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## Effect of renin-angiotensin system activation by dietary sodium restriction and upright position on plasma leptin concentration in patients with essential hypertension

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### Summary

**Background:**

Both leptin and the renin-angiotensin system (RAS) are involved in the regulation of arterial blood pressure. This study was undertaken to assess the relationship between RAS and plasma leptin concentration in hypertensive patients under conditions of normal and restricted sodium supply and upright position.

**Material/Methods:**

In 31 patients with essential hypertension (EHP – 14 F, 17 M, age  $44 \pm 14$  years, BMI  $29.3 \pm 6.4$  kg/m<sup>2</sup>) and 8 healthy subjects (NHS – 4 F, 4 M, age 37(17 years, BMI  $25.3 \pm 6.6$  kg/m<sup>2</sup>) plasma leptin concentration, plasma renin activity (PRA), and 24-hour urinary sodium excretion ( $U_{Na}$ ) were evaluated twice: first on a diet containing 100–120 mmol sodium per day and after 8 hours overnight bed rest, and a second time after 3 days of dietary sodium restriction (10–20 mmol daily) and 3 hours in upright position.

**Results:**

Dietary sodium restriction and upright position was followed by a significant increase in PRA and decrease of  $U_{Na}$ . By contrast, plasma leptin concentration showed a moderate decrease both in EHP and NHS. No significant correlation was found between PRA and plasma leptin concentrations in either of the groups examined.

**Conclusion:**

From the results obtained in this study we may conclude that dietary sodium restriction and upright position exerts only a moderate effect on plasma leptin concentration, in contrast to PRA, in both hypertensive and normotensive subjects.

**key words:**

essential hypertension • leptin • dietary sodium • plasma renin activity

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## BACKGROUND

Leptin is a protein hormone containing 167 aminoacids, which is predominantly produced by adipocytes [1]. The main determinants of leptinemia are body fat and gender [2,3]. Plasma leptin concentration is significantly higher in obese than in lean subjects, and higher in females than in males [2–5]. Plasma leptin concentration is not constant, but shows circadian variations [2,3]. One of the potential mechanisms regulating leptin secretion seems to be diurnal changes in the activity of sympathetic nerve system [3].

Leptin plays an important role in the regulation of food intake and energy expenditure [2,3]. The results of recent studies have showed that leptin is not only a satiety hormone, but is also involved in the regulation of a number of very different physiological processes, such as reproduction [2,3], puberty [2,3], osteogenesis [6], erythropoiesis [7,8], angiogenesis [9] and regulation of blood pressure [10,11].

There is both clinical and experimental evidence suggesting that leptin is involved in blood pressure regulation. It has been shown that intracerebroventricular injection [12,13] or chronic intravenous infusion of leptin increases peripheral resistance and blood pressure in normotensive rats [14]. These cardiovascular effects of leptin are at least partially mediated by stimulation of the sympathetic nerve system [15,16,17]. Transgenic mice overexpressing leptin have also been shown to be characterized by hyperleptinemia, elevated blood pressure and sympathetic nerve hyperactivity [18]. In vitro, leptin stimulates the proliferation of aortic smooth muscle cells [19] and secretion of endothelin by endothelial cells [20]. Therefore leptin seems to play an important role in the regulation of blood pressure by influencing the activity of the sympathetic nerve system, endothelium function and vascular remodeling.

Clinical studies have revealed that leptin may be involved in the pathogenesis of essential hypertension. In patients with essential hypertension (EHP) increased plasma leptin concentrations have been found in some studies [10,21,22], but not all [11,23]. Significant positive correlations have been found between blood pressure and plasma leptin concentration in EHP [11,21–24]. Moreover, the results of multivariate regression analysis suggest that leptin influences blood pressure in EHP independently of body mass index [11,23]. It is also suggested that leptin may contribute to the pathogenesis of organ complications of hypertension, such as hypertensive retinopathy [25] and left ventricular hypertrophy [26].

Recently published data suggest that the function of the renin-angiotensin system may be associated with leptin secretion [10,23,27]. Like other authors [10,27], we found a significant positive correlation between leptinemia and plasma renin activity (PRA) in EHP [23].

Since restricted dietary sodium intake and upright position are potent stimuli both for renin secretion and sym-

pathetic nerve activity, the assessment of plasma leptin concentration under these conditions would seem to be of pathophysiological interest in EHP.

The present study was designed to answer the question as to whether renin-angiotensin system activation by dietary sodium restriction and upright position influences plasma leptin concentration in hypertensive patients.

## MATERIAL AND METHODS

31 EHP patients (14 females, 17 males, age  $44 \pm 14$  years, BMI  $29.3 \pm 6.4$  kg/m<sup>2</sup>) and 8 normotensive subjects (NTS) (4 females, 4 males, age  $37 \pm 17$  years, BMI  $25.3 \pm 6.6$  kg/m<sup>2</sup>) were enrolled in this study. The diagnosis of essential hypertension was established after exclusion of secondary hypertension by careful clinical, biochemical, hormonal and radiological examinations performed in the Department of Nephrology, Endocrinology and Metabolic Diseases, Silesian University Medical School, Katowice, Poland. PRA and plasma leptin concentration were measured twice: (I) after administration of a normally salty diet (100–120 mmol sodium / 24h) for 3 days and 8 hours overnight recumbency, and (II) after 3 days of dietary sodium restriction (10–20 mmol sodium / 24h) and 3 hours of upright position. In all subjects, 24h urinary sodium excretion was also evaluated twice: (I) during the third day of administration of a normally salty diet and (II) during the third day of administration of a low-salt diet. All antihypertensive drugs were withdrawn at least 7 days before the study.

PRA was estimated by the radioimmunological method [28]. Plasma leptin concentration was assessed by radioimmunoassay method using kits from Linco Research Inc. (USA) (coefficients of intraassay and interassay variation were 7.1% and 10.8% respectively). Urinary sodium excretion was estimated by flame photometry.

EHP were divided according to the response of blood pressure to changes of sodium intake into two subgroups: sodium sensitive (mean arterial blood pressure – MAP – down at least 3 mmHg after 3 days of dietary sodium restriction) and sodium insensitive (decrease by less than 3 mmHg, no change or even increase of MAP after 3 days of dietary sodium restriction).

## Statistical analysis

Statistical evaluation of the results was performed using the Mann-Whitney U test for unpaired variables and the Wilcoxon test for paired variables. Correlation coefficients were calculated according to the Kendall Tau correlation test. All results are expressed as means  $\pm$  standard deviation (SD).

## RESULTS

As shown in Table 1, dietary sodium restriction and upright position was followed by a significant increase of

**Table 1.** Urinary sodium excretion (UNa), mean arterial blood pressure (MAP), plasma renin activity (PRA), and plasma leptin concentration in patients with essential hypertension (EHP) and in normotensive healthy subjects (NHS) on the third day of intake of a normally salted diet (I), and on the third day of dietary salt restriction (II). Mean  $\pm$  standard deviation.

	UNa [mmol/24 hours]	MAP [mmHg]	PRA [ng/ml/h]	Leptin [ng/ml]
EHP I	97 $\pm$ 65	117 $\pm$ 13*	2.8 $\pm$ 2.9	18.0 $\pm$ 15.0
II	24 $\pm$ 12 <sup>c</sup>	115 $\pm$ 16*	10.9 $\pm$ 12.6 <sup>c</sup>	16.6 $\pm$ 14.9 <sup>a</sup>
NHS I	111 $\pm$ 47	96 $\pm$ 7	1.8 $\pm$ 1.4	13.4 $\pm$ 8.7
II	23 $\pm$ 16 <sup>a</sup>	93 $\pm$ 8	8.9 $\pm$ 9.9 <sup>a</sup>	10.1 $\pm$ 7.3 <sup>a</sup>

<sup>a</sup>p<0.05 vs I; <sup>b</sup>p<0.001 vs I; \*p<0.05 vs NHS

PRA both in normotensive and hypertensive subjects. In contrast to PRA, plasma leptin concentration decreased significantly in both examined groups. Plasma leptin concentration showed at least a tendency to decrease after dietary sodium restriction and upright position in both salt-sensitive and salt-insensitive subjects (Table 2), regardless of gender (Table 2). This tendency reached statistical significance in the subgroup of EHP with sodium insensitive hypertension and the subgroup of male EHP (Table 2). Dietary sodium restriction was followed by a slight decrease in blood pressure in both NHS and EHP (all hypertensive patients analyzed together) (Table 1). It should be pointed out that 15 of the 31 patients were salt-sensitive and showed a decrease of MAP after salt restriction and upright position. PRA was significantly higher in hypertensive males than in females (Table 2).

No significant correlations were found between plasma leptin concentration and urinary sodium excretion, MAP and PRA respectively, in either hypertensive or normotensive patients. As expected, a significant positive correlation was found between plasma leptin concentration (I) and BMI in EHP ( $\tau=0.45$ ,  $p=0.004$ ).

## DISCUSSION

The main finding of the present study was a moderate decrease in plasma leptin concentration after 3 days of

marked dietary sodium restriction and 3 hours of upright position. This reduction in leptinemia was observed in both normotensive and hypertensive subjects, as well as in all subgroups of patients with essential hypertension (males and females, sodium-sensitive and sodium-insensitive hypertension).

Short term dietary sodium restriction leads to stimulation of the renin-angiotensin system. Previous clinical studies have suggested that the activity of the renin-angiotensin system and leptinemia may be interrelated. We ourselves [23] and other authors [10,27] have found a significant positive relationship between leptinemia and PRA in essential hypertensive patients. There are only a few experimental studies concerning the influence of leptin on PRA. Shek et al. showed that PRA did not change significantly during infusion of leptin [14]. Bornstein et al. found the opposite: that is, an increase of PRA during intravenous leptin infusion [29]. Thus the relationship between renin and leptin secretion remains unclear.

The findings presented here (decreased leptinaemia during stimulation of renin secretion), when analyzed together with previous reports [significant positive relationship between leptinemia and PRA observed under basal conditions - 10,23,27], suggest that the secretion of leptin and renin are not interrelated directly in hypertensive subjects. As shown in other studies, leptin stimulates the activity of the sympathetic nerve system [3]. It is also well known that stimulation of the sympathetic nervous system is followed by increased renin production and release [30]. These findings are consistent with our previous studies, in which a positive correlation was found between leptinemia and PRA assessed under basal conditions.

Short term, marked dietary sodium restriction leads not only to an increased renin secretion, but also to stimulation of sympathetic nervous system activity. It has been shown (both in hypertensive and normotensive subjects) that muscle sympathetic nerve activity (MSNA) is significantly higher during a low-sodium diet than during a high-sodium diet [31]. Severe sodium restriction is also

**Table 2.** Body mass index (BMI), urinary sodium excretion (UNa), mean arterial blood pressure (MAP), plasma renin activity (PRA), and plasma leptin concentration on the third day of intake of a normally salted diet (I) and on the third day of dietary salt restriction (II) in essential hypertensive females (F-EHP) and males (M-EHP), and in hypertensive patients with sodium sensitive (SS-EHS) and sodium insensitive hypertension (SI-EHP). Mean  $\pm$  standard deviation.

		F-EHP n=14	M-EHP n=17	SS-EHP n=15 (6 F, 9 M)	SI-EHP n=16 (8 F, 8 M)
UNa [mmol/24 hours]	I	94 $\pm$ 48	99 $\pm$ 78	103 $\pm$ 68	91 $\pm$ 63
	II	27 $\pm$ 15 <sup>c</sup>	21 $\pm$ 9 <sup>c</sup>	23 $\pm$ 10 <sup>c</sup>	25 $\pm$ 14 <sup>c</sup>
MAP[mmHg]	I	112 $\pm$ 8	122 $\pm$ 15	118 $\pm$ 12	117 $\pm$ 14
	II	111 $\pm$ 14	118 $\pm$ 18	107 $\pm$ 12 <sup>#,c</sup>	123 $\pm$ 17 <sup>b</sup>
PRA[ng/ml/h]	I	1.4 $\pm$ 1.4**	3.9 $\pm$ 3.4	2.6 $\pm$ 2.1	2.9 $\pm$ 3.5
	II	7.1 $\pm$ 9.5* <sup>c</sup>	13.9 $\pm$ 14.2 <sup>c</sup>	7.3 $\pm$ 5.5 <sup>c</sup>	14.2 $\pm$ 16.3 <sup>c</sup>
Plasma leptin [ng/ml]	I	27.1 $\pm$ 17.3***	10.5 $\pm$ 6.8	18.5 $\pm$ 18.4	17.5 $\pm$ 11.5
	II	25.9 $\pm$ 17.0***	8.9 $\pm$ 6.3 <sup>b</sup>	17.6 $\pm$ 19.2	15.6 $\pm$ 9.8 <sup>a</sup>
BMI [kg/m <sup>2</sup> ]	I	30.6 $\pm$ 7.1	28.2 $\pm$ 5.7	30.3 $\pm$ 8.2	28.4 $\pm$ 4.2

<sup>a</sup>p<0.05 vs I; <sup>b</sup>p<0.01 vs I; <sup>c</sup>p<0.001 vs I; \*p<0.05 vs M-EHP; \*\*p<0.01 vs M-EHP; \*\*\*p<0.001 vs M-EHP; <sup>#</sup>p<0.05 vs SI-EHP

accompanied by an increase of plasma noradrenaline concentration [32] and increased noradrenaline and vanillylmandelic acid urinary excretion [33-35].

As shown by other authors, the stimulation of the sympathetic nervous system inhibits leptin secretion very quickly [36-40]. The administration of  $\beta$ -adrenergic agonists reduces plasma leptin and leptin mRNA in the white adipose tissue of rodents [36]. Exposure to cold (a strong stimulant of sympathetic nervous system activity) dramatically decreases leptin expression in the adipose tissue of mice [36]. These reductions can be prevented by the administration of nonselective  $\beta$ -adrenergic antagonists [37]. Isoproterenol (a nonselective  $\beta$ -adrenergic agonist) decreases leptin release from human cultured adipose tissue [38]. In humans, infusion of isoproterenol or adrenaline decreases plasma leptin concentration [39,40]. Moreover, acute cold exposure decreases leptinemia in women [41]. Thus  $\beta$ -adrenergic stimulation seems to influence leptinemia in humans by a direct effect on adipocytes. On the other hand, long-term treatment with  $\beta$ -adrenergic antagonists (celiprolol, pindolol) results in decreased plasma leptin concentration [42,43].

From the above-mentioned studies it can be inferred that the reduction in plasma leptin concentration after 3 days of sodium dietary restriction and upright position is due more to stimulation of the sympathetic nervous system than to renin-angiotensin system activation.

## CONCLUSION

From the results obtained in our study we may conclude that 3 days of dietary sodium restriction and upright position leads to a moderate decrease in plasma leptin concentration in both hypertensive and normotensive subjects. This decrease does not seem to be directly related to activity changes of the renin-angiotensin system.

## REFERENCES:

- Zhang Y, Proenca R, Maffei M et al: Positional cloning of the mouse obese gene and its human homologue. *Nature*, 1994; 372: 425-32
- Wauters M, Considine RV, Van Gaal LF: Human leptin: from an adipocyte hormone to an endocrine mediator. *Eur J Endocrinol*, 2000; 143: 293-311
- Himms-Hagen J: Physiological roles of the leptin endocrine system: differences between mice and humans. *Crit Rev Clin Lab Sci*, 1999; 36: 575-655
- Considine RV, Sinha MK, Heiman ML, et al: Serum immunoreactive-leptin concentrations in normal-weight and obese humans. *N Engl J Med*, 1996; 334: 292-5
- Rosenbaum M, Nicolson M, Hirsch J et al: Effects of gender, body composition, and menopause on plasma concentration of leptin. *J Clin Endocrinol Metab*, 1996; 81: 3424-7
- Thomas T, Gori F, Khosla S et al: Leptin acts on human marrow stromal cells to enhance differentiation to osteoblast and to inhibit differentiation to adipocytes. *Endocrinology*, 1999; 140: 1630-8
- Cioffi JA, Shafer AW, Zupanic TJ et al: Novel B219/OB receptor isoforms: Possible role of leptin in hematopoiesis and reproduction. *Nature Med*, 1996; 2: 585-9
- Gainsford T, Wilson TA, Metcalf D et al: Leptin can induce proliferation, differentiation and functional activation of hemopoietic cells. *Proc Natl Acad Sci USA*, 1996; 93: 14564-8
- Sierra-Honigsmann MR, Nath AK, Murakami C et al: Biological action of leptin as an angiogenic factor. *Science*, 1998; 281: 1683-6
- Suter PM, Locher R, Häslar E, Vetter W: Is there a role of the ob gene product leptin in essential hypertension? *Am J Hypertens*, 1998; 11: 1305-11
- Kokot F, Adamczak M, Więcek A, Cieplik J: Does leptin play a role in the pathogenesis of essential hypertension? *Kidney Blood Pres Res*, 1999; 22: 154-60
- Casto RM, Van Ness JM, Overton JM: Effects of central leptin administration on blood pressure in normotensive rats. *Neurosci Lett*, 1998; 246: 29-32
- Dunbar JC, Hu Y, Lu H: Intracerebroventricular leptin increases lumbar and renal sympathetic nerve activity and blood pressure in normal rats. *Diabetes*, 1997; 46: 2040-3
- Shek EW, Brands MW, Hall JE: Chronic leptin infusion increases arterial pressure. *Hypertension*, 1998; 31(2): 409-14
- Haynes WG, Morgan DA, Walsh SA et al: Receptor-mediated regional sympathetic nerve activation by leptin. *J Clin Invest*, 1997; 100: 270-8
- Haynes WG, Morgan DA, Walsh SA et al: Sympathetic activation to leptin is mediated by the hypothalamus. *J Hypertens*, 1998; 16(Suppl. 2): 11
- Matsumura A, Abe I, Tsuchinashi T, Fujishima M: Central effects of leptin on cardiovascular and neurohormonal responses in conscious rabbits. *Am J Physiol*, 2000; 278: 1314-20
- Aizawa-Abe M, Ogawa Y, Masuzaki H et al: Pathophysiological role of leptin in obesity-related hypertension. *J Clin Invest*, 2000; 105: 1243-52
- Oda A, Taniguchi T, Takahashi A et al: Leptin stimulates rat aortic smooth muscle cell proliferation and migration. *Atherosclerosis*, 1997; 134: 321
- Quehenberger P, Exner M, Ruzicka K et al: Leptin-mediated endothelin-1 induction is under control of the transcriptional factor AP-1. *Diabetes*, 1999; 48(Suppl 1): 309
- Agata J, Masuda A, Takada M et al: High plasma immunoreactive leptin level in essential hypertension. *Am J Hypertens*, 1997; 10: 1171-4
- Hirose H, Saito I, Tsujioka M et al: The obese gene product, leptin: possible role in obesity-related hypertension in adolescents. *J Hypertens*, 1998; 16: 2007-12
- Adamczak M, Kokot F, Więcek A: Relationship between plasma renin profile and leptinaemia in patients with essential hypertension. *J Hum Hypertens*, 2000; 14: 503-9
- Sheu WH, Lee WJ, Chen YT: High plasma leptin concentrations in hypertensive men but not in hypertensive women. *J Hypertens*, 1999; 17: 1289-95
- Ückaya G, Ozata M, Sonmez A et al: Is leptin associated with hypertensive retinopathy? *J Clin Endocrinol Metab*, 2000; 85: 683-7
- Paoloso G, Tagliamonte MR, Galderisi M et al: Plasma leptin concentration, insulin sensitivity, and 24-hour ambulatory blood pressure and left ventricular geometry. *Am J Hypertens*, 2001; 14: 114-20
- Ückaya G, Ozata M, Sonmez A et al: Plasma leptin levels strongly correlate with plasma renin activity in patients with essential hypertension. *Horm Metab Res*, 1999; 31: 435-8
- Kokot F, Stupnicki R: Radioimmunological and radiocompetitive methods used in clinical practice. Warsaw: Polish Medical Publisher-PZWL, 1985
- Bornstein SR, Torpy DJ: Leptin and the renin-angiotensin-aldosterone system. *Hypertension*, 1998; 32: 376
- Osborn JL, DiBona GF, Thames MD: (1- receptor mediation of renin secretion elicited by low frequency renal nerve stimulation. *J Pharmacol Exp Ther*, 1981; 216: 265-9
- Anderson EA, Sinkey CA, Lawton WJ, Mark AL: Elevated sympathetic nerve activity in borderline hypertensive humans. Evidence from direct intraneural recordings. *Hypertension*, 1989; 14: 177-83
- Vitello MV, Prinz PN, Halter JB: Sodium-restricted diet increases nighttime plasma norepinephrine and impairs sleep patterns in man. *J Clin Endocrinol Metab*, 1983; 56: 553-6
- Sharma AM, Schorr U, Thiede HAT, Distler A: Effect of dietary salt restriction on urinary serotonin and 5-hydroxyindoloacetic acid excretion in man. *J Hypertens*, 1993; 11: 1381-6

34. Warren SE, Viweg WV, O'Connor DT: Sympathetic nervous activity during sodium restriction in essential hypertension. *Clin Cardiol*, 1980; 3: 348-51
35. Wocial B, Januszewicz W, Chodakowska J, Feltynowski T: Changes in sodium excretion of catecholamines and their metabolites in patients with essential hypertension during sodium intake restriction. *Cor Vasa*, 1981; 23: 222-8
36. Trayhurn P, Duncan JS, Rayner DV: Acute cold-induced suppression of ob (obese) gene expression in white adipose tissue of mice: mediation by the sympathetic system. *Biochem J*, 1995; 311: 729-33
37. Evans BA, Agar L, Summers RJ: The role of the sympathetic nervous system in the regulation of leptin synthesis in C57BL/6 mice. *FEBS Lett*, 1999; 444: 149-54
38. Ricci MR, Fried SK: Isoproterenol decreases leptin expression in adipose tissue of obese humans. *Obesity Res*, 1999; 7: 233-40
39. Pinkey JH, Coppack SW, Mohamed Ali V: Effect of isoprenaline on plasma leptin and lipolysis in humans. *Clin Endocrinol Oxf*, 1998; 48: 407-11
40. Carruli L, Ferrari S, Bertolini M et al: Regulation of ob gene expression: evidence for epinephrine-induced suppression in human obesity. *J Clin Endocrinol Metab*, 1999; 84: 3309-12
41. Ricci MR, Fried SK, Mittleman KD: Acute cold exposure decreases plasma leptin in women. *Metabolism*, 2000; 49: 421-3
42. Malminiemi K: Long-term celiprolol therapy lowers fasting plasma leptin levels. Celiprolol Multicenter Study Group. *Cardiovasc Drug Ther*, 2000; 14: 67-75
43. Cieplak J, Kokot F, Chudek J et al: Wpływ leczenia perindoprylem, pindololem lub felodypiną na stężenie leptyny w surowicy u chorych na samoistne nadciśnienie tętnicze. *Nadciśnienie Tętnicze*, 2000; 4: 295

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