

## Leptin and Hypertension- A Perspective

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### Abstract

Leptin, a peptide discovered more than 10 years ago, is a 16-kDa-peptide hormone that is primarily synthesized and secreted by adipose tissue.

One of the major actions of this hormone is the control of energy balance by binding to receptors in the hypothalamus, leading to reduction in food intake and elevation in temperature and energy expenditure. In addition, Leptin, through both direct and indirect mechanisms, may play an important role in cardiovascular and renal regulation.

Leptin was initially believed to be an anti-obesity hormone, due to its metabolic effects. However, obese individuals, for unknown reasons, become resistant to the satiety and weight-reducing effect of the hormone, but preserve leptin-mediated sympathetic activation to non-thermogenic tissue such as kidney, heart, and adrenal glands.

Leptin has been shown to influence nitric oxide production, and along with chronic sympathetic activation, especially to kidney, it may lead to sodium retention, sympathetic vasoconstriction and blood pressure elevation. Consequently, leptin is currently considered to play an important role in the development of hypertension.

**Keywords:** *Leptin (LPT); Hypertension (HT); Nitric Oxide*

### Introduction

Several studies suggest that leptin is involved in the pathogenesis of arterial hypertension in humans. It was first observed that significantly higher plasma leptin in patients with essential hypertension, even in those with normal body weight [1]. Many subsequent studies reported a significant positive correlation between plasma leptin and blood pressure, independent of body weight, both in normotensive and in hypertensive subjects [2].

In addition, humans with inherited leptin deficiency are normotensive despite massive obesity. The results of some studies are discrepant, for example demonstrating significantly higher leptin only in males, or only in females) [3,4], with essential hypertension; these differences could be attributed to various populations studied. Interestingly, it has been observed that leptin may be elevated in hypertensive subjects only at night [5].

Recently, it was demonstrated that plasma leptin is elevated in lean normotensive subjects with a high normal blood pressure in comparison to those with optimal blood pressure. Few studies have reported higher leptin levels in healthy offspring of hypertensive patients and suggested that genetically determined hyperleptinemia may precede and contribute to the development of hypertension [6].

The first identified effect of leptin relevant for cardiovascular physiology was stimulation of the SNS. Apart from reducing food intake, leptin increases energy expenditure, which is achieved by stimulating sympathetic outflow to brown adipose tissue (BAT), resulting in increased thermogenesis [7].

Surprisingly, leptin also stimulates sympathetic traffic to other tissues, such as the kidney, adrenals and hind limbs. Several studies have suggested that leptin induces reflex stimulation of SNS by activating afferent nerve endings in adipose tissue. Thus, leptin injected into the epididymis not only stimulates efferent sympathetic nerves to the adipose tissue of epididymis but also to other tissues such as BAT, adrenal medulla, pancreas and liver [7].

In addition, injection of leptin into peri-renal adipose tissue increases renal sympathetic nervous activity (SNA) in a dose-dependent manner. These studies suggest that leptin released within the adipose tissue may act locally on afferent fibers to stimulate SNS in a paracrine manner. However, the majority of studies strongly suggest that the sympatho-excitatory effect of leptin is mediated via the central nervous system (CNS), intracerebroventricular injection of leptin increases SNS activity at doses which do not elevate systemic leptin level [8], and damage to the hypothalamic arcuate nucleus abolishes the sympatho-excitatory effect of leptin. The precise neurohumoral pathways linking leptin to SNS activity have been extensively reviewed [8].

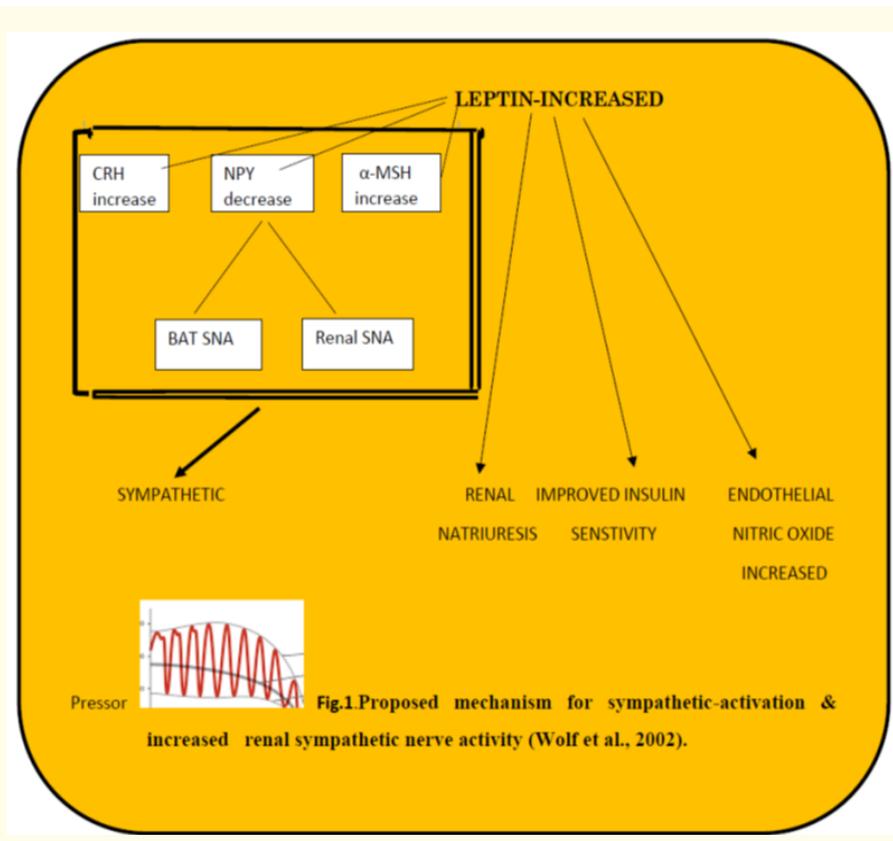


Figure 1: Proposed mechanism for sympathetic-activation and increased renal sympathetic nerve activity (Wolf, et al. 2012).

Many experimental studies have demonstrated that, although both central and peripheral leptin administration stimulates the SNS, blood pressure increases only when hormone is administered centrally [9].

Fruhbeck [9] first demonstrated that bolus intravenous leptin administration increases plasma concentration of nitric oxide metabolites; nitrates (NOX). In addition, in rats receiving NO synthase inhibitor “L-nitro-arginine methylester” (L-NAME) together with leptin, blood pressure was higher than after L-NAME alone. Conversely, leptin decreased blood pressure in animals in which SNS was pharmacologically inhibited, these data suggest that, under normal conditions, leptin induces balanced activation of the SNS and NO resulting in any net changes in arterial pressure [10,11].

**Leptin and secondary hypertension**

Leptin may also be involved in the pathogenesis of specific forms of secondary hypertension. In particular, because leptin is vigorously metabolized in the kidney, its concentration is markedly elevated in renal failure and thus could contribute to hypertension in these patients [12].

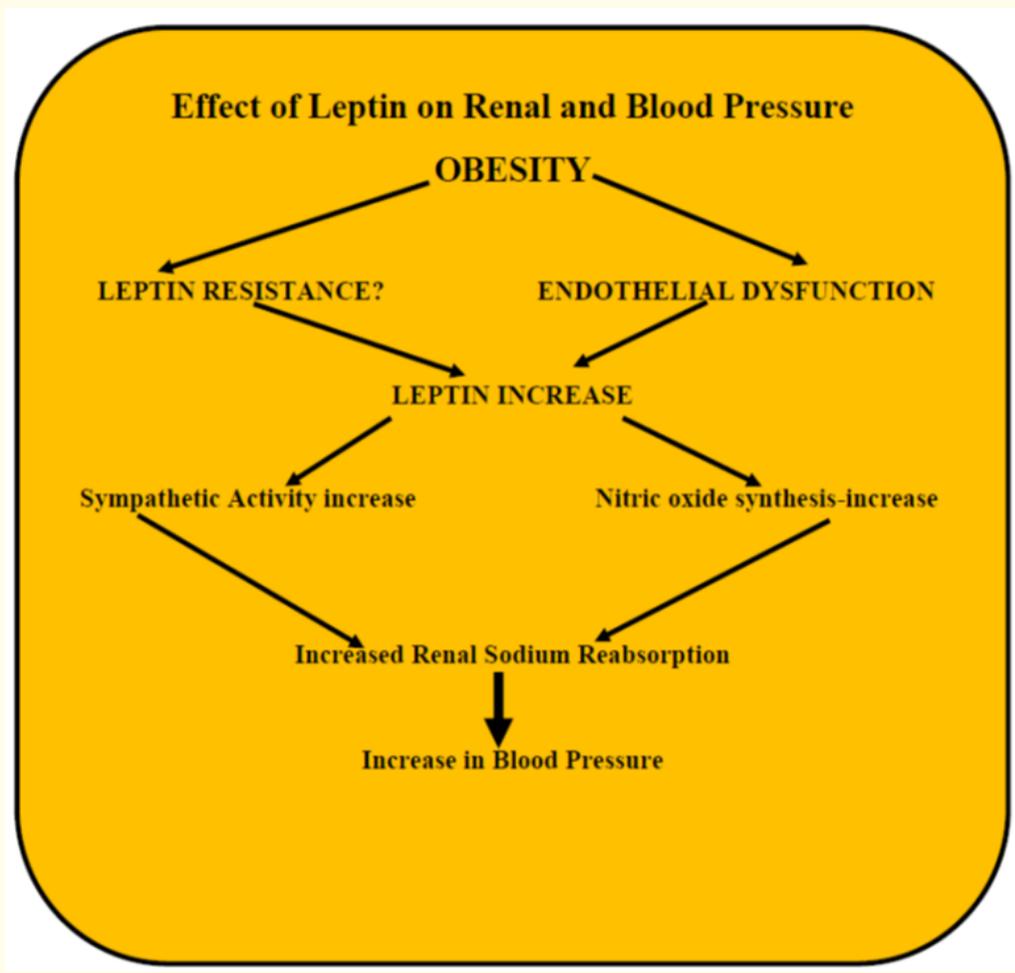


Figure 2: Leptin (LPT) and secondary cause of hypertension.

Many studies have demonstrated increased plasma leptin in pregnant women with pre-eclampsia in comparison to normal pregnancy. Interestingly, hyperleptinemia may precede the development of hypertension during pregnancy [13].

Finally, plasma leptin is higher in patients with obstructive sleep apnea than in healthy controls with similar body weight, suggesting that hyperleptinemia may contribute to increased sympathetic drive and hypertension associated with this syndrome [14].

Nevertheless, because clinical studies are based almost exclusively on correlation data, one cannot definitely conclude if leptin plays a causal role in human hypertension. Controversial data exist about the influence of antihypertensive therapy on plasma leptin in humans [15].

### Leptin and hypertension in obesity

Chronic hyperleptinemia, as mentioned, augments the blood pressure by means of different mechanisms in animal models. In humans, there have been several studies attempting to link leptin to hypertension. Serum leptin levels are elevated in obesity due to increase amount of adipose tissue which is the main source of the hormone and possibly secondary to some degree of central resistance to its action. A number of studies have found leptin to be positively correlated with systolic and diastolic blood pressure in both obese and non-obese individuals [16].

It is reported further that serum levels of LPT in normotensive men could be a risk factor for developing HPT independently of BMI and insulin resistance [6]. LPT is reported to play a role in stimulating vascular inflammation, vascular smooth muscle hypertrophy, and augment blood pressure in hypertensive patients. Therefore it is found that LPT is able to cause hypertension in various animal and clinical studies [17].

### Conclusions

In summary, it seems evident that serum leptin levels are significantly elevated in obese hypertensive individuals when compared with obese normotensives. However this relationship between leptin and blood pressure may not always be as evident after controlling for BMI in some subjects, making the assumption of leptin as one of the potential causes of hypertension in obesity, less consistent.

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