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Leptin Beyond the Lipostat: Key Component of Blood Pressure Regulation

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Abstract

Obese individuals often struggle with increases in blood pressure that ultimately lead to an enhanced cardiovascular disease risk. The mechanistic basis for this association has remained largely unknown. While 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 blood pressure. Recent data suggests that the adipokine leptin, whose circulating levels are typically proportional to fat mass, is a major driving force for the obesity-associated increases in blood pressure. The effects of leptin on blood pressure are mediated by neuronal circuits, including leptin-responsive neurons in the dorsomedial hypothalamic nucleus.

Keywords

Adipokine; Blood Pressure; Obesity

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 blood pressure (BP), which is a major contributor to chronic hypertension and the risk for cardiovascular disease (CVD)-related mortality. The obese state is associated with dysfunctional adipose tissue exhibiting an abnormal secretory profile of bioactive adipokines[1]; this contributes to impaired regulation of appetite, an unfavorable adipose tissue distribution, reduced insulin sensitivity, endothelial dysfunction, inflammation and an elevation in BP[1].

Last year marked the 20th anniversary since the discovery of leptin from rodent adipose tissue in 1994 by Friedman and colleagues[2]. This discovery, along with the initial description of adiponectin around the same time, ignited a wealth of interest in adipose tissue as an endocrine organ and, in the case of leptin, enhanced our understanding in the biology of appetite and the maintenance of body weight control in obesity. Leptin is a

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pleiotropic hormonal signal that exhibits numerous neurobiological and physiological functions that regulate food intake, energy expenditure, fat mass, fertility, reproductive function and atherogenesis[3].

The 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 (POMC) and agouti-related protein (AgRP) neurons in the arcuate nucleus, and to a lesser extent, neurons expressing leptin receptors in other sites including the ventromedial and dorsomedial nuclei[4]. 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[5]. 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[5], to orchestrate energy intake and expenditure. Leptin activates POMC 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 AgRP neurons[6]. Mice selectively deficient for LepR's in POMC neurons exhibit modest obesity due to a decrease in energy expenditure, independent of alterations in food intake[7]. Conversely, re-expression of LepR's specifically in POMC neurons results in only moderate body weight improvements, however restores normoglycemia[8, 9].

The 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 sympatho-excitation as a critical site of action of the hypertensive effects of leptin[10]. Specifically, pharmacological administration or transgenic overexpression of leptin elevates systolic BP (SBP) in rodents[11]. In contrast, obese leptin-deficient *ob/ob* mice exhibit markedly lower BP than their lean controls[12]. Taken together, these studies suggest that the central hypothalamic actions of leptin contribute substantially to DIO-induced elevations in BP.

In terms of specific anatomical regions of the brain mediating these leptin effects on BP, Hall and colleagues reported that Shp2 deficiency in POMC neurons attenuates the ability of leptin to increase BP and improve glucose homeostasis[13]. Interestingly, several studies have suggested that melanocortin 4 receptors are also key regulators of BP. The elegant study by Simonds and colleagues in the December 2014 issue of *Cell* adds another hypothalamic site to the list and highlights the dorsomedial hypothalamic (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 *prior* to an increase in heart rate (HR) and BP, implicating leptin-responsive neurons in the DMH as key upstream regulators of

hypertension. Subsequent inhibition of leptin signaling either through intraperitoneal (i.p) 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 HR 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 employed is that the authors utilized technology that permits silencing of endogenous LepR activity in a highly specific neuronal population[14]. Re-activation of LepR's (through injection of AAV-Cre recombinase into the DMH of obese normotensive LepR-null mice that carry a floxed transcriptional silencer element)[8] increased HR 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 utilized to define states in which hyperleptinemia, as seen in obesity, results in reduced responses to leptin. Though 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/or desensitization of central and peripheral leptin signaling in specific neuronal sub-sets, the inability of leptin to cross the blood brain barrier, in addition to oxidative stress and/or inflammatory events, have been suggested as possible steps leading to ineffective leptin action[15]. Specific brain regions are implicated, in particular the hypothalamic arcuate nucleus as a critical mediator of the metabolic sympathetic actions of leptin[16]. SOCS3-mediated resistance to the effects of leptin on JAK2-STAT3 activation in POMC neurons[17], as well as the arcuate nucleus and the ventral tegmental area are known to exhibit DIO-associated leptin resistance[18].

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, body-weight and brown adipose tissue (BAT) thermogenesis[19]. Such studies have raised the question as to how leptin can contribute to an elevation in BP during DIO-induced hyperleptinemia, while many other leptin-mediated effects are impaired due to 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 and colleagues reported DIO-driven leptin resistance in the arcuate nucleus and the ventral tegmental area, while several medial basal hypothalamic regions remained sensitive to the hormone[20]. Upon examination of other brain regions, the DMH neuronal population has garnered attention over the years as an underappreciated site of leptin action and thus 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 BAT thermoregulation[21].

With the focus on the findings by Simonds and colleagues, how do these findings 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 very elegantly. Consistent with these observations, Marsh and colleagues reported that injection of leptin into the DMH increases HR and BP, however fails to enhance renal SNA[22]. Studies like this pinpoint the DMH as a key site for leptin-driven increases in BAT 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 POMC neurons have also been identified to contribute to the renal sympathetic and BP actions of leptin[13, 23], 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[24]. Selective leptin resistance may therefore entail distinct leptin signal transduction pathways that appear to produce differential regulation of sympathetic metabolic *versus* sympathetic cardiovascular/renal function. Future studies will have to delineate the precise molecular mechanism and brain site-specific regions, in addition to the sub-populations of neurons responsible for the central pathway-specific selective leptin resistance phenomenon.

Central Leptin Action and Blood Pressure 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 due to the rare nature of mutations in leptin or the LepR and/or failure of the existing studies to address BP within these cohorts. A key strength in the study by Simonds and colleagues is that this group of investigators identified a link between leptin and BP both in murine models of leptin deficiency and in individuals carrying rare leptin or LepR mutations (e.g. documenting lower SBP in a cohort of children with leptin deficiency compared to age- and BMI-matched controls); thereby re-enforcing the notion that the findings in rodents on leptin-associated hypertension translate very effectively to humans.

Clinical and Translational Implications of Leptin and Future Directions

A better understanding of the “endocrinology of the adipocyte”, i.e. 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 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 and colleagues 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, future studies will have to address how thermogenic and/or 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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