High-Fat Food, Sympathetic Nerve Activity, and Hypertension: Danger Soon After the First Bite?

Virginia L. Brooks and John W. Osborn

Hypertension. 2012;60:1387-1388; originally published online October 22, 2012;
doi: 10.1161/HYPERTENSIONAHA.112.201301
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0194-911X. Online ISSN: 1524-4563

Editorial Commentary

High-Fat Food, Sympathetic Nerve Activity, and Hypertension

Danger Soon After the First Bite?

Virginia L. Brooks, John W. Osborn

See related article, pp 1498–1502

Obesity is a rapidly escalating epidemic accounting for more than $150 billion per year in healthcare expenditures in the United States, more than any other medical condition. The consequences are severe. Obese humans exhibit increased incidence of type II diabetes mellitus, obstructive sleep apnea, hypertension, and regionally specific sympathoexcitation, in particular to the kidneys and legs.[1–4] However, whether increased sympathetic nerve activity (SNA) is a cause or a consequence of obesity has been debated.[3] Moreover, although obesity-induced hypertension is associated with increased SNA, the mechanisms are unclear.[1–4] Two recent articles[5,6] in *Hypertension* address these questions by characterizing the time course of the increases in SNA, monitored using telemetry, as lean animals initiate a high-fat diet (HFD).

In the article by Armitage et al,[5] male New Zealand white rabbits were instrumented for telemetric recordings of arterial pressure (AP) and renal SNA (RSNA). One week later, blood samples were collected for the measurements of glucose, insulin, and leptin, and basal levels of AP, heart rate (HR), and RSNA were measured in the laboratory. Rabbits were then randomized into 2 groups: 1 group was fed 110 g/d of standard rabbit chow (4.2% fat) and the other 190 g/d of a HFD (standard diet with 13.3% fat). Weekly measurements continued for 3 weeks and after a 1-week recovery period. After 1 week, HFD-fed rabbits exhibited elevations in AP (by 6%), HR (by 11%), and RSNA (by ≈50%), in association with increments in body weight, fat mass, and plasma glucose, insulin, and leptin levels. The increases in HR, RSNA, glucose, insulin, and leptin remained level for the subsequent 2 weeks, whereas body weight and AP increased further. Interestingly, during the recovery period, glucose, insulin, leptin, and HR returned to baseline; however, AP remained elevated and RSNA continued to increase.

In this issue of *Hypertension*, Muntzel et al[6] report similar findings from a study of female Wistar rats. AP, HR, and lumbar SNA (LSNA) were measured continuously by telemetry while the rats remained in their home cage. After 4 days of surgical recovery, 2 days of baseline measurements were followed by a 2-week period during which half the rats continued consumption of regular rat chow (4.5% fat); the second group also consumed a cafeteria-style HFD (average 23.4% fat). In the cafeteria diet-fed rats, LSNA increased such that it was ≈50% higher than control rats after 12 days of an HFD. However, AP did not increase significantly (P=0.09). At the end of the experiment, fasted cafeteria diet-fed rats exhibited increases in fat mass and plasma leptin levels; blood glucose concentrations were unaltered.

A key common feature of these studies was that SNA and AP were measured directly by telemetry before and after the initiation of a HFD, so that the time at which increases in SNA and AP first occurred could be pinpointed within animals. Direct longitudinal recording of SNA in experimental animals has been technically challenging because of the difficulty of maintaining the stability and fidelity of the signal. From that perspective, both studies are noteworthy because of the technical accomplishment and, therefore, their novel findings regarding increases in SNA induced by a HFD. In particular, before the study of Muntzel et al,[6] only 1 report of long-term continuous recordings of SNA in rats had been published. In that study,[7] RSNA and LSNA were recorded over a 28-day period in tethered rats using external amplifiers. Muntzel et al[6] are the first to report successful recordings (over 20 days) in nontethered rats using telemetry. However, each study also has limitations. In Armitage et al,[5] although AP and RSNA were measured by telemetry, the measurements were made only once a week in the laboratory and, therefore, the exact temporal pattern, as well as day/night changes in SNA, was not available. Indeed, these sporadic measurements may explain the failure to detect a significant increase in basal RSNA until week 3 of an HFD in the parallel set of baroreflex experiments. Moreover, SNA recordings eventually failed in a subset of the rabbits; therefore, correlations between SNA and other variables may have been affected. In the study of Muntzel et al,[6] it appears that measurements were initiated too soon after instrumentation (4 days), because the baseline for LSNA had not stabilized before initiation of the HFD period, although the normal chow rats controlled for this. In addition, their protocol did not include a recovery period to measure the off response of LSNA after returning to a normal diet.

Despite these drawbacks, each study reported 50% elevations in SNA as soon as 1 to 2 weeks after initiating the HFD, even with several substantial differences in experimental design, including the species, sex, recorded nerve, and the nature of the HFD. Importantly, parallel results have been reported in humans.[4] Lean young men were overfed ≈1000 kcal/d with a liquid dietary supplement, until

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

From the Department of Physiology and Pharmacology, Oregon Health & Science University, Portland, OR (V.L.B.); Department of Integrative Biology and Physiology, University of Minnesota, Minneapolis, MN (J.W.O.).

Correspondence to Virginia L. Brooks, Department of Physiology and Pharmacology, Oregon Health & Science University, L-334, 3181 SW Sam Jackson Park Rd, Portland, OR 97239. E-mail brooksv@ohsu.edu

(***Hypertension*. 2012;60:1387-1388.**)

***Hypertension* is available at http://hyper.ahajournals.org**
DOI:10.1161/HYPERTENSIONAHA.112.201301

they had gained ≈5 kg, after 10 to 12 weeks. Muscle SNA (MSNA) increased by 6 bursts/min (from 32±2 bursts/min), and significant increases in systolic AP of 3 to 4 mm Hg (but not diastolic AP) were observed. The increments in MSNA were correlated with the increases in body weight and in body fat and were associated with elevations in fasted plasma levels of leptin and in plasma renin activity but not plasma insulin concentration.

Given that such a short period of high-fat intake can trigger sympathoexcitation, what does this tell us about the mechanism? While correlative, all 3 studies observed parallel rapid increases in plasma leptin levels and visceral fat mass. Previous work also implicates a contribution from leptin, including studies showing that acute intracerebroventricular leptin infusion increases SNA, that chronic leptin infusion increases AP, and that leptin-deficient mice have normal AP despite massive obesity.[2,8] However, other studies refute a necessary role. Zucker rats[9] and db/db mice,[10] each of which has defective leptin receptors that lead to obesity, exhibit hypertension and sympathoexcitation. Moreover, intracerebroventricular infusion of a leptin antagonist failed to reverse hypertension in rats with diet-induced obesity, although it reversed the hypertension evoked by hypothalamic overexpression of leptin.[11] Finally, in humans, the increases in plasma leptin and MSNA are often not related.[1,3,4,12] Indeed, although subcutaneous fat is the major source of leptin, increased MSNA is observed only in men with increased visceral fat.[4] The 1-week recovery period after termination of the HFD in the study by Armitage et al[5] demonstrates a similar failure of RSNA and AP to track changes in plasma leptin; although leptin levels rapidly normalized, AP remained elevated and RSNA increased even more.

Do these data again counter a potential contribution of leptin (or other circulating sympathoexcitatory factors, like insulin)? Recent studies investigating obesity-induced changes in brain responsiveness to leptin leave the door open. Although the anorexic effects of leptin are clearly muted in obese individuals, the ability of leptin to increase SNA is preserved in mice.[8] In rabbits, the sympathoexcitatory effects of leptin are enhanced.[13] Therefore, the circulating levels of leptin or insulin would not accurately reflect the sympathoexcitatory potential of these hormones. The recovery period in Armitage et al[5] provides a clue as to the mechanism of this brain sensitization. Although circulating leptin and insulin fell, body weight and visceral fat content remained elevated. Therefore, it may be that a factor released from the dysfunctional adipose of obese rabbits, in particular from visceral fat, such as saturated free fatty acids, cytokines, or components of the renin-angiotensin system, acts centrally to enhance the effects of leptin.[14] Alternatively, during the initial stages of overnutrition, before the advent of systemic inflammation, the HFD itself may induce hypothalamic inflammation[15] and brain sensitization to circulating sympathoexcitatory factors. Regardless of the mechanism, this work emphasizes that, as in other hypertensive models, the cause of the sympathoexcitation and high AP is likely multifactoral.

Finally, although both studies indicate that obesity triggers sympathoexcitation (not the other way around) and implicate increased SNA in hypertension development, neither is entirely conclusive. Ideally, temporal changes in SNA and AP would be tightly linked. Moreover, functional evidence should establish a hypertensive role for increased SNA on end-organ function. In the study of Armitage et al,[5] although AP and RSNA did increase in parallel when rabbits initiated a HFD, they tended to dissociate during the last week of HFD and recovery. In the study by Muntzel et al,[6] LSNA increased by 50%, but AP was not significantly elevated, as has been commonly observed in obese humans. It is noteworthy that renal denervation ameliorates obesity-induced hypertension,[1,2] but it remains to be shown that increased MSNA contributes. Nevertheless, the documented links between elevated SNA and end-organ damage,[16,17] coupled with the results of these highlighted articles, suggest that increased dietary fat begins its insidious path to cardiovascular disease soon after the first bite.

Sources of Funding

We acknowledge fiscal support from National Institutes of Health HL 088552 and a Grant-in-Aid from the American Heart Association.

Disclosures

J.W. Osborn is a paid consultant for Medtronic Cardiovascular. The other author has no conflicts to report.

References

1. Esler M, Straznicky N, Eikelis N, Masuo K, Lambert G, Lambert E. Mechanisms of sympathetic activation in obesity-related hypertension. *Hypertension*. 2006;48:787–796.
2. Hall JE, da Silva AA, do Carmo JM, Dubinion J, Hamza S, Munusamy S, Smith G, Stec DE. Obesity-induced hypertension: role of sympathetic nervous system, leptin, and melanocortins. *J Biol Chem*. 2010;285:17271–17276.
3. Lambert GW, Straznicky NE, Lambert EA, Dixon JB, Schlaich MP. Sympathetic nervous activation in obesity and the metabolic syndrome: causes, consequences and therapeutic implications. *Pharmacol Ther*. 2010;126:159–172.
4. Davy KP, Orr JS. Sympathetic nervous system behavior in human obesity. *Neurosci Biobehav Rev*. 2009;33:116–124.
5. Armitage JA, Burke SL, Prior LJ, Barzel B, Eikelis N, Lim K, Head GA. Rapid onset of renal sympathetic nerve activation in rabbits fed a high-fat diet. *Hypertension*. 2012;60:163–171.
6. Muntzel MS, Al-Naimi OAS, Barclay A, Ajasin D. Cafeteria diet increases fat mass and chronically elevates lumbar sympathetic nerve activity in rats. *Hypertension*. 2012;60:1498–1502.
7. Yoshimoto M, Miki K, Fink GD, King A, Osborn JW. Chronic angiotensin II infusion causes differential responses in regional sympathetic nerve activity in rats. *Hypertension*. 2010;55:644–651.
8. Rahmouni K. Leptin-induced sympathetic nerve activation: signaling mechanisms and cardiovascular consequences in obesity. *Curr Hypertens Rev*. 2010;6:104–209.
9. Huber DA, Schreihofer AM. Attenuated baroreflex control of sympathetic nerve activity in obese Zucker rats by central mechanisms. *J Physiol (Lond)*. 2010;588(pt 9):1515–1525.
10. Goncalves AC, Tank J, Diedrich A, Hilzendeger A, Plehm R, Bader M, Luft FC, Jordan J, Gross V. Diabetic hypertensive leptin receptor-deficient db/db mice develop cardioregulatory autonomic dysfunction. *Hypertension*. 2009;53:387–392.
11. Tümer N, Erdös B, Matheny M, Cudykier I, Scarpace PJ. Leptin antagonist reverses hypertension caused by leptin overexpression, but fails to normalize obesity-related hypertension. *J Hypertens*. 2007;25:2471–2478.
12. Gentile CL, Orr JS, Davy BM, Davy KP. Modest weight gain is associated with sympathetic neural activation in nonobese humans. *Am J Physiol Regul Integr Comp Physiol*. 2007;292:R1834–R1838.
13. Prior LJ, Eikelis N, Armitage JA, Davern PJ, Burke SL, Montani JP, Barzel B, Head GA. Exposure to a high-fat diet alters leptin sensitivity and elevates renal sympathetic nerve activity and arterial pressure in rabbits. *Hypertension*. 2010;55:862–868.
14. Cai D, Liu T. Inflammatory cause of metabolic syndrome via brain stress and NF-κB. *Aging (Albany NY)*. 2012;4:98–115.
15. Thaler JP, Yi CX, Schur EA, et al. Obesity is associated with hypothalamic injury in rodents and humans. *J Clin Invest*. 2012;122:153–162.
16. Fisher JP, Young CN, Fadel PJ. Central sympathetic overactivity: maladies and mechanisms. *Auton Neurosci*. 2009;148:5–15.
17. Lambert E, Sari CI, Dawood T, Nguyen J, McGrane M, Eikelis N, Chopra R, Wong C, Chatzivlastou K, Head G, Straznicky N, Esler M, Schlaich M, Lambert G. Sympathetic nervous system activity is associated with obesity-induced subclinical organ damage in young adults. *Hypertension*. 2010;56:351–358.