Leptin Beyond the Lipostat
Key Component of Blood Pressure Regulation

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Leptin Mediates the Increase in Blood Pressure Associated With Obesity
Simonds et al
Cell. 2014;159:1404–1416

Obese individuals often struggle with increases in blood pressure (BP) that ultimately lead to an enhanced cardiovascular disease (CVD) risk. The mechanistic basis for this association has remained largely unknown. Although a large number of metabolic signals are altered in obese individuals, including dyslipidemia, associated changes in sphingolipids, and an overall increase in subclinical inflammation, none of these parameters are thought to greatly influence BP. Recent data suggest that the adipokine leptin, whose circulating levels are typically proportional to fat mass, is a major driving force for the obesity-associated increases in BP. The effects of leptin on BP are mediated by neuronal circuits, including leptin-responsive neurons in the dorsomedial hypothalamic (DMH) nucleus.

Obesity is a widespread global health burden. It is intuitively obvious that obesity is a direct consequence of an imbalance between energy intake and energy expenditure, resulting in gross expansion of adipose tissue and an associated increase in BP, which is a major contributor to chronic hypertension and the risk for CVD-related mortality. The obese state is associated with dysfunctional adipose tissue exhibiting an abnormal secretory profile of bioactive adipokines; this contributes to impaired regulation of appetite, an unfavorable adipose tissue distribution, reduced insulin sensitivity, endothelial dysfunction, inflammation, and an elevation in BP.

Last year marked the 20th anniversary since the discovery of leptin from rodent adipose tissue in 1994 by Zhang et al. Leptin is a pleotropic hormonal signal that exhibits numerous neurobiological and physiological functions that regulate food intake, energy expenditure, fat mass, fertility, reproductive function, and atherogenesis.

Central Actions of Leptin
Studies over the decades have established a key role for the central nervous system in sensing, integrating, and regulating metabolic tone, with recent findings identifying the importance of specific hypothalamic circuits as key sites of leptin action. Much emphasis has been placed on effects on the melanocortin system with populations of proopiomelanocortin and agouti-related protein neurons in the arcuate nucleus, and to a lesser extent, neurons expressing leptin receptors in other sites including the ventromedial and dorsomedial nuclei. Nutrient and hormonal adiposity signals, such as insulin and leptin, communicate with central regions to regulate energy balance and to coordinate glucose and lipid homeostasis. In particular, leptin binds the long form of its receptor (LepR) in several neuronal populations to activate the Janus kinase 2/signal transducer and activator of transcription 3 (JAK2-STAT3) signaling pathway, to orchestrate energy intake and expenditure. Leptin activates proopiomelanocortin neurons in the arcuate nucleus and enhances the levels of the anorectic peptide α-melanocyte-stimulating hormone (the endogenous agonist of the melanocortin 4 receptor), while inhibiting agouti-related protein neurons. Mice selectively deficient for LepRs in proopiomelanocortin neurons exhibit modest obesity caused by a decrease in energy expenditure, independent of alterations in food intake. Conversely, re-expression of LepRs specifically in proopiomelanocortin neurons results in only moderate body weight improvements, however, restores normoglycemia.

Hypertensive Effects of Central Leptin Action
Leptin has been implicated in the pathogenesis of diet-induced obesity (DIO)–associated hypertension. The majority of studies pinpoint the central melanocortin system in obesity-induced sympathoexcitation as a critical site of action of the hypertensive effects of leptin. Specifically, pharmacological administration or transgenic overexpression of leptin elevates systolic BP (SBP) in rodents. In contrast, obese leptin-deficient ob/ob mice exhibit markedly lower BP than their lean controls. Taken together, these studies suggest that the central hypothalamic actions of leptin contribute substantially to DIO-induced elevations in BP.

In terms of specific anatomic regions of the brain mediating these leptin effects on BP, do Carmo et al reported that Shp2 deficiency in proopiomelanocortin neurons attenuates the ability of leptin to increase BP and improve glucose homeostasis. Interestingly, several studies have suggested that melanocortin 4 receptors are also key regulators of BP. The elegant study by

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DOI: 10.1161/CIRCRESAHA.115.305937.)
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Circulation Research is available at http://circres.ahajournals.org
DOI: 10.1161/CIRCRESAHA.115.305937
Simonds et al in the December 2014 issue of *Cell* adds another hypothalamic site to the list and highlights the DMH region of the brain as an important site in the regulation of cardiovascular sympathetic responses to leptin during DIO. Specifically, using a series of refined time-courses, the group demonstrated that DIO drives an increase in systemic leptin levels before an increase in heart rate and BP, implicating leptin-responsive neurons in the DMH as key upstream regulators of hypertension. Subsequent inhibition of leptin signaling either through intraperitoneal injection of an anti-leptin antibody or through injection of a leptin receptor antagonist into the DMH of DIO hypertensive mice effectively lowered the elevated heart rate and SBP. The authors also performed a plethora of experiments confirming that the underlying mechanism for the hypertensive actions of leptin in DIO mice is the leptin-driven depolarization of DMH neurons. A LepR knockdown or a targeted LepR knockout in the DMH of DIO mice lowers SBP. The strength of the genetic approach used is that the authors used technology that permits silencing of endogenous LepR activity in a highly specific neuronal population. Reactivation of LepRs (through injection of AAV-Cre recombinase into the DMH of obese normotensive LepR-null mice that carry a floxed transcriptional silencer element) increased heart rate and SBP. Multiple targeted gain and loss of function approaches were, therefore, used in this context to pinpoint the exact site of leptin action in the brain vis-à-vis its effects on BP.

**Selective Leptin Resistance in DIO**

Leptin resistance is a term widely used to define states in which hyperleptinemia, as seen in obesity, results in reduced responses to leptin. Although leptin has a wide array of effects, this term is typically used in the context of reduced responses with respect to the anorexic effects of leptin. Albeit the precise mechanisms underlying leptin resistance remain only partially understood, inhibition and desensitization of central and peripheral leptin signaling in specific neuronal subsets, the inability of leptin to cross the blood brain barrier, in addition to oxidative stress and inflammatory events, have been suggested as possible steps leading to ineffective leptin action. Specific brain regions are implicated, in particular the hypothalamic arcuate nucleus, as a critical mediator of the metabolic sympathetic actions of leptin. SOCS3-mediated resistance to the effects of leptin on JAK2-STAT3 activation in proopiomelanocortin neurons, as well as the arcuate nucleus and the ventral tegmental area, are known to exhibit DIO-associated leptin resistance.

Notably, the paradigm of selective leptin resistance has emerged over the years. Leptin action on BP represents a prime example of selective resistance: hyperleptinemia-driven elevations in BP and cardiovascular/renal sympathetic responses are preserved, despite complete attenuation of the anorectic actions of leptin in regulating food intake, bodyweight and brown adipose tissue thermogenesis. Such studies have raised the question as to how leptin can contribute to an elevation in BP during DIO-induced hyperleptinemia, whereas many other leptin-mediated effects are impaired because of resistance? How can this differential leptin sensitivity in the areas of cardiovascular/renal SNA responses versus the metabolic anorexic actions exist simultaneously? Would they be selective based on the severity of DIO and the circulating concentrations of leptin? Indeed, one plausible explanation for the DIO-related leptin resistance phenomenon may be the existence of site-specific selective leptin resistance in the brain, such that different neuronal populations are activated and others desensitized depending on the extent of DIO. Matheny et al reported DIO-driven leptin resistance in the arcuate nucleus and the ventral tegmental area, whereas several medial basal hypothalamic regions remained sensitive to the hormone. On examination of other brain regions, the DMH neuronal population has garnered attention over the years as an under-appreciated site of leptin action and serves as likely candidate for selective central leptin resistance. In light of this, Zhang et al recently documented that LepR-expressing neurons in the DMH are critical in circuits mediating brown adipose tissue thermoregulation.

With the focus on the findings by Simonds et al, how do these results relate to the selective leptin resistance paradigm? In particular, while the authors describe activation of cardiovascular SNA responses to leptin via the DMH leading to elevation of BP in DIO mice, did the authors further observe any loss in the metabolic anorexic effects of leptin? Interestingly, antagonism or reducing the levels of the LepR in DIO mice produced no significant differences in food intake or body weight changes. This indicates that leptin-responsive anorectic pathways are unaffected (presumably mainly in the hypothalamus), while hypertensive leptin-induced signaling responses in the DMH are heightened. This also suggests that the LepR-expressing neurons localized to the DMH are not critical for the effects of leptin on body weight. Collectively, the study by Simonds et al illustrates the notion of site-specific selective leptin resistance in differential brain regions elegantly. Consistent with these observations, Marsh et al reported that injection of leptin into the DMH increases heart rate and BP; however, fails to enhance renal SNA. Studies like this pinpoint the DMH as a key site for leptin-driven increases in and brown adipose tissue and cardiovascular, but not renal SNA activity, and overall provide sophisticated examples of selective leptin resistance in anatomically distinct regions of the brain. Shp2 and PI3K signaling pathways in proopiomelanocortin neurons have also been identified to contribute to the renal sympathetic and BP actions of leptin, independent of leptin-induced regulation of body-weight and appetite. In contrast, JAK2-STAT3 signaling has been implicated in sympathetic metabolic control, however, does not contribute to renal sympathetic activity. Selective leptin resistance may, therefore, entail distinct leptin signal transduction pathways that seem to produce differential regulation of sympathetic metabolic versus sympathetic cardiovascular/renal function. Additional studies will have to delineate the precise molecular mechanism and brain site-specific regions, in addition to the subpopulations of neurons responsible for the central pathway-specific selective leptin resistance phenomenon.

**Central Leptin Action and BP in Humans**

Despite the extensive literature on the effects that leptin has on BP in animal models of DIO and leptin deficiency, studies
investigating the hypertensive actions of leptin in human subjects that completely lack leptin or exhibit leptin receptor deficiency are extremely limited. This is partly because of the rare nature of mutations in leptin or the LepR and failure of the existing studies to address BP within these cohorts. A key strength in the study by Simonds et al is that this group of investigators identified a link between leptin and BP both in murine models of leptin deficiency as well as in individuals carrying rare leptin or LepR mutations (eg, documenting lower SBP in a cohort of children with leptin deficiency compared with age- and BMI-matched controls), thereby re-enforcing the notion that the findings in rodents on leptin-associated hypertension translate effectively to humans.

Clinical and Translational Implications of Leptin and Future Directions

A better understanding of the endocrinology of the adipocyte, ie, the contributions of specific adipokines to systemic energy homeostasis and how they interact with other endocrine loops, has great potential for clinical use and the future pharmacotherapy of obesity and CVD. However, the field has yet to define leptin resistance and the underlying teleological reasons for such a phenomenon. We need to gain a better understanding of the role of individual central neuronal populations and peripheral leptin signals in the control of metabolism; this will hopefully enable the identification of key sites of the emerging selective leptin resistance paradigm and potential therapeutic targets of obesity and CVD. The observations by Simonds et al contribute to these ongoing efforts based on the modification of the effects of leptin on specific subpopulations of neurons and will undoubtedly represent a potentially useful therapeutic strategy for the treatment of obesity-associated hypertension and CVD. More specifically, however, additional studies will have to address how thermogenic and renal SNA responses to LepR inactivation/activation in the DMH are altered, as a means of further delineating mechanisms of the selective leptin resistance. This will involve further mechanistic insights into molecular signaling pathways that leptin takes advantage of to mediate its effects on BP in the DMH.

Sources of Funding

This study was supported by US National Institutes of Health grants R01-DK55758, R01-DK099110 and P01-DK088761 (to PE. Scherer).

Disclosures

None.

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Key Words: adipokines | blood pressure | obesity
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Circ Res. 2015;116:1293-1295
doi: 10.1161/CIRCRESAHA.115.305937

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