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Exposure to a High-Fat Diet Alters Leptin Sensitivity and Elevates Renal Sympathetic Nerve Activity and Arterial Pressure in Rabbits

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Abstract—The activation of the sympathetic nervous system through the central actions of the adipokine leptin has been suggested as a major mechanism by which obesity contributes to the development of hypertension. However, direct evidence for elevated sympathetic activity in obesity has been limited to muscle. The present study examined the renal sympathetic nerve activity and cardiovascular effects of a high-fat diet (HFD), as well as the changes in the sensitivity to intracerebroventricular leptin. New Zealand white rabbits fed a 13.5% HFD for 4 weeks showed modest weight gain but a 2- to 3-fold greater accumulation of visceral fat compared with control rabbits. Mean arterial pressure, heart rate, and plasma norepinephrine concentration increased by 8%, 26%, and 87%, respectively ($P<0.05$), after 3 weeks of HFD. Renal sympathetic nerve activity was 48% higher ($P<0.05$) in HFD compared with control diet rabbits and was correlated to plasma leptin ($r=0.87$; $P<0.01$). Intracerebroventricular leptin administration (5 to 100 μg) increased mean arterial pressure similarly in both groups, but renal sympathetic nerve activity increased more in HFD-fed rabbits. By contrast, intracerebroventricular leptin produced less neurons expressing c-Fos in HFD compared with control rabbits in regions important for appetite and sympathetic actions of leptin (arcuate: −54%, paraventricular: −69%, and dorsomedial hypothalamus: −65%). These results suggest that visceral fat accumulation through consumption of a HFD leads to marked sympathetic activation, which is related to increased responsiveness to central sympathoexcitatory effects of leptin. The paradoxical reduction in hypothalamic neuronal activation by leptin suggests a marked "selective leptin resistance" in these animals.

Key Words: obesity-related hypertension ■ sympathetic nervous system ■ hypothalamus ■ leptin ■ leptin resistance ■ New Zealand white rabbit

Obesity is associated with an elevated risk of cardiovascular morbidity and mortality with both clinical and animal studies reporting a strong association between body weight and blood pressure.[1] Several candidate mechanisms are implicated in the development of obesity-related hypertension and include hemodynamic alterations, endothelial dysfunction, impaired renal-pressure natriuresis, and activation of the renin-angiotensin and sympathetic nervous systems (SNS).[2–4] Converging lines of evidence from animals[5,6] and humans[7,8] indicate that obesity is characterized by a marked sympathetic activation. In humans, norepinephrine spillover and sympathetic nerve recording have established a greater sympathetic outflow to the kidneys and skeletal muscle vasculature in obese subjects, whereas cardiac sympathetic nerve activity is reduced.[7–9] Despite these observations, convincing direct evidence for elevated renal sympathetic nerve activity (RSNA) in obesity-related hypertension is lacking, and it is unknown whether SNS activation occurs early in the process or secondary to long-standing obesity. To date, studies measuring RSNA related to high fat feeding in experimental animals have been performed under anesthesia using techniques that do not allow for RSNA comparisons between groups.[6,10,11]

Short-term feeding of a high-fat diet (HFD) to a rabbit produces many of the hemodynamic and hormonal changes that are characteristic of human obesity.[12] Rabbits readily accumulate adipose tissue, particularly visceral white adipose tissue (WAT), when exposed to an HFD.[13] In humans, abdominal visceral fat accumulation has been suggested to be a major risk factor for metabolic syndrome and cardiovascular disease.[14] The hypertension observed in HFD-fed rabbits is maintained by a shift in the pressure-natriuresis curve to the right with a similar slope indicating that HFD–fed rabbits do not become salt sensitive,[15] which is consistent with an

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elevated RSNA and subsequent increase in renin. Indeed, pharmacological blockade of the SNS during high-fat feeding attenuates the hypertension, reduces the tachycardia, and normalizes sodium balance.[5] Importantly, the rabbit provides a major advantage for measuring sympathetic changes in response to high-fat feeding, because we have established a method of normalizing nerve electrode characteristics in rabbits using the nasopharyngeal reflex that allows for comparisons between groups.[16] Hence, the first aim of the present study was to determine the cardiovascular and RSNA changes in rabbits in the first 3 weeks after commencing an HFD.

The factors that cause the elevation in sympathetic drive are clearly key to understanding the etiology of obesity-induced hypertension. The adipose-derived hormone leptin is thought to be a major mechanism linking excess adipose mass and hypertension.[17,18] Leptin exerts its pressor effects through its action at the hypothalamic nuclei that project to hindbrain centers, resulting in activation of the SNS.[19–21] Administration of leptin both acutely and chronically leads to increases in arterial pressure and heart rate (HR).[17,18] Intracerebroventricular (ICV) administration of leptin increases mean arterial pressure (MAP) and RSNA in rabbits.[22] Thus, elevated levels of circulating leptin associated with obesity[23] may contribute to the development of hypertension in response to high-fat feeding. To examine this hypothesis, we determined the effect of centrally administered leptin on cardiovascular variables and RSNA in HFD-fed rabbits and evaluated which hypothalamic and hindbrain nuclei are active after central administration of leptin using c-Fos as a marker of neuronal activation.

Methods

Animals

Experiments were conducted in 28 male New Zealand white rabbits (2.6 to 3.1 kg), housed under controlled light (6:00 AM to 6:00 PM) and temperature (22±2°C) conditions. Experiments were approved by the Alfred Medical Research Education Precinct Animal Ethics Committee and conducted in accordance with the Australian Code of Practice for Scientific Use of Animals.

Experimental Procedures and Protocol

Under isoflurane anesthesia, rabbits were implanted with an ICV cannula (22 gauge, Plastics One) into the lateral ventricle (coordinates from bregma; 3-mm lateral and 4-mm ventral), as described previously.[24] After 1-week recovery, baseline MAP and HR were measured via an arterial catheter. Rabbits were then randomized into 2 groups and meal fed 130 g of a normal fat diet (control; n=14) or an ad libitum HFD (n=14) for 4 weeks (please see the online Data Supplement at http://hyper.ahajournals.org for dietary details).

Two weeks after commencement of the diets, a recording electrode was implanted on the left renal nerve[25] under isoflurane anesthesia. One week later, MAP, HR, and RSNA were recorded (please see the online Data Supplement). After a 1-hour baseline recording, a 50-μL ICV injection of the vehicle (Ringer's solution, Baxter) was given, followed by increasing doses of leptin (5, 10, 50, and 100 μg; recombinant murine leptin 450-31, Pepro Tech, Inc) delivered ICV in 50 μL of vehicle at 30-minute intervals. A subset of animals (n=4 to 7 per group) was given the same dose of leptin IV to confirm that actions were centrally mediated or given a series of 4 ICV vehicle (50 μL) injections to control for the effects of time.

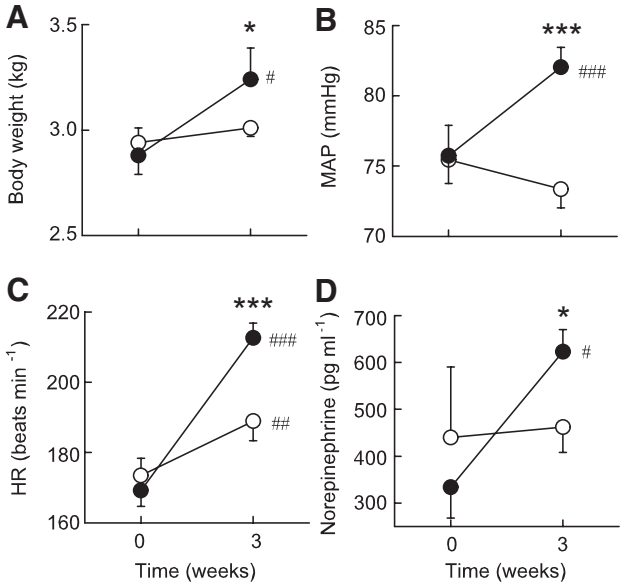

Figure 1. Body weight (A), MAP (B), HR (C), and plasma norepinephrine concentration (D) of rabbits before (week 0) and 3 weeks after commencement of control (○; n=11) or HFD (●; n=12). NB, norepinephrine was measured in 6 of the animals from each group. Error bars are SEM indicating variance between animals. #$P_{time}<0.05$, ##$P_{time}<0.01$, ###$P_{time}<0.001$ for week 0 vs week 3 within each group; *$P_{group}<0.05$, ***$P_{group}<0.001$ for control vs HFD at week 3.

Tissue and Blood Collection

After 4 weeks of diet, rabbits (control: n=9; HFD: n=7) were administered leptin (100 μg in 50 μL, ICV) or given a control Ringer's injection 90 minutes before being killed by an anesthetic overdose (sodium pentobarbitone: 100 mg/kg, IV) and transcardially perfused with 4% paraformaldehyde (please see the online Data Supplement).[26] WAT pads were dissected from the mesenteric viscera, the perirenal area, testicles, and bladder and weighed. Brains were removed (control: n=5; HFD: n=4) and coronally sectioned and processed for c-Fos immunohistochemistry.[26] Arterial blood samples were taken for measurement of plasma catecholamine concentrations by high-performance liquid chromatography[27] or leptin by radioimmunoassay (please see the online Data Supplement).

Data Analysis

MAP and HR derived from the ear artery pressure pulse were digitized online and averaged for over 2 seconds. RSNA was normalized to the maximum RSNA recorded during the nasopharyngeal response evoked by smoke, taken to be 100 normalized units.[16] Values averaged over 30 minutes were expressed as mean±SEM or mean difference±SE of the difference. Data were analyzed by split plot repeated-measures ANOVA, which allowed for within-animal and between-animal (group) contrasts and adjusted for multiple testing using the Bonferroni method. Correlation analysis was performed using a least-squares regression. Fat pad mass was analyzed using an independent t test. A probability of $P<0.05$ was considered significant.

Results

Effect of HFD on Body Weight and WAT

The initial body weight before the onset of the diets did not differ between groups ($P=0.6$; Figure 1A). Rabbits fed a HFD gained 367±90 g compared with 79±36 g in control rabbits with 3 weeks of diet ($P=0.002$; Figure 1A). HFD rabbits showed a 2- to 3-fold greater WAT weight compared

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Table. Weight of Fat Pads From Rabbits Fed a Control or HFD

WAT Depot	Control (n=7)	HFD (n=6)
Mesenteric WAT, g	26.02±2.35	75.71±16.45*
Mesenteric WAT, %BW	0.86±0.08	2.35±0.43*
Perirenal WAT, g	25.50±4.64	68.52±18.30*
Perirenal WAT, %BW	0.85±0.16	2.11±0.50*
Test/blad WAT, g	3.93±0.42	7.40±0.68*
Test/blad WAT, %BW	0.13±0.04	0.24±0.02†

BW indicates body weight; test/blad, testicular and bladder.
*$P_{group}<0.05$ for control vs HFD.
†$P_{group}<0.01$ for control vs HFD.

with control rabbits in absolute terms or when expressed as a percentage of body weight (Table).

Effect of HFD on MAP, HR, RSNA, Plasma Norepinephrine, and Plasma Leptin

Baseline MAP and HR at week 0 were similar between groups (Figure 1), but after 3 weeks on a HFD, both MAP and HR were elevated (8% and 26%, respectively; $P<0.001$). There was a small but significant increase in HR over 3 weeks in control rabbits (9%) but no change in MAP (Figure 1B). Thus, after 3 weeks, MAP and HR were markedly higher in HFD rabbits compared with control ($P<0.001$; Figure 1). Plasma norepinephrine concentration increased by 87% in rabbits after they were fed an HFD for 3 weeks ($P=0.011$; n=6) but did not change in control rabbits (Figure 1D). HFD rabbits had 49% higher plasma levels of leptin (3.0±0.3 ng/mL; n=11) compared with control animals (2.0±0.1 ng/mL; n=12; $P=0.009$).

After 3 weeks of diet, total RSNA, whether measured in raw microvolts or expressed relative to the nasopharyngeal response (normalized units) was 42% ($P=0.02$) and 48% ($P=0.015$) higher, respectively, in HFD rabbits compared with rabbits fed a control diet (Figure 2). RSNA burst amplitude was 50% greater in HFD rabbits compared to control ($P=0.017$). Although RSNA frequency did not differ between groups, frequency, when expressed per heartbeat, was less in HFD rabbits (Figure 2). There was no difference in the nasopharyngeal reflex between groups (control: 54±13 μV; HFD: 51±9 μV; $P>0.05$). Plasma leptin levels were linearly correlated with visceral fat, MAP, and RSNA ($r>0.8$; $P<0.05$; please see Figure S2 in the online Data Supplement).

Effect of Leptin on Cardiovascular Variables and RSNA

After 3 weeks of diet, MAP, HR, and RSNA responses to ICV administration of leptin at increasing doses (5, 10, 50, and 100 μg) were measured and calculated as changes from vehicle (Ringer's solution, 50 μL) administration. Injection

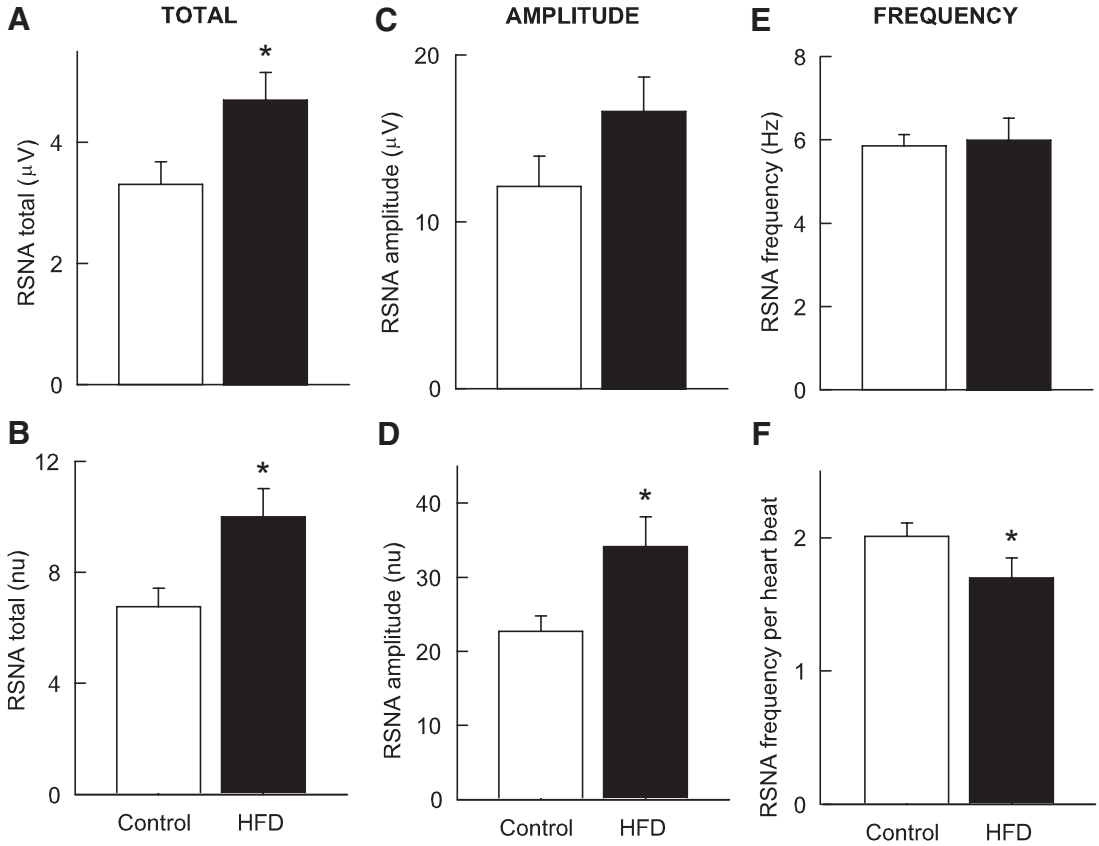

Figure 2. RSNA in total in microvolts (A), in normalized units (nu; B), RSNA amplitude in microvolts (C), in normalized units (D), frequency in bursts per second (E), and frequency per heartbeat (F) from rabbits fed a control (□; n=11) or a HFD (■; n=12) for 3 weeks. The maximum of the nasopharyngeal response was used for normalizing the data. Error bars are SEM indicating variance between animals. *$P_{group}<0.05$ for control vs HFD.

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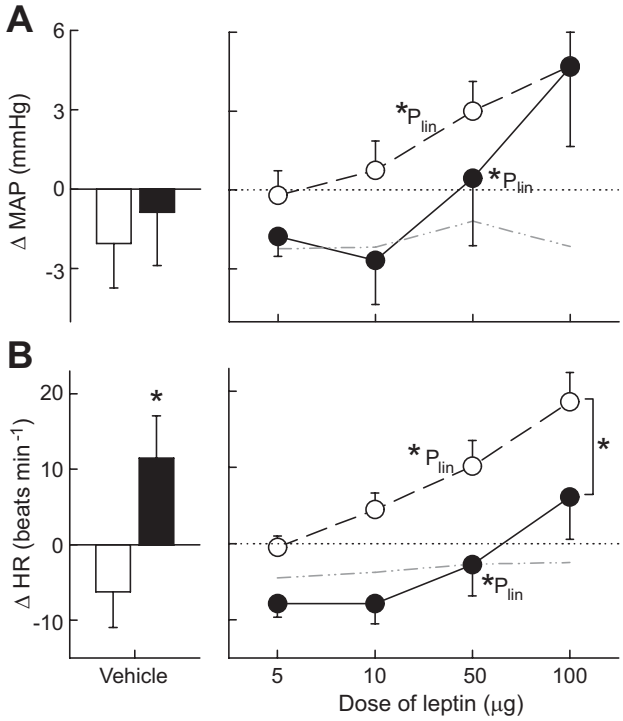

Figure 3. Left, Changes from baseline in MAP (A) and HR (B) after ICV administration of vehicle (Ringer's solution, 50 μL) in rabbits fed a control (□; n=14) or HFD (■; n=14) for 3 weeks. Right, 30-minute averages of the changes in MAP (top) and HR (bottom) from vehicle (left) after ICV administration of leptin to control (○) and HFD (●) rabbits. The gray dashed line represents a vehicle time control averaged from both groups. Error bars are SEM indicating variance between animals. *$P<0.05$ for comparison between groups. *$P_{lin}<0.05$ for significance of linear trend effect of leptin.

of vehicle had no statistically significant effect on parameters except for a 5% increase in HR from baseline in the HFD group ($P=0.02$; Figure 3). Subsequent vehicle administration (ICV) caused no further changes to MAP, HR, or RSNA (Figure 3). Leptin administration produced dose-dependant increases in MAP and HR in both groups, but the tachycardia in control rabbits was greater than that in HFD rabbits ($P_{groups}<0.001$; Figure 3). Leptin evoked dose-dependent increases in RSNA in HFD-fed rabbits (expressed as total, percentage total, and burst amplitude change from vehicle) and in the control rabbits only when total RSNA was expressed as a percentage change from vehicle (Figure 4). The leptin-induced increases in total RSNA were 5-fold greater in HFD rabbits compared with controls (Figure 4). Intravenous leptin administration (5, 10, 50, and 100 μg) did not produce any dose-dependent changes in MAP, HR, or RSNA in either group (Figure S3).

Effect of ICV Administration of Leptin on Hypothalamic c-Fos Activation

Representative photomicrographs through the rostral paraventricular nucleus of the hypothalamus (PVN) and medial preoptic nucleus are shown in Figure S4. After ICV leptin injection, rabbits fed an HFD had 30% to 50% fewer c-Fos-positive cells compared with control rabbits in all of the hypothalamic areas examined, except for the ventromedial hypothalamus (VMH), where a low number of c-Fos-positive cells was observed in both groups (Figure 5). There was very little activation by leptin within the medulla (Figure 5).

Discussion

The major findings of the current study are that short-term high-fat feeding in rabbits is associated with activation of the SNS, elevated blood pressure, and HR and that this occurred with only a modest increase in body weight but a large increase in WAT mass. Although the hypertension and tachycardia are consistent with previous observations,[5,15] the finding that high-fat feeding is associated with greater RSNA measured directly via a nerve recording in a conscious animal is novel. The increase in RSNA is attributed to increased sympathetic burst amplitude, suggesting either recruitment of sympathetic units or multiple firing within the burst of active fibers.[28] By contrast, the frequency of bursts was unchanged and actually decreased if the higher HR was considered (ie, bursts per heartbeat decreased in fat-fed rabbits). Because plasma norepinephrine concentrations were raised substantially in HFD–fed animals, the SNS activation may not be limited to the renal vasculature and may reflect SNS activation of other visceral beds as well. Hence, these findings provide direct evidence supporting the hypothesis that the activation of the SNS associated with high-fat feeding and WAT accumulation can contribute to the hypertension induced by obesity.

The mechanism may well involve central activation of sympathetic pathways by greater levels of leptin, because fat-fed rabbits had greater RSNA responses to ICV leptin compared with control rabbits, and there was a very strong relationship among plasma leptin, blood pressure, and RSNA. Interestingly, rabbits fed an HFD were observed to have a reduced number of cells expressing c-Fos in all of the hypothalamic nuclei activated by leptin including the arcuate nucleus (ARC), dorsomedial hypothalamus, and PVN, which are important in both the appetite and sympathetic actions of leptin. Taken together, these findings suggest that the general reduction of leptin-activated cells in the hypothalamus of HFD rabbits, which is indicative of a central leptin resistance, does not reflect those pathways mediating the cardiovascular and RSNA responses to leptin in these HFD animals. A number of studies have suggested that the nucleus of the solitary tract is a major sympatho-excitatory site of central leptin,[29,30] but we found little evidence in the current study suggesting that the nucleus of the solitary tract or other brain stem regions were activated, suggesting mainly a hypothalamic mechanism.

Evidence for "selective leptin resistance" first came from the agouti yellow obese mice, which showed preserved pressor actions of leptin despite resistance to the appetite and weight-reducing effects.[20,21] More recently, studies in diet-induced obesity in mice have revealed this same phenomenon.[10,11] However, these previous studies were conducted on anesthetized mice in which differences in baseline nerve activity cannot be accounted for, thus limiting the validity of comparing sympatho-excitatory responses between groups. The advantage of the current study is that experiments were

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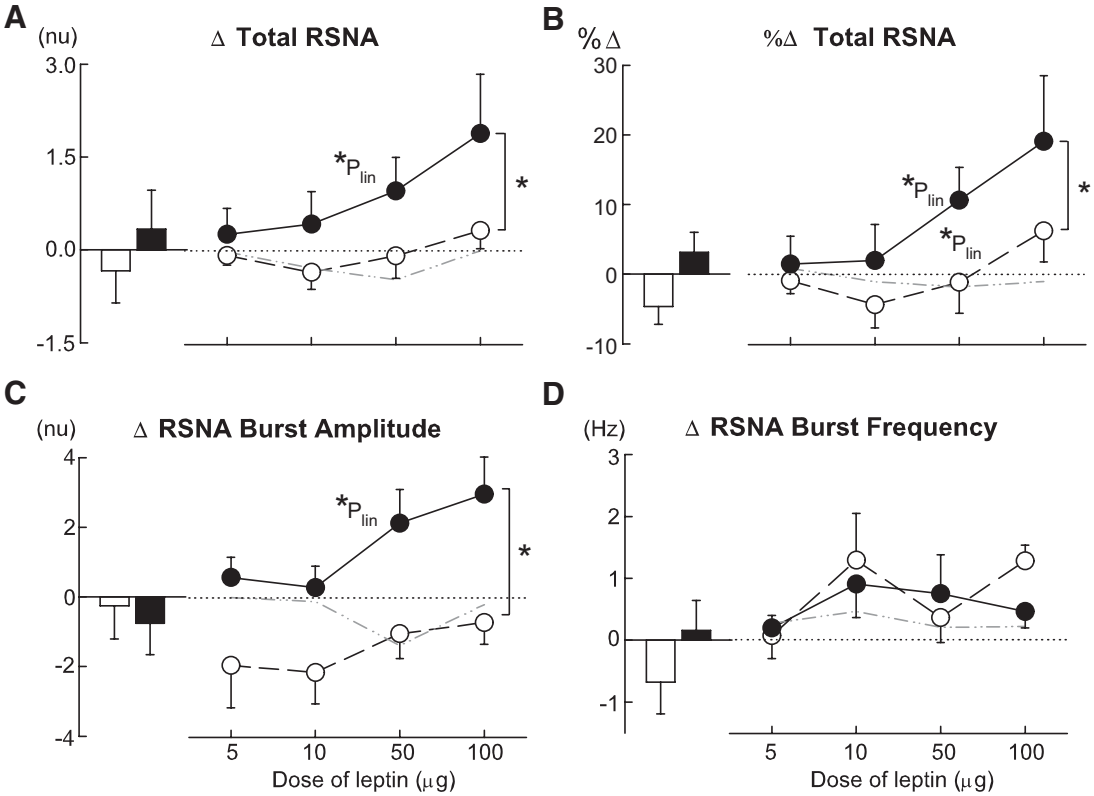

Figure 4. Changes (A) and percentage changes (B) in total RSNA, changes in sympathetic burst amplitude (C) and sympathetic burst frequency (D) from baseline after ICV administration of vehicle (Ringer's solution shown as bars in left part of panel) or increasing doses of leptin (shown as lines in right part of panel) in rabbits fed a control (□ and symbols; n=11) or HFD (■ and symbols; n=12) for 3 weeks. The gray dashed line represents a vehicle time control averaged from both groups. Error bars are SEM indicating variance between animals. *$P<0.05$ for comparisons between groups. *$P_{lin}<0.05$ for significance of linear trend effect of leptin.

conducted in conscious rabbits, allowing us to demonstrate that RSNA responses are actually markedly enhanced after feeding an HFD. Furthermore, only a short period of high-fat feeding in rabbits was required to invoke these changes, indicating that the sympathetic activation is pivotal in the development of hypertension rather than a secondary effect produced by long-standing obesity. This appears characteristic of the rabbit and is similar to previous studies where HFD led to an increase in MAP and HR after only 1 week of the diet.[15] This differs from previous studies of diet-induced obesity where selective leptin resistance was observed after prolonged fat feeding in mice.[10,11]

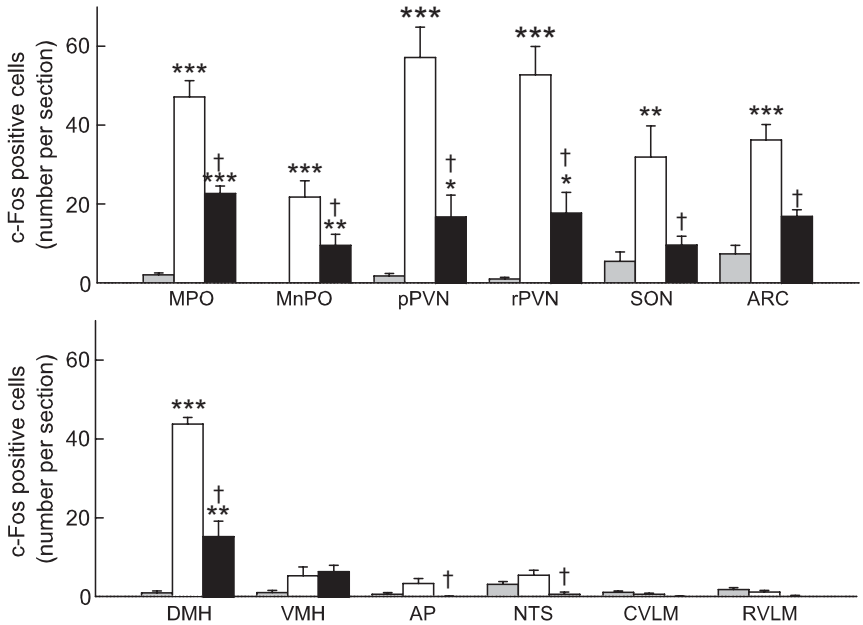

Figure 5. Mean number of activated neurons in regions of the hypothalamus and brain stem as detected by c-Fos immunoreactivity induced by ICV infusion of leptin (100 μg) in rabbits fed a control (n=3; □) or HFD (n=3; ■) for 4 weeks. Control injections of Ringer's (n=3; ▨). *$P<0.05$, **$P<0.01$, ***$P<001$ for effect of leptin compared with control injections. †$P<0.05$ for the effect of diet on response to leptin. Error bars are SEM, indicating between-animal variance. MPO indicates medial preoptic nucleus; MnPO, median preoptic nucleus; pPVN, periventricular paraventricular nucleus of the hypothalamus; rPVN, rostral paraventricular nucleus; SON, supraoptic nucleus; ARC, arcuate nucleus; DMH, dorsomedial hypothalamus; VMH, ventromedial hypothalamus; AP, area postrema; NTS, nucleus of the solitary tract; CVLM, caudal ventrolateral medulla; RVLM, rostral ventrolateral medulla.

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The contribution of the increased RSNA to the hypertension observed after an HFD may be via decreasing renal excretory function through increased renal tubular sodium reabsorption leading to renal sodium retention. In support of this, a recent study by Michaels et al[13] suggests this to be the case as well, where renal nerve stimulation in rabbits fed an HFD produced a greater antinatriuresis and lesser medullary blood flow compared with controls. Also the studies of Antic et al[5] showed that pharmacological blockade of the SNS prevented the rise of MAP in rabbits fed an HFD.

To assess the hypothalamic regions activated by leptin, immunoreactive staining for the c-Fos protein was used.[31] Consistent with previous findings, leptin administration activated nuclei in the hypothalamus of all animals, particularly in sites surrounding the median eminence, including the ARC, preoptic nucleus, and supraoptic nucleus, as well as the PVN and dorsomedial hypothalamus.[32,33] Neurons in these areas express mRNA for the long form of the leptin receptor, which is believed to mediate the physiological effects of leptin in the hypothalamus.[34] Interestingly, the number of c-Fos–activated neurons in HFD rabbits was lower than in control rabbits in all of the hypothalamic nuclei except the VMH, which exhibited very low levels of c-Fos staining in both groups. The overall pattern of activation reflected a generalized insensitivity to leptin at the level of the central nervous system in HFD-fed rabbits, which is consistent with the view that obesity leads to leptin resistance. No particular area activated by leptin showed greater or even similar levels of c-Fos staining, suggesting that the autonomic pathways activated, and that remain activated during a HFD, are few compared with the metabolic (appetite) actions of leptin in the hypothalamus. Importantly, the combination of the enhanced sympathetic responses to leptin and the reduced generalized activation of the hypothalamus to leptin in HFD rabbits suggest that the leptin resistance is selective for the noncardiovascular component of the response. To our knowledge, this is the first study to demonstrate a reduction in leptin-induced c-Fos activation in a large number of hypothalamic nuclei from animals fed an HFD. Previous studies using phosphorylated signal transducer activator of transcription 3 as a marker of activation have indicated that mice fed an HFD have selectively reduced leptin signaling in the ARC and not in other nuclei examined, including the VMH and dorsomedial hypothalamus, indicating that the ARC is the major site of leptin resistance.[35] This pattern of phosphorylated signal transducer activator of transcription 3 expression in the hypothalamus may be because of high levels of suppressor of cytokine signaling 3 activation that occurs selectively in the ARC of diet-induced obese mice.[35] Because the ARC c-Fos activation was decreased, the reduction in other hypothalamic nuclei may reflect less downstream activation. This contrasts the current study, where all of the hypothalamic nuclei showed leptin resistance and not just the ARC. However, the difference between studies may simply reflect the different routes of administration.

The c-Fos immunohistochemical technique does have limitations in that it only signals an acute increase in neuronal activity and is not necessarily a direct measure of neuronal cell activity. In the current context, the lesser Fos accumulation in an HFD animal may be attributed to higher levels of activity that are relatively static, and, thus, the administration of leptin is unable to activate the cells further. This is unlikely, because the detailed analysis of the ARC in terms of c-Fos levels, as well as signal transducer activator of transcription 3 and MAP kinase, suggest that preleptin levels of activation are relatively normal.[36]

One methodological issue is that we have used relatively high levels of leptin ICV compared with plasma levels. However, this appears to be required in all species studied. In mice, 1 μg is often given ICV,[37] in rats 4 to 5 μg[38,39] and 50 μg for rabbits.[22] Given the different brain sizes, this equates to very similar concentrations. Although the explanation for it is not known, it is likely to relate to the diffusion gradient from the cerebrospinal fluid to the site of action, because only nanogram doses are required when injected directly into nuclei.[40] Furthermore, it is not a given that the sites of action of leptin given ICV "transiently" are the same as when leptin concentrations are raised by an HFD. However, all of the regions studied except the VMH and the brain stem nuclei showed leptin resistance (by Fos), suggesting that they had been exposed to the higher leptin levels. A second issue is whether a doubling of the plasma levels of leptin induced by an HFD could be responsible for the higher sympathetic activity and blood pressure induced by the HFD. Studies in mice that have infused leptin peripherally at relatively high doses (0.2 μg/h) produced a 50% increase in plasma leptin (similar to the current study) over 30 days, resulting in a significant weight loss and leptin resistance. In a rabbit, this would equate to an infusion of 200 μg/h of leptin.[41] These findings, in addition to the very strong association between plasma leptin and RSNA in our study, strongly suggest that plasma leptin is likely to be responsible for the high blood pressure in our rabbit study.

Perspectives

The current study is the first to provide direct evidence that renal sympathetic outflow is elevated in response to high-fat feeding and increased visceral fat deposits. It establishes that activation of the SNS occurs early in the onset of obesity and most likely drives the hypertension seen in obesity. The mechanism is likely to involve a marked facilitation of the central sympathoexcitatory responses to leptin that occur in the presence of a generalized lesser responsiveness to leptin, as shown by the c-Fos accumulation in the hypothalamic nuclei. Alternate actions of leptin may also be involved, and the precise sites and mechanisms within the central nervous system by which the sympathetic responses to leptin are enhanced still require further research.

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Disclosures

None.

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