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Differential Control of the Sympathetic Nervous System by Leptin: Implications for Obesity

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SUMMARY

1. Leptin is a hormone that is secreted by adipocytes and delivered to the brain to regulate appetite and energy expenditure. Other effects of leptin include activation of the sympathetic nervous system and an increase in arterial pressure.

2. Mounting evidence suggests that the sympathetic nervous system subserving different tissues is differentially controlled by leptin. For instance, leptin-induced regional increases in sympathetic nerve activity do not respond uniformly to baroreflex activation and hypothermia.

3. In several mouse models of obesity, the ability of leptin to increase renal sympathetic nerve activity is preserved, despite resistance to leptin's effect on food intake, body weight and thermogenic sympathetic tone. Furthermore, obese mice also retain the increase in arterial pressure in response to leptin.

3. Although they display a lack of metabolic responses to leptin, animal models of obesity preserve renal sympathetic and arterial pressure responses that potentially cause the adverse cardiovascular consequences of obesity. Thus, it is possible that excess leptin contributes to cardiovascular complications, even when a subject shows metabolic resistance to leptin.

Keywords

Leptin; obesity; sympathetic nerve activity; hypothalamus; blood pressure

INTRODUCTION

Leptin is a peptide hormone known to play a major role in regulating the body's energy balance.¹ This hormone is produced mainly by adipocytes, in proportion to fat mass, and then is released into the bloodstream. Leptin decreases appetite and increases energy expenditure by activating leptin receptors on specific neurons in the brain. These neurons lie in regions of the brain that are known to control energy homeostasis, such as the arcuate nucleus of the hypothalamus.² In rodents and humans, a missense mutation in the *ob* gene (leptin gene), or in the gene encoding the leptin receptor, leads to severe obesity; this demonstrates the physiological significance of leptin and its importance in controlling energy homeostasis.^{1,3}

In addition to its effects on food intake and energy expenditure, leptin action has been shown to influence several other functions including the neuroendocrine and reproductive functions, insulin secretion and blood pressure. In this review, I will focus on how leptin

activates the sympathetic nervous system and the implications this has for the risk factors of cardiovascular disease that are associated with obesity.

Leptin and the sympathetic nervous system

The sympathetic nervous system is an important regulator of metabolic functions. It was initially suggested that leptin might increase energy expenditure via the sympathetic nervous system, because leptin induces weight loss that cannot be fully explained by its appetite-suppressing effects. Indeed in leptin-deficient *ob/ob* mice, the weight loss induced by leptin treatment is greater than the effect of pair-feeding alone.^{1,2} Consistent with this observation, leptin was found to increase sympathetic nerve activity (SNA) to thermogenic brown adipose tissue (BAT).⁴ Surprisingly, leptin was also found to cause sympathoactivation to other beds, not usually considered thermogenic, such as the kidney, hindlimb, and adrenal gland.⁴ The low sympathetic tone associated with leptin deficiency in rodents and humans further demonstrates that leptin is involved in regulating sympathetic tone.

Numerous data support the concept that leptin regulates regional sympathetic outflow to peripheral tissues in a way that is highly differential. For instance, after leptin exposure, the magnitude of SNA increases varies by region;⁴ and leptin-induced regional increases in SNA respond non-uniformly to baroreflex activation.⁵ Increased renal SNA can be suppressed by baroreflex activation, suggesting that the increase in renal SNA affects circulatory functions. In contrast, leptin-induced BAT sympathoactivation was not prevented by baroreflex activation, suggesting that the recruitment of sympathetic fibers to BAT affect thermogenic or metabolic, rather than circulatory functions.

In response to hypothermia, leptin's effect on regional SNA also differs, and depends on whether sympathetic fibers affect circulatory or thermogenic functions. In response to hypothermia in rats, leptin acutely enhances sympathetic outflow to BAT. This effect is specific for thermogenic SNA because leptin does not influence the response of renal SNA to hypothermia.⁵ Thus, leptin's impact on renal vs. BAT SNA depend on the stimuli, suggesting that leptin controls sympathetic nervous system in a tissue-specific manner.

Leptin increases blood pressure

Leptin's activation of autonomic function has implications for cardiovascular function. Indeed in rats, chronic intravenous infusion of leptin increases both the arterial pressure and heart rate.⁶ Also, transgenic mice overexpressing leptin have significantly higher baseline arterial pressure, as compared to non-transgenic littermate controls.⁷ These transgenic mice also have increased urinary excretion of norepinephrine. Furthermore, agouti yellow, genetically obese KKA^y mice have elevated arterial pressure; and Aizawa-abe et al. demonstrated that this elevated arterial pressure is dependent on elevated levels of leptin.⁷

Further insights into the role of leptin in controlling arterial pressure come from studies involving mice and humans deficient in leptin. Indeed, despite body weights 2 to 3 times higher than the lean controls, leptin-deficient *ob/ob* mice have lower arterial pressure. Administering leptin to these *ob/ob* mice (so-called leptin reconstitution) increased systolic blood pressure by as much as 25 mmHg, despite concurrent decreases in food intake and body weight.⁷ In addition, Ozata et al. showed that leptin deficiency in humans is associated with postural hypotension and an absence of risk factors for cardiovascular disease, despite severe obesity.³ Together, these findings demonstrate that leptin does contribute to physiological maintenance of arterial pressure and that hyperleptinemia may mediate the cardiovascular morbidity associated with obesity.

The importance of the sympathetic nervous system in the arterial pressure rise in response to leptin was demonstrated using adrenergic blockade. Adrenergic blockade reversed the

increased arterial pressure induced by intravenous infusion or transgenic overexpression of leptin.^{6,7} Particularly, leptin-induced renal sympathoactivation seems to play a pivotal role in increasing arterial pressure. Indeed, loss of leptin's ability to increase renal SNA, such as in the melanocortin-4 receptor knockout mice, is associated with normal arterial pressure at baseline and a lack of elevated arterial pressure after leptin treatment.⁵

Selective leptin resistance

Obesity in rodents and humans is commonly associated with high circulating levels of leptin, reflecting a state of "leptin resistance". In agouti obese mice, leptin resistance is selective, preserving the effects of leptin on renal SNA.⁵ The anorexic and weight-reducing effects of leptin were less in agouti obese mice, compared to lean littermates. However, the increase in renal SNA in response to leptin, was identical in both lean and obese mice.

This phenomenon of selective leptin resistance is also observed in a model of acquired obesity, namely mice with diet-induced obesity. Indeed, these obese mice preserve the renal sympathetic activation to leptin, despite being resistant to leptin's anorectic and weight-reducing effects.⁸ Interestingly, preservation of the regional SNA responses to leptin are not uniform, but instead are specific to the kidney. Indeed, although renal sympathoactivation to leptin was preserved in diet-induced obese mice, their BAT and lumbar SNA responses to leptin were significantly attenuated.⁸

In diet-induced obese mice that had been fed a high-fat diet, arterial pressure also responded to leptin, as chronic leptin treatment significantly increased arterial pressure. Leptin caused comparable increases in arterial pressure in both the obese (~10 mmHg) and lean mice (~11 mm Hg).⁸ These novel findings demonstrate that a preserved renal SNA response to leptin does, in fact, translate into a preserved arterial pressure response; this enhances the potential pathophysiologic significance of the selectivity observed in the leptin resistance phenomenon.

In conclusion, the concept of selective leptin resistance may represent an important pathophysiologic mechanism that explains leptin's role in obesity-associated hypertension. Accumulating data suggest that in obese humans, leptin has a pathological role in causing hypertension and sympathetic overactivity. For instance, in humans there is evidence of a positive correlation between plasma leptin levels and blood pressure.⁹ A strong correlation between leptin plasma concentration and renal SNA across a broad range of leptin values in men of widely differing adiposity has been reported.¹⁰ This indicates that leptin may be the main cause of the hypertension and sympathetic activation that is associated with obesity, not only in animal models, but also in humans.

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Figure 1.

The concept of selective leptin resistance holds that there is resistance to the metabolic (appetite- and weight-reducing) actions of leptin, but preservation of the cardiovascular sympatho-excitatory actions of leptin. This phenomenon might explain how hyperleptinemia could be accompanied by increased adiposity leading to obesity, but still contribute to sympathetic overactivity and hypertension because of preservation of the sympathetic actions of leptin to some organs involved in the blood pressure regulation such as the kidney.