Leptin Beyond the Lipostat
Key Component of Blood Pressure Regulation

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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 transcripitional 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 anorexic 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 BA 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.

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None.

References


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