Risk estimates from the Farmington Heart Study suggest that ≈78% of essential hypertension in men and 65% in women can be directly attributed to obesity. Several lines of evidence strongly indicate that activation of the sympathetic nervous system contributes to the etiology of obesity-induced hypertension. First, renal norepinephrine spillover is approximately doubled in obese versus lean subjects. Second, muscle sympathetic nerve activity assessed by microneurography is higher in obese humans. Consistent with this notion, pharmacological blockade of peripheral adrenergic receptors or ganglionic blockade reduces arterial blood pressure (ABP) to a greater extent in obese versus lean subjects. Similar observations have been reported in animal models of obesity hypertension. For example, bilateral renal denervation prevents the development of obesity-induced hypertension in dogs. Despite the importance of sympathetic nervous system activation in obesity-induced hypertension, the central neural mechanisms and pathways that support the elevated sympathetic outflow and ABP are poorly understood.

Basal sympathetic outflow arises from the tonic drive of neurons in the rostral ventrolateral medulla (RVLM) to preganglionic neurons in the thoracic and lumbar spinal cord. Although other hypothalamic and pontomedullary structures innervate sympathetic preganglionic neurons, and stimulation of these regions can increase sympathetic outflow and ABP through pathways independent of the RVLM, the RVLM is regarded as the major vasomotor center within the central nervous system. For example, a myriad of studies indicate that RVLM neurons mediate numerous reflexive adjustments in sympathetic outflow under physiological conditions. Electrical stimulation or chemical excitation of this region profoundly increases sympathetic nerve activity and ABP. Moreover, several studies have suggested that RVLM neurons contribute to the elevated sympathetic outflow and ABP in several experimental animal models of hypertension. Interestingly, Lohmeier et al reported an increased level of Fos expression, a marker of synaptic activation, in the RVLM of obese hypertensive dogs.

The purpose of the present study was to determine whether RVLM neurons contribute to the elevated ABP in obesity-induced hypertension. Previous studies have demonstrated that feeding rats a moderate high-fat diet for an extended period of time results in the segregation of obesity-resistant (OR) and obesity-prone (OP) rats. The latter group has an elevated ABP that is associated with activation of the sympathetic nervous system. Therefore, we hypothesized that the major vasomotor region (RVLM) in the spinal cord plays a critical role in the elevation of ABP in OP rats. The present study sought to determine whether sympathetic regulatory neurons of the rostral ventrolateral medulla contribute to the elevated blood pressure in obese rats. Male Sprague-Dawley rats (350 to 425 g) were placed on a moderately high-fat diet (32% kcal as fat) or a low-fat (LF) diet (10.6% kcal as fat). After 13 weeks, rats fed the moderately high-fat diet segregated into obesity-prone (OP) and obesity-resistant (OR) groups based on their body weight (OP: 839 ± 22 g; OR: 668 ± 15 g; LF: 680 ± 18 g; n = 15 for all groups; P < 0.01). Under isoflurane anesthesia, baseline mean arterial blood pressure was significantly elevated in the OP rats versus the OR and LF rats (OP: 108 ± 2 mm Hg; OR: 100 ± 2 mm Hg; LF: 97 ± 3 mm Hg; n = 7; P < 0.05). Inhibition of the rostral ventrolateral medulla with bilateral microinjection of the GABA_A receptor agonist muscimol (200 pmol/100 nL) decreased mean arterial blood pressure to similar levels across the groups (OP: 49 ± 1 mm Hg; OR: 50 ± 2 mm Hg; LF: 49 ± 1 mm Hg), but the magnitude of this decrease was significantly greater in the OP versus the OR and LF rats (OP: −58 ± 2 mm Hg; OR: −49 ± 1 mm Hg; LF: −48 ± 3 mm Hg; P < 0.01). These differences in mean arterial blood pressure cannot be explained by changes in vascular reactivity as the ED_50 in response to phenylephrine and norepinephrine was similar across the groups. The present findings suggest that the elevated sympathetic nerve activity and arterial blood pressure in obese rats depends on the tonic activity of rostral ventrolateral medulla sympathetic neurons.
renin–angiotensin system, hyperleptinemia, hyperinsulinemia, and elevated sympathetic outflow. All of these characteristics parallel those observed in obese, hypertensive humans. In addition, the segregation of OP and OR rats allows studies to distinguish between the effects of obesity versus diet composition. Using this model, we hypothesized that RVLM neurons contribute to the elevated ABP in OP rats. If this greater contribution is related to obesity rather than diet, then the maintenance of ABP by RVLM neurons should be equivalent between OR and rats fed a low-fat (LF) diet.

Methods

Animals

All of the experimental procedures were approved by the University of Kentucky Institutional Animal Care and Use Committee and were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Male Sprague–Dawley rats (Charles River Laboratories) weighing 350 to 425 g were housed individually in a temperature-controlled room (22° to 23°C) with a 14-hour/10-hour light-dark cycle (lights on at 7:00 AM). Rats were placed on an LF diet (10% kcal from fat; Research Diets, Inc, D12489B) or a moderate high-fat diet (32% kcal from fat, Research Diets, Inc, D12266B) for 13 weeks. After 5 weeks, rats fed the moderately high-fat diet segregate into OP and OR based on the body weight distribution as described previously. Briefly, a body weight histogram was constructed and resulted in a distribution of one third of rats, respectively.

Measurement of Food Intake and ABP

One group of LF (n=8), OR (n=8), and OP (n=8) rats was maintained on the respective diet for 13 weeks. Daily food intake was measured throughout the 13-week regimen. ABP was measured every other week for the initial 8 weeks by tail cuff (CODA2, Kent Scientific Corporation). Then, telemetry blood pressure transmitters (TA11PA-C40, Data Sciences International) were implanted into the femoral artery, and the transmitter was sutured to the internal abdominal wall while rats were anesthetized with isoflurane (2% to 3% in 100% O2). Rats received an injection of ampicillin (100 mg/kg, IM) and were returned to home cages. At least 1 week later, ABP and heart rate (HR) were measured by telemetry for 2 weeks. Then, rats were euthanized with isoflurane, and the epididymal and retroperitoneal fat pads were isolated and weighed for calculation of the adiposity index (see below). Transmitter offsets were measured before implantation and at the end of the study. These values were factored into the reported MABP values.

Measurement of Osmolarity, Hematocrit, and Blood Volume

A second set of LF (n=7), OR (n=7), and OP (n=7) rats was maintained on the respective diet for 13 weeks. On week 12, rats were anesthetized with isoflurane (2% to 3% in 100% O2) and instrumented with catheters in the left femoral artery and vein. After ABP stabilized for 10 minutes, a blood sample (0.25 mL) was collected from the arterial line into microcentrifuge tubes containing heparin (5 U) and centrifuged (10 000 g) immediately. Plasma osmolarity was determined in duplicate by freezing point depression (model 3320, Advanced Instruments), and plasma protein concentration was determined by protein refractometry (Refractometer Veterinary ATC, VWR International). Then, Evan’s Blue Dye (200 µL; 0.5%) was injected intravenously to determine plasma volume. After 5 minutes, a blood sample (0.5 mL) was collected from the arterial line as described above, and hematocrit was determined from duplicate capillary tubes. The remainder of the blood sample was centrifuged (10 000g, 1 minute), and 100 µL of plasma was diluted in 900 µL of isotonic saline. The absorbance was measured at 610 nm, and the values were compared with a standard curve using donor blood with known amounts of dye to calculate plasma volume. Blood volume was calculated as described elsewhere. For all of the samples, blood volume was replaced with isotonic saline. Catheters were removed, the incision sutured, and animals were returned to home cages for 1 week until RVLM microinjection experiments.

Microinjection into the RVLM

To determine whether RVLM neurons contribute to the elevated ABP in obesity hypertension, LF, OR, and OP rats were anesthetized with isoflurane (2% to 3% in 100% O2) and instrumented with catheters in the femoral artery and vein to measure ABP and administration of drugs, respectively. After tracheal cannulation, rats were ventilated with isoflurane, and end-tidal Pco2 was maintained between 4% and 5% by adjusting the ventilation rate (60 to 80 breaths per minute) or tidal volume (2 to 3 mL). Body temperature was maintained at 37±1°C by a water-circulating blanket. Animals were placed into a stereotaxic head frame with the incisor bar positioned 11 mm below the interaural line. A small portion of the occipital bone was removed, and the area postrema was visualized. Throughout these procedures, the level of anesthesia was examined by the lack of corneal reflexes, and the amount of isoflurane was adjusted accordingly. After all of the surgical procedures and a stable level of anesthesia was obtained, rats were paralyzed with a continuous infusion of gallamine triethiodide (25 mg/kg per hour at 25 µL/h in 5% dextrose), and RVLM injections were performed 15 minutes later.

A glass micropipette was angled 20° rostrally and lowered into the RVLM at the following coordinates with reference to the dorsal surface and caudal tip of the area postrema: 1.8 mm lateral, 1.8 mm rostral, and 2.9 mm ventral. Initially, the RVLM on each side was located functionally by a pressor response (>20 mm Hg) to microinjection of L-glutamate (1 nmol per 100 nL). It was common in these animals that the rostral coordinate was adjusted to 2.0 to 2.2 mm rostral to the caudal tip of the area postrema. The pipette was removed, rinsed with isotonic saline, and filled with the GABA_A receptor agonist muscimol. Once baseline variables stabilized for 10 minutes, muscimol (200 pmol per 100 nL per side) was microinjected into the left and right RVLM separated by 2 to 3 minutes. At least 5 minutes after the second muscimol injection, the ganglionic blocker hexamethonium (30 mg/kg, IV) was administered. At the end of experiments, microinjection sites were marked with 2% Chicago Sky Blue (100 nL).

Assessment of In Vivo Vascular Reactivity

After RVLM microinjection and ganglionic blockade with hexamethonium, vascular reactivity was assessed in LF, OR, and OP rats by multiple bolus injections of phenylephrine (0.3 to 100 µg/kg, IV) or norepinephrine (0.03 to 10 µg/kg, IV). Each dose was given in a randomized order, and the next dose was given when MABP returned to baseline levels. Baseline MABP values were sampled from the 30 s immediately before the bolus injection and compared with the 1-s peak response. MABP values were expressed as a percentage of the maximum response within each rat, and the ED50 was determined using Graph Pad Prism software.

Histology

At the end of all of the experiments, animals were euthanized with 5% isoflurane or 1 mL of saturated KCl. Epididymal and retroperitoneal fat pads were isolated and weighed in all of the animals. The adiposity index was calculated for each rat using the following equation: 100 × (epididymal fat + retroperitoneal fat)/(body weight – sum of epididymal and retroperitoneal fat pads). For microinjection experiments, brains were removed and immersed in 4% paraformaldehyde at 4°C for 1 week and then transferred to 30% sucrose. Brain stems were sectioned on a vibratome at 50 µm. All of the injection sites were confined to the RVLM as defined by the triangular region located 0 to 500 µm caudal to the caudal tip of the facial nucleus and bordered dorsally by nucleus ambiguous, medially...
ABP in Awake LF, OR, and OP Rats

Figure 1. Body weight and average daily caloric intake (kcal) as a function of time for LF, OR, and OP rats. A, Although baseline body weight did not differ among groups, OP had a significantly higher body weight than LF or OR rats by week 3 and remained significantly higher throughout the duration of the experiment. B, OP rats had a significantly greater daily caloric intake vs LF and OR rats. *Significant difference between OP vs LF and OR rats (P<0.01). †Significant difference between OP vs LF and OR rats (P<0.0001). # Significant difference within OP rats from week 0 (P<0.01). Values are mean±SEM.

Results

Body Weight, Food Intake, and Measurement of ABP in Awake LF, OR, and OP Rats

Initial body weight was not significantly different among LF, OR, and OP rats (Figure 1A). By week 3, there was a significant difference in body weight between OP versus LF and OR rats, and this effect was significantly greater by week 5 and throughout the remainder of the study. There was no difference in body weight between those rats used for blood pressure measurements in awake rats versus those used in microinjection experiments. In a subset of animals, we measured daily food and caloric intake. OP rats had a significantly higher daily caloric intake than LF and OR rats throughout the 13 weeks (Figure 1B). There was no difference in caloric intake between LF and OR rats.

Increases in body weight and caloric intake observed in OP rats were associated with greater accumulation of fat mass in the epididymal and retroperitoneal fat pads (Table). As expected, the adiposity indices were significantly greater in OP versus LF and OR rats (Table). There were no significant differences in body weight, fat pad mass, or adiposity indices between LF and OR rats.

In a subset of these rats, we measured ABP by 2 different methods: tail cuff and telemetry. Tail cuff did not reveal any significant differences in baseline mean ABP (MABP) or HR or any point during the study (data not shown). For example, there was no significant difference at 8 weeks in MABP (LF: 111±3 mm Hg; OR: 106±4 mm Hg; OP: 114±2 mm Hg; n=8 for all groups) or HR (LF: 412±9 bpm; OR: 420±6 bpm; OP: 415±4 bpm; n=8 for all groups). In contrast, telemetry recording of MABP during weeks 10 to 13 indicated a significant increase in 24-hour average MABP of OP rats versus LF or OR rats (LF: 103±3 mm Hg; OR: 102±4 mm Hg; OP: 111±3 mm Hg; P<0.05). HR did not differ among groups (LF: 368±9 bpm; OR: 365±11 bpm; OP: 377±12 bpm).

Plasma Osmolality and Protein Concentration, Hematocrit, and Plasma and Blood Volume in LF, OR, and OP Rats

There were no significant differences in plasma osmolality, plasma protein concentration, and hematocrit among LF, OR, and OP rats (Table). Similarly, we did not observe any significant differences in plasma or blood volume among LF, OR, and OP rats despite a significant difference in body weight (Table). When blood volume was normalized for 100-g body weight, OP rats had a significantly lower blood volume than OR rats. There was no significance difference between LF and OP rats.

By the inferior olive or pyradimal tracts, and laterally by the spinal trigeminal nucleus.30,31

Statistical Analysis

All of the data are expressed as mean±SEM. All of the variables were analyzed by an ANOVA with repeated measures when appropriate. When a significant F value was obtained, Fisher’s posthoc test (group variable) or paired t tests with a layered Bonferroni correction (within group) was used. For RVLM microinjection experiments, the peak response (30 s) was compared with a 5-minute baseline immediately before the first injection.
Effect of RVLM Inhibition on MABP and HR in LF, OR, and OP Rats

Initially, we functionally identified the RVLM by successfully evoking a pressor response to microinjection of L-glutamate. Injection of L-glutamate produced a significant increase in MABP of LF, OR, and OP rats that was not different among groups (31±5, 24±1, and 34±6 mm Hg, respectively).

If the RVLM contributes to the elevated sympathetic outflow and ABP in obesity-induced hypertension, then inhibition of the RVLM with the GABA<sub>A</sub> receptor agonist muscimol should produce a greater drop in MABP in OP versus LF or OR rats. Figure 2 shows examples of these responses in all 3 of the groups. Injection of muscimol into the left and right RVLM produced a precipitous fall in ABP and HR in LF, OR, and OP rats. Group responses are summarized in Figure 3. Baseline MABP was significantly elevated in OP versus LF and OR rats (Figure 3A). Inhibition of the RVLM significantly decreased MABP to similar levels across the groups, but the magnitude of the fall in MABP was significantly larger in the OP versus the LF or OR rats (Figure 3B). Administration of the ganglionic blocker hexamethonium did not further reduce MABP in any group (Figure 3).

Vascular Reactivity in LF, OR, and OP Rats

Intravenous bolus injection of phenylephrine produced dose-dependent increases in MABP in all 3 of the groups (Figure 4). These changes in MABP were not different whether these values were plotted as a function of the dose per body weight or amount of phenylephrine administered (Figure 4). When values were expressed as a percentage of the maximum change in MABP for each rat, the calculated ED<sub>50</sub> was not significantly different across groups as a function of body weight (LF: 13.8±2.0 μg/kg; OR: 15.0±2.7 μg/kg; OP: 12.2±1.5 μg/kg) or amount of phenylephrine (LF: 8.4±1.2 μg; OR: 10.5±1.8 μg; OP: 10.5±1.1 μg). Similarly, norepinephrine produced dose-dependent increases in MABP that were not different across LF, OR, and OP rats regardless of the dose per body weight or amount (Figure 5). Again, the ED<sub>50</sub> for norepinephrine was not different across groups as a function of body weight (LF: 1.4±0.1 μg/kg; OR: 1.4±0.2 μg/kg; OP: 1.4±0.1 μg/kg) or amount of norepinephrine (LF: 1.4±0.1 μg; OR: 1.7±0.2 μg; OP: 1.6±0.1 μg). These experiments were performed in ganglionic-blocked rats to remove baroreflex-induced compensations, and this was confirmed by the lack of any bradycardia during administration of phenylephrine and norepinephrine. In fact, both drugs significantly increase HR at higher doses (data not shown).

Discussion

Compelling evidence in both clinical studies and animal models indicates that elevated sympathetic nerve activity contributes to obesity-induced hypertension. However, the central neural mechanisms and pathways that support the elevated ABP in obesity are poorly understood. The present study demonstrates that neurons of the RVLM contribute to elevated sympathetic outflow and ABP in a rodent model of diet-induced obesity, and, therefore, provides the first identification of a central nervous system region that contributes to obesity hypertension.

The present experiments assessed the contribution of RVLM neurons to the elevated ABP in a rodent model of diet-induced obesity. Previous studies have demonstrated that feeding rats a moderately high-fat diet produces a differential weight gain profile that permits the segregation of OP and OR rats. This model has 2 advantages: the segregation of OP and OR rats allows studies to distinguish between the effects of obesity versus diet composition, and it closely mimics the neurohumoral and hemodynamic characteristics of human obesity, because OP rats have elevated cholesterol, insulin, leptin, activation of the renin–angiotensin and sympathetic nervous systems, and an elevated ABP. In the present study, we observed a clear segregation of OR and OP rats with the latter group characterized by a higher daily caloric intake, a significantly larger weight gain, greater accumulation of visceral fat mass (and higher adiposity...
index), and an elevated ABP. Although a recent report suggests that there is no difference in ABP in this rodent model, telemetry recording of MABP in the present study revealed a difference between OP versus LF or OR rats and is in agreement with the elevated ABP reported by several other laboratories.

RVLM neurons play a pivotal role in cardiovascular regulation. These neurons project to the spinal cord and

Figure 4. Vascular reactivity in vivo to phenylephrine (PE) was not different among LF, OP, and OR rats regardless of whether the changes in MABP were plotted as a function of (A) dose (micrograms per kilogram) or (B) amount (microgram) of PE. The calculated EC50 values were not different irrespective of dose or amount of PE. Values are mean ± SEM.

Figure 5. Vascular reactivity in vivo to norepinephrine (NE) was not different among LF, OP, and OR rats regardless of whether the changes in MABP were plotted as a function of (A) dose (micrograms per kilogram) or (B) amount (microgram) of NE. The calculated EC50 values were not different irrespective of the dose or amount of NE. Values are mean ± SEM.
directly innervate sympathetic preganglionic neurons in the thoracic and lumbar segments. We hypothesized that the elevated ABP in obese rats depends on the tonic activity of RVLM neurons. If this greater contribution of RVLM neurons to the elevated ABP was related to obesity rather than diet, then OP rats and not OR rats should display a greater drop in ABP compared with LF rats after inhibition of the RVLM. The present findings support this hypothesis, because injection of muscimol into the RVLM produces a significantly greater fall in the ABP of OP rats versus OR or LF rats. In addition, we confirmed that sympathetic outflow is elevated in OP rats via the RVLM, as ganglionic blockade did not further reduce MABP. Although sympathetic outflow could be equivalent among LF, OR, and OP rats, and the increased contribution of the RVLM to the elevated ABP in OP rats is reflected by an enhanced vascular reactivity to sympathetic input, we did not observe any difference in the ED50 of phenylephrine or norepinephrine among LF, OR, and OP rats. Therefore, our findings indicate that the elevated MABP in OP rats is due to a greater contribution of RVLM neurons. However, these findings do not necessarily demonstrate that the tonic activity of RVLM neurons is elevated in OP rats but does indicate that the tonic activity of RVLM neurons is necessary for the elevated ABP in obesity hypertension. Although stimulation of hypothalamic structures can increase sympathetic outflow and ABP after inhibition of the RVLM, ganglionic blockade did not further reduce ABP after inhibition of the RVLM, and this suggests that diet-induced obesity may directly activate RVLM to elevate ABP. The neural pathways underlie that activation of RVLM neurons in obesity hypertensive merits further investigation.

The activity of RVLM neurons and its contribution to sympathetic outflow and ABP is maintained by a balance of excitatory and inhibitory inputs. Previous studies have suggested that this balance shifts to an increased excitatory drive in rodent models of experimental hypertension associated with an elevated sympathetic outflow. For example, blockade of excitatory amino acid and angiotensin II type 1 receptors lowers ABP in the spontaneously hypertensive rat, Dahl salt-sensitive rat, and Goldblatt models of hypertension. In some models, this shift in excitatory balance is associated with an increase in the sensitivity of the RVLM to l-glutamate, but we did not observe a difference in glutamate-evoked pressor responses among LF, OR, and OP rats. Future studies are needed to identify whether the elevated ABP in obesity depends on excitatory amino acid and/or angiotensin II inputs or whether diet-induced obesity recruits a mechanism within the RVLM that is unique to this condition.

The mechanism(s) by which obesity activates the sympathetic nervous system to increase ABP is largely unknown, although hyperleptinemia has been postulated to play a significant role. Acute administration of leptin increases lumbar, renal, and brown adipose sympathetic nerve activity, whereas chronic administration of leptin increases ABP through activation of peripheral adrenergic receptors. The acute and chronic renal sympathoexcitatory effects of leptin are blocked by central administration of melanocortin-4 receptor antagonists or are eliminated in melanocortin-4 receptor knockout mice. Interestingly, acute administration of leptin reportedly increases the discharge of neurons in the region of the RVLM. A second mechanism that may activate the sympathetic nervous system in obesity is the peripheral renin–angiotensin system. In humans, plasma renin activity declines with weight loss and is correlated with the reduction in ABP. Furthermore, angiotensin II receptor blockade reduces sympathetic nerve activity in obese, hypertensive humans. Interestingly, administration of losartan through the drinking water produces a significantly greater fall in MABP of OP versus OR rats. Circulating angiotensin II acts at circumventricular organs to subsequently activate complex pathways, including those using central angiotensin II as a neurotransmitter, to increases sympathetic outflow. Whether these mechanisms, independently or in combination with others, underlie the increased contribution of the RVLM to the elevated sympathetic outflow and ABP in OP rats awaits further investigation.

**Perspectives**

Accumulating evidence in obesity indicates that elevated sympathetic outflow contributes to the elevated ABP. However, human obesity increases sympathetic outflow in a regionally specific manner to the kidney and hindlimb vasculature. Although much speculation remains about the afferent signal(s) that activate the sympathetic nervous system in obesity, the regional specificity of sympathetic outflow raises the question of whether any one of these signals selectively increases sympathetic nerve activity to the kidney and hindlimb vasculature. For example, acute administration of leptin to rats increases sympathetic nerve activity to brown adipose tissue, hindlimb vasculature, kidney, and adrenal gland. This general increase in sympathetic outflow does not seem to occur in human obesity, because clinical studies indicate that sympathetic outflow is increased to the kidney and hindlimb but decreased or unchanged in the heart and adrenal gland. Additional insight into the specific neuronal pathways and neurochemical phenotype of sympathetic-regulatory neurons that mediate selective activation of regional sympathetic outflow in obesity would represent an important step toward the development of centrally acting drugs for the treatment of the elevated ABP. The present study provides the first identification of a specific central nervous system region that contributes to the elevated ABP in obesity. Although obesity-induced hypertension is generally thought to occur from a sympathetically mediated increase in tubular sodium and water reabsorption, this study also suggests that a sympathetically mediated vasoconstriction and increase in vascular resistance contributes to obesity hypertension. Whether 1 or both mechanisms ultimately contribute to the long-term maintenance of hypertension in obese humans is not known.

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