High fat food, sympathetic nerve activity and hypertension: Danger soon after the first bite?

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Obesity is a rapidly escalating epidemic accounting for over $150 billion per year in health care expenditures in the U.S, 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 (for reviews, see[1–4]). However, whether increased sympathetic nerve activity (SNA) is a cause or a consequence of obesity has been debated.[3] Moreover, while obesity-induced hypertension is associated with increased SNA, the mechanisms are unclear.[1–4] Two recent papers[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 paper 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 measurements of glucose, insulin and leptin, and basal levels of AP, HR and RSNA were measured in the laboratory. Rabbits were then randomized into 2 groups; one group was fed 110 g/day of standard rabbit chow (4.2% fat) and the other 190 g/day 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%), heart rate (HR; by 11%), and RSNA (by ~50%), in association with increments in body weight (BW), fat mass, and plasma glucose, insulin and leptin. The increases in HR, RSNA, glucose, insulin, and leptin remained level for the subsequent 2 weeks, while BW and AP increased further. Interestingly, during the recovery period, glucose, insulin, leptin and HR all returned to baseline; however, AP remained elevated and RSNA continued to increase.

In this issue of *Hypertension*, Muntzel *et al* 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 a 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 due to 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, prior to the study of Muntzel *et al*, only one 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* are the first to report successful recordings (over 20 days) in non-tethered rats using telemetry. However, each study also has limitations. In Armitage *et al*,[5] even though 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, were not available. Indeed, these sporadic measurements may explain the failure to detect a significant increase in basal RSNA until week 3 of a 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* it appears that measurements were initiated too soon after instrumentation (4 days) as the baseline for LSNA had not stabilized prior to initiation of the HFD period, although the normal chow rats control for this. Also, 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 1–2 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/day with a liquid dietary supplement, until they had gained ~5 kg, after 10–12 wk. Muscle SNA (MSNA) increased by 6 burst/min (from 32±2 bursts/min), and significant increases in systolic AP of 3–4 mmHg (but not diastolic AP) were observed. The increments in MSNA were correlated to the increases in BW 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 three 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 (icv)

leptin infusion increases SNA, that chronic leptin infusion increases AP, and that leptin-deficient mice have normal AP despite massive obesity (for reviews, see[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 leads to obesity, exhibit hypertension and sympathoexcitation. Moreover, icv infusion of a leptin antagonist failed to reverse hypertension in rats with diet-induced obesity, even though 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, while subcutaneous fat is the major source of leptin, increased MSNA is observed only in men with increased visceral fat.[4] The 1-wk recovery period following termination of the HFD in the study by Armitage *et al* demonstrates a similar failure of RSNA and AP to track changes in plasma leptin: while 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. While 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* provides a clue as to the mechanism of this brain sensitization. While circulating leptin and insulin fell, BW 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*, 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 Muntzel study, 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 muscle SNA contributes. Nevertheless, the documented links between elevated SNA and end organ damage,[16;17] coupled with the results of these highlighted papers, suggest that increased dietary fat begins its insidious path to cardiovascular disease soon after the first bite.

Acknowledgments

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