (Figure 2C). Thus, despite the fact that SHU-9119 treatment did not lower HR to the same values observed in normotensive rats treated with SHU-9119, it still caused a comparable reduction in HR when compared with the HR values of the 2 groups infused with Ang II. HR returned to control values 7 to 8 days after cessation of SHU-9119 infusion. These observations indicate that Ang II does not seem to blunt the bradycardic action of chronic central MC3/4R antagonism.

Similar to what we observed in the L-NAME–treated group, the initial bradycardia caused by Ang II infusion was associated with an increase in parasympathetic tone to the heart with no change in cardiac sympathetic tone (Table 1). Furthermore, MC3/4R antagonism with SHU-9119 markedly reduced cardiac sympathetic tone (Table 1).

Acute Ganglionic Blockade Reduced MAP in Both Groups

Ganglionic blockade with hexamethonium markedly reduced MAP in both groups of hypertensive rats, and this reduction was similar in L-NAME and Ang II hypertensive rats (Figure 3).

Discussion

In the present study, we demonstrated that chronic CNS MC3/4R antagonism results in comparable increases in appetite and reductions in HR in normotensive rats and in 2 distinct models of experimental hypertension caused by chronic intravenous L-NAME or Ang II infusion. However, the effect of central MC3/4R blockade on BP regulation markedly differed in these 3 groups. Although MC3/4R antagonism significantly attenuated the hypertension induced by L-NAME and exerted a modest BP lowering effect in normotensive rats, it completely failed to alter BP levels in Ang II–induced hypertensive rats.
Our results together with previous studies highlight an important role of the brain melanocortin system in the development or maintenance of hypertension in distinct models of hypertension (eg, L-NAME– and obesity-induced hypertension, as well as in SHRs). Moreover, another novel aspect of the present study is that it shows that not all forms of hypertension (eg, Ang II–induced hypertension) involve the brain MC3/4R receptors, and it demonstrates that the exacerbated BP lowering effect of MC3/4R antagonism observed in L-NAME (present study) or in SHRs are not simply because of a higher baseline BP level where 1 may speculate that any antihypertensive therapy may exert a more profound reduction in BP than in normotensive controls.

Although the precise mechanisms by which MC3/4R influence BP regulation are not completely understood, previous studies suggest that MC3/4R modulate SNA. For instance, acute ICV injections of MC4R agonists raise SNA to several tissues, including the kidneys, and combined α- and β-adrenergic receptors blockade completely prevented the hypertension caused by chronic central MC3/4R stimulation using the synthetic agonist MTII. A role for modulation of SNA by CNS MC3/4R as the main mechanism by which the brain melanocortin system contributes to BP regulation is also supported by our finding that Ang II hypertensive rats are unresponsive to the BP lowering effects of SHU-9119. Using an elegant approach, Yoshimoto et al showed that chronic Ang II infusion in rats is associated with normal or even reduced renal SNA. Reduced renal SNA during chronic Ang II–induced hypertension has also been reported in rabbits and dogs on normal sodium diets using direct measurements of renal SNA or by quantifying renal norepinephrine spillover. It is important to note that not all studies have observed reduced SNA during chronic Ang II infusion and that Ang II–induced changes in renal SNA may be time-dependent as shown by Yoshimoto et al. Thus, although there is strong evidence to suggest that, in forms of hypertension where SNA is reduced (especially renal SNA), the brain melanocortin system may not contribute to the elevated BP, it is possible that the brain melanocortin system may also modulate cardiovascular function via an alternative mechanism.

Contrary to what we observed in Ang II–induced hypertension, MC3/4R blockade markedly attenuated the hypertension caused by L-NAME infusion. Although we are not certain of the mechanisms leading to a greater fall in BP in this model caused by SHU-9119, a simple explanation would be that the hypertension induced by chronic L-NAME treatment may be associated with increased renal SNA. This explanation would be consistent with our previous observation that chronic MC3/4R antagonism in SHR, a model of high baseline SNA, marked lowered BP by an amount comparable to adrenergic receptor blockade and with our current data showing no change in blood pressure in Ang II–treated rats during chronic SHU-9119 infusion. Previous studies in rabbits and rats, however, showed normal renal SNA in conscious animals made hypertensive by chronic L-NAME treatment. Conversely, Young and colleagues showed that skin SNA, which is not under baroreflex control, was markedly elevated by short-term L-NAME infusion in healthy subjects. Thus, L-NAME may lead to increased SNA in organs/tissues not regulated by the baroreflex but not to organs under baroreflex control, such as the kidneys. This possibility, however, may not explain the long-term reduction in BP caused by SHU-9119. Thus, an alternative explanation is that renal SNA, although not altered by L-NAME, is inappropriately high, given the severity of the hypertension induced by L-NAME, which would be expected to reduce renal SNA. But, independently of whether SNA to cardiovascular relevant tissues is inappropriately elevated or not during L-NAME–induced hypertension, it is also possible that peripheral blockade of NO formation sensitizes the blood vessels and renal tubules to the pressor actions of adrenergic receptor stimulation, so that the sodium retaining effects of any given level of SNA would be increased in the presence of L-NAME. For instance, Doodson et al showed enhanced centrally induced sympathetic coronary vasoconstriction in cats pretreated with L-NAME. We also found marked accentuated sympathetically mediated hypertension induced by chronic MC3/4R activation in rats treated with L-NAME. However, Hilzendeger et al showed that blockade of brain AT1 receptors failed to alter the increase in renal SNA elicited by the MC3/4R agonist, MTII. This observation is in agreement with our findings that MC3/4R antagonism with SHU-9119 did not alter Ang II–induced hypertension, whereas it reduced BP in L-NAME hypertension. However, it is possible that an adrenergic-independent mechanism could explain the fall in BP during MC3/4R blockade in L-NAME hypertensive rats because acute ganglionic blockade lowered BP by a similar degree to our findings that MC3/4R antagonism with SHU-9119. Thus, an equal overall importance of SNA to the maintenance of BP in these models. Nevertheless, it is also important to recognize that acute ganglionic blockade may not recapitulate the effects of chronically blocking the SNS, especially if the chronic effects are mediated mainly by decreased renal SNA which, in turn, decreases renal tubular sodium reabsorption and leads to a slowly developing decrease in blood pressure over several days. It is possible that renal SNA may be differentially affected by Ang II versus L-NAME hypertension. These differential effects on renal SNA could be particularly important if suppression of renal SNA mediates most of the chronic BP lowering effect of MC3/4R antagonism. We, however, are not certain of the precise mechanism by which central MC3/4R blockade reduced BP in L-NAME but not...
Ang II–treated hypertensive rats. Although we hypothesize an involvement of renal SNA, our results may also suggest that a renal SNA-independent mechanism contributes to the differential BP effect of chronic MC3/4R antagonism observed in these 2 distinct hypertensive models.

Although the effect of MC3/4R antagonism on BP regulation was remarkably different between L-NAME and Ang II–induced hypertension, the effects of MC3/4R blockade on HR and food intake regulation were similar and resulted in significant reduction of HR concomitant with a doubling of food consumption. This finding is in accordance with our previous study showing that the bradycardic action of SHU-9119 was not different in SHRs compared with normotensive Wistar controls, despite a marked reduction in BP in SHRs that was not seen in Wistar rats.16 This supports the concept of differential control of appetite, HR, and BP by the brain melanocortin system and highlights the importance of MC3/4R activation for increased weight gain to cause elevations in HR and BP. Our findings also suggest, albeit indirectly, that increased circulating levels of Ang II or reduced NO availability, which often occur in obesity, do not alter the importance of the brain MC3/4R in regulating appetite.

The reduction in HR in all groups receiving SHU-9119 was associated with increased parasympathetic and reduced sympathetic tone to the heart. Although the brain areas where MC3/4R exert their effects on the autonomic nervous system and BP regulation are still poorly understood, MC4R are abundant in the paraventricular nucleus of the hypothalamus and in brain stem areas involved in autonomic regulation, as well as in the intermediolateral medulla.32,33 For example, acute stimulation of MC4R in the paraventricular nucleus or intermediolateral medulla raises renal SNA and HR, respectively,32 whereas MC4R located on cholinergic preganglionic parasympathetic and sympathetic neurons seem to contribute, at least in part, to obesity hypertension.34 However, additional studies are needed to determine the brain regions where the melanocortin system is most important for modulating cardiovascular function.

Perspectives

The CNS melanocortin system plays a key role linking obesity with sympathetic activation and hypertension. Our studies also support an important participation of brain MC3/4R in regulating BP in nonobese models of hypertension (eg, SHR and L-NAME–induced hypertension). The fact that MC34R antagonism did not attenuate Ang II hypertension reinforces the notion that elevated baseline BP does not always predict the notion that elevated baseline BP does not always predict treatment-specific effects of chronic melanocortin-3/4 receptor activation. Hypertension. 2011;57:428–434.


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**Novelty and Significance**

- Chronic melanocortin 3 and 4 receptor (MC3/4R) antagonism significantly attenuates L-arginine methyl ester hydrochloride (L-NAME)–induced hypertension.

- Chronic MC3/4R antagonism does not alter angiotensin II (Ang II)–induced hypertension.

- MC3/4R blockade markedly increases appetite and reduces heart rate to a similar extent in Ang II– and L-NAME–treated rats.

- Higher baseline blood pressure (BP) does not predict the effect of chronic MC3/4R antagonism on BP regulation.

- The brain melanocortin system contributes to hypertension induced by chronic nitric oxide synthase inhibition but not to Ang II hypertension, suggesting that the brain melanocortin system may contribute to the elevated BP in specific models of hypertension.

- Our results support the concept that the brain melanocortin system exerts a differential control of appetite, heart rate, and BP regulation.

**Summary**

Despite exerting similar effects to increase appetite and to reduce heart rate in normotensive rats and in 2 distinct models of hypertension (eg, chronic Ang II or L-NAME infusion), MC3/4R antagonism markedly attenuated L-NAME–induced hypertension, where-as no attenuation of the increased BP caused by Ang II infusion was observed. Thus, although L-NAME hypertension seems to involve the brain melanocortin system, Ang II–induced hypertension is independent of the brain melanocortin system.
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