

## Obesity, Sympathetic Overdrive, and Hypertension The Leptin Connection

Kamal Rahmouni

If not reversed, the steady rise in overweight and obesity is expected to become the leading cause of death and to outweigh the health benefits resulting from improved therapies and cardiovascular risk management and continued reductions in the prevalence of behavioral risk factors, such as smoking.<sup>1</sup> Indeed, obese patients often develop diabetes mellitus and have increased cardiovascular risk factors, including hypertension.

The discovery of the adipocyte-derived hormone leptin brought a new perspective to the pathophysiological mechanisms of obesity and associated diseases. Initial studies of leptin showed that it regulates appetite and enhances energy expenditure by activating sympathetic nerve activity to thermogenic brown adipose tissue. Additional studies demonstrated that leptin also causes sympathetic excitation to the kidney that, in turn, increases arterial pressure.<sup>2</sup>

Prior et al,<sup>3</sup> in the present issue of *Hypertension*, provide compelling evidence implicating leptin in obesity-associated cardiovascular adverse effects. These authors first performed a longitudinal analysis of the hemodynamic parameters and sympathetic tone in diet-induced obese rabbits. Importantly, sympathetic nerve activity was assessed using several approaches, including multifiber recording in the conscious state. As expected, the development of obesity was associated with an increase in arterial pressure and heart rate. The obese rabbits also exhibited higher sympathetic tone, as indicated by the elevated plasma catecholamines and renal sympathetic nerve activity. These data demonstrate a close relationship among excessive adiposity, hypertension, and overactivity of renal sympathetic nerves. Overactivity of the sympathetic nervous system is a common feature of obesity in humans. Study of regional sympathetic activity in obese humans using norepinephrine spillover has demonstrated that obesity is associated with increased sympathetic nerve traffic to the kidney.<sup>4</sup> The critical role of the renal nerves in obesity-induced hypertension has also been demonstrated using bilateral renal denervation in dogs.<sup>2</sup> However, the mechanisms responsible for the renal sympathetic activation in obesity have remained elusive.

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From the Center on Functional Genomics of Hypertension, Department of Internal Medicine, University of Iowa Carver College of Medicine, Iowa City, Iowa.

Correspondence to Kamal Rahmouni, Center on Functional Genomics of Hypertension, Department of Internal Medicine, University of Iowa Carver College of Medicine, 3135C MERF, Iowa City, IA 52242. E-mail kamal-rahmouni@uiowa.edu

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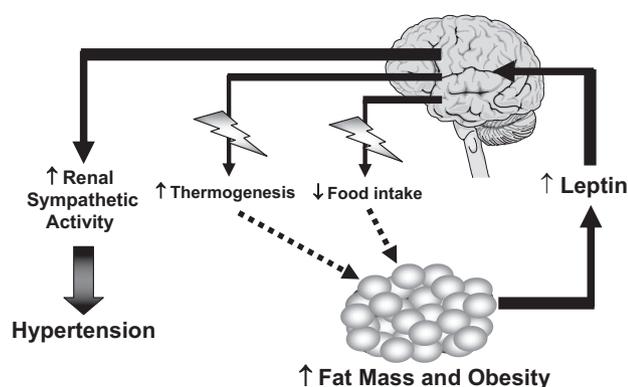
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Prior et al<sup>3</sup> found a strong relationship between plasma leptin concentrations and renal sympathetic nerve activity in rabbits. These findings recapitulate the robust correlation between circulating levels of leptin and renal sympathetic tone described previously across a broad range of leptin values in men with various degree of adiposity,<sup>5</sup> indicating that leptin is a key determinant of obesity-associated renal sympathetic activation. To demonstrate this, the authors examined the ability of exogenous leptin to increase arterial pressure and renal sympathetic traffic in obese rabbits and lean controls. The dose-dependent arterial pressure increase in response to leptin was comparable between the obese and lean animals. Leptin also caused a dose-related renal sympathetic excitation, but this response was more pronounced in the obese animals. These findings further support a pathophysiological role of leptin in obesity-associated hypertension and renal sympathetic overdrive.

Although Prior et al<sup>3</sup> did not assess the anorectic and weight-reducing actions of leptin in the obese rabbits, the increased circulating levels of leptin indicate that these animals may be resistant to the metabolic effects of leptin. Together, these results confirm and extend the concept that leptin resistance in obesity is selective, which originated from studies with several mouse models of obesity, including diet-induced obesity (Figure). Preservation of the regional sympathetic nerve responses to leptin is not uniform but is instead specific to the kidney,<sup>6</sup> supporting the conclusion that leptin regulates regional sympathetic outflow to various tissues in a highly differential manner.

Additional evidence for the critical role of leptin in obesity-related hypertension and sympathetic overdrive derives from studying 3 mouse models of a human obesity syndrome, Bardet-Biedl syndrome (BBS).<sup>7</sup> Although all 3 of the BBS mouse models were obese and resistant to the metabolic actions of leptin, the ability of leptin to increase renal sympathetic activity was preserved in BBS4 and BBS6 but not in BBS2 null mice. Consequently, BBS4 and BBS6 null mice showed higher baseline renal sympathetic tone and arterial pressure and a greater reduction in arterial pressure in response to ganglionic blockade. The findings on arterial pressure in the 3 mouse models of BBS parallel observations in humans where patients with several BBS genotypes, including BBS4 and BBS6, were found to be accompanied by hypertension, except for patients with BBS2 who remain normotensive (see Reference 7).

Additional analysis of the mouse models of BBS demonstrated that hyperleptinemia causes the increase in arterial pressure and renal sympathetic activity in BBS4 and BBS6 knockout mice, because fasting-induced decreases in plasma leptin normalized arterial pressure and renal sympathetic



**Figure.** Selective leptin resistance helps explain how high levels of circulating leptin in obesity may contribute to hypertension and sympathetic overdrive despite resistance to metabolic effects of this hormone. Long-term renal sympathetic stimulation caused by high leptin levels could raise renal sympathetic tone leading to hypertension, whereas loss of leptin's ability to decrease food intake and increase thermogenesis promotes obesity by increasing adiposity.

tone.<sup>7</sup> In contrast, arterial pressure and renal sympathetic activity remained elevated in BBS4 and BBS6 knockout mice when chronic hyperleptinemia was maintained by exogenous administration of leptin in these mice during fasting.

As in BBS2 null mice, the lack of renal sympathetic response to leptin in melanocortin 4 receptor knockout mice is associated with loss of arterial pressure response to leptin and absence of hypertension despite obesity.<sup>2</sup> Consistent with these data in rodents, a recent study demonstrated that human subjects carrying a mutation in the melanocortin 4 receptor are protected against hypertension and sympathetic overdrive, which are commonly associated with obesity.<sup>8</sup>

Despite the increasing evidence implicating hyperleptinemia in obesity-induced hypertension, the mechanisms enabling leptin to cause a normal (or enhanced) increase in renal sympathetic outflow and arterial pressure in spite of the resistance to its metabolic actions in obesity have not been identified. Prior et al<sup>3</sup> show that obese rabbits have significantly impaired leptin-induced *c-fos* activation in nearly all of the brain regions analyzed, including the hypothalamus and brain stem. At first glance, these findings seem to exclude the possibility that the preservation of the renal sympathetic nerve and arterial pressure responses to leptin in obesity occurs because some brain nuclei remain leptin sensitive. However, *c-fos* is not a specific indicator of leptin receptor signaling but rather is considered as a transient and generic marker of neuronal activation, which may not be expressed in chronically activated neurones.<sup>9</sup>

A previous study in mice demonstrated that impairment in leptin receptor signaling in diet-induced obesity was restricted to the hypothalamic arcuate nucleus.<sup>10</sup> Although leptin activation of signal transducer activator of transcription 3 was dramatically reduced in the arcuate nucleus, other

hypothalamic and extrahypothalamic nuclei, including the nucleus tractus solitarius, remained leptin sensitive in mice with diet-induced obesity. Consistent with this, the expression level of suppressor of the cytokine signaling 3 protein, a molecular that attenuates leptin receptor signaling, was specifically increased in the arcuate nucleus of diet-induced obese mice.<sup>10</sup> Thus, it is possible that selectivity in leptin resistance is caused by the inability of leptin to activate downstream signaling pathways in the arcuate nucleus but preservation of leptin actions in other cardiovascular-related brain areas. Selective leptin resistance could also occur as a result of differential disruption of the molecular pathways downstream of the leptin receptor.

The study by Prior et al<sup>3</sup> reinforces the evidence implicating leptin in obesity-associated sympathetic overdrive and hypertension and suggests that elucidation of the mechanisms for preservation of the renal sympathetic nerve and arterial pressure responses to leptin in diet-induced obesity might advance substantially our understanding of the cardiovascular and metabolic complications of obesity and the metabolic syndrome.

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### Disclosures

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