Original Paper

Human Soluble Leptin Receptor Concentration in Healthy Offspring of Hypertensive Parents

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Essential hypertension is associated with increased plasma leptin levels and decreased human soluble leptin receptor (hsLR) concentration. The aim of this study was to determine whether the concentration of hsLR differs among offspring of hypertensive compared with nonhypertensive parents. Subjects in the 2 groups were matched for age, sex, and body mass index. Forty-six (24 male, 22 female; mean age, 18±3 years; body mass index, 22.4±1.4 kg/m^2) healthy offspring of hypertensive parents (group A) and 50 (28 male, 22 female; mean age, 18±3.2 years; body mass index, 22.6±1.7 kg/m^2) healthy offspring of healthy parents (group B) were studied. The hsLR concentration (enzyme-linked immunosorbent assay method) and leptin plasma levels (radioimmunoassay method) were determined in the study population. Plasma leptin levels were significantly higher (10±5 vs 6±3 ng/mL; P<.001), while hsLR concentration was significantly lower (20±7 vs 29±8 U/mL; P<.001) in group A compared with group B. Our findings suggest that offspring of hypertensive parents have significantly higher plasma leptin levels and significantly lower hsLR concentrations compared with healthy offspring of healthy normotensive parents. Further studies are needed to determine the clinical significance of these observations. (J Clin Hypertens. 2006;8:797–802) ©2006 Le Jacq

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Leptin, a recently discovered 146–amino acid hormone, is synthesized and secreted primarily by adipocytes, and especially by an adipocyte-specific obese gene. Leptin concentration in the serum is directly proportional to the amount of adipose tissue. Serum leptin levels have been associated with cardiovascular risk factors after correction for adiposity. Recent studies suggest that hyperleptinemia may play a role in obesity-associated cardiovascular diseases, including atherosclerosis. Leptin exerts potentially atherogenic effects such as induction of endothelial dysfunction; inflammation; oxidative stress; and migration, hypertrophy, and proliferation of vascular smooth muscle cells. Leptin can promote platelet aggregation, which requires expression of functional leptin receptors on the platelet. Leptin-induced increases in sympathetic nerve activity have been suggested to contribute to hypertension, and has been observed to increase oxidative stress in cultured endothelial cells. Leptin-deficient and leptin receptor–deficient mice are protected from arterial thrombosis and neointimal hyperplasia in response to arterial wall injury.[1,2]

Several clinical studies have demonstrated that a high leptin level predicts acute cardiovascular events, restenosis after coronary angioplasty, and strokes, independently of traditional risk factors. In addition, plasma leptin correlates with markers of subclinical atherosclerosis such as carotid artery intima–media thickness and coronary artery calcifications. Clinical studies have shown elevated plasma leptin in hypertensive patients and a significant positive correlation between leptin and blood pressure (BP), independent of body adiposity, both in normotensive and in hypertensive individuals. Additionally, leptin may contribute to end-organ damage in hypertensive individuals, such as left ventricular hypertrophy, independently of BP.[2–4]

Leptin receptor has been identified as a leptin-binding protein that is a member of the class I cytokine receptor family, with a large extracellular domain comprising 816 amino acid residues. Leptin receptor exists in multiple forms and in multiple tissues in the body, with common extracellular domain and a variable-length cytoplasmic portion.[5–11]

The aim of this study was to test the hypothesis that elevated plasma leptin levels and a decreased concentration of human soluble leptin receptor (hsLR) exist in healthy offspring of hypertensive parents, and compare these levels to healthy offspring of parents without a history of cardiovascular disease.

METHODS

Two groups of patients were studied. Group A comprised 46 (24 male, 22 female; mean age, 18±3 years; body mass index [BMI], 22.4±1.4 kg/m^2) healthy offspring of at least 1 hypertensive parent. Group B comprised 50 (28 male, 22 female; mean age, 18±3.2 years; BMI, 22.6±1.7 kg/m^2) healthy offspring of parents without a history of essential hypertension, cardiovascular disease, or diabetes mellitus. Group B subjects were recruited when their parents had preoperative (mainly orthopedic or ophthalmologic) cardiac examinations a few days before surgery. They were included if they were normotensive (clinic BP within normal values), with no other serious illnesses.

The presence of hypertension was documented by BP measurements made in accordance with the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) criteria.[12] Mean systolic BP of hypertensive parents was 142±8 mm Hg, while mean diastolic BP was 95±4 mm Hg at baseline measurements (before any medication). The mean ages of the hypertensive and normotensive parents were 48±2.6 years and 46±3 years, respectively. Fifteen of the 46 healthy offspring in group A had 2 hypertensive parents and 31 had 1 hypertensive parent. The 2 groups had similar socioeconomic status and educational levels, while none of the participants or their parents had any metabolic abnormalities (eg, diabetes).

The participants from both groups were not taking medication and were nonsmokers. All subjects were on a standardized diet before sampling, and none had any thyroid abnormalities. Alcohol consumption was expressed in g/d, determined by a detailed questionnaire. Information concerning physical activity was obtained from a previously described questionnaire.[13] Before the study, written informed consent that was approved by the hospital review committee was obtained from each participant. The entire study population underwent routine clinical examination.

Blood Pressure and Laboratory Investigations

Systolic and diastolic BP were measured at the time of the first and fifth Korotkoff sounds, respectively. Measurements were made on the right arm to the nearest millimeter of mercury with a mercury sphygmomanometer. All measurements were made in the supine position after the patient had rested for 15 minutes. Results reported are the average of measurements obtained on at least 3 separate occasions. Recordings were performed by the same trained nurse, who was not aware of the history of the subjects. If the systolic BP and diastolic BP readings belonged to different categories, the higher of the 2 was used to assign the BP category.[14] Blood sampling was performed after 12 hours of fasting at 8–9 AM to determine plasma leptin levels and hsLR concentration. Plasma immunoreactive leptin (p-leptin) levels were measured by radioimmunoassay (Linco Research, Inc, St Charles, MO) and the plasma levels of hsLR were measured by immunoassay (RD194002100 Human Leptin Receptor, BioVendor Laboratory Medicine, Inc, Modrice, Czech Republic). Investigators performing the assays were not aware of the source of the samples. Results are reported as concentration of leptin (ng/mL) and hsLR (U/mL) in samples.

Statistical Analyses

Values are expressed as mean ± SD. An unpaired Student *t* test was used to assess differences between the 2 groups. A $P<.05$ was considered statistically significant. All analyses were performed with the SPSS statistical package (SPSS Inc, Chicago, IL).

RESULTS

As shown in Table I, baseline characteristics were similar between the 2 groups. There were no statistically significant differences for age, sex, and BMI between the 2 groups. None of the participants were smokers. No differences were found for physical activity or alcohol consumption (data not shown).

As is shown in Table II and depicted in the Figure, significantly higher ($P<.01$) plasma leptin levels were found in group A compared with group B (10±5 vs 6±3 ng/mL; $P<.001$) while the hsLR concentration was significantly lower in group A compared with group B (20±7 vs 29±8 U/mL; $P<.001$).

Table I. Demographic Characteristics of the Study Groups

Characteristic	Group A* (n=46)	Group B† (n=50)
Age, y	18±3	18±3.2
Body mass index, kg/m^2	22.4±1.4	22.6±1.7
Sex, male/female, No.	24/22	28/22
Serum glucose, mg/dL	90±7	91±7.4
Serum creatinine, mg/dL	0.90±0.35	0.90±0.32
Total cholesterol, mg/dL	205±18	204±20
HDL-C, mg/dL	48±3	49±4
Triglycerides, mg/dL	80±12	79±13

No significant differences were found between the groups for any characteristic shown. *Healthy offspring of at least 1 hypertensive parent. †Healthy offspring of healthy parents. HDL-C indicates high-density lipoprotein cholesterol.

Table II. Results and Comparison Between Groups

	Group A N=46	Group B N=50	*P*
Systolic BP, mm Hg	120±12	112±9.5	<.001
Diastolic BP, mm Hg	78±6	73±8	<.05
hsLR, U/mL	20±7	29±8	<.001
Leptin, ng/mL	10±5	6±3	<.001

See Table I for description of groups. BP indicates blood pressure; hsLR, human soluble leptin receptor.

DISCUSSION

The current study demonstrated that the mean hsLR concentration was lower, while the mean plasma leptin level was higher, in healthy offspring of hypertensive parents compared with healthy offspring of normotensive parents, even when age, sex, and BMI were matched for the 2 groups.

Data from human studies have demonstrated a significant correlation between plasma leptin levels and arterial hypertension. Uckaya et al[15] demonstrated significantly higher plasma leptin levels in patients with essential hypertension than in controls, while Hirose et al[16] confirmed a significant correlation between mean BP and leptin after adjustment for age and BMI. Suter et al[17] and Kennedy et al[18] demonstrated a clear association between leptin levels and BP in hypertensive men and women. Wallerstedt et al[19] indicated that serum leptin is associated with myocardial infarction in a hypertensive population. Leptin concentrations may be of practical importance when estimating the risk of myocardial infarction, especially in women, where leptin was found to be the most important predictor for myocardial infarction.[19]

Ren[20] showed that elevated plasma leptin levels have been correlated with hyperphagia, insulin resistance, and other markers of the metabolic syndrome including obesity, hyperlipidemia, and hypertension, independent of total adiposity. In another study, Schutte et al[21] confirmed that leptin is independently associated with systolic BP, pulse pressure, and arterial compliance in hypertensive African women with increased adiposity. Makris et al[22] have shown a significant correlation between leptin levels and BP in healthy offspring of hypertensive parents compared with healthy offspring of normotensive parents, which is in agreement with our results.

In a recently published study from our laboratory,[23] we calculated the concentration of hsLR in patients with high-normal BP according to the European guidelines for hypertension.[24] We found that subjects with high-normal BP have significantly elevated plasma leptin levels and a significantly decreased concentration of hsLR compared with individuals with normal BP. This observation may explain in part the pathogenesis of cardiovascular events in this group of patients.

Data from the Trial of Preventing Hypertension (TROPHY) substudy,[25–27] which aims to assess whether early pharmacologic treatment in subjects with high-normal BP (prehypertension) might prevent or delay the development of clinical hypertension, suggest that the risk of cardiovascular disease begins to increase before a definitive diagnosis of hypertension is made. The risk of incident hypertension was reduced in these patients by the use of an angiotensin receptor blocker compared with a placebo. These data support the practice of examining healthy normotensive individuals with high-normal BP in an attempt to categorize them according to their cardiovascular risk as a basis for the prevention of future heart disorders.

The results of our study support the hypothesis that a link exists among hypertension, leptin, and its receptor. Levels of leptin and its receptor could be considered an independent risk factor for

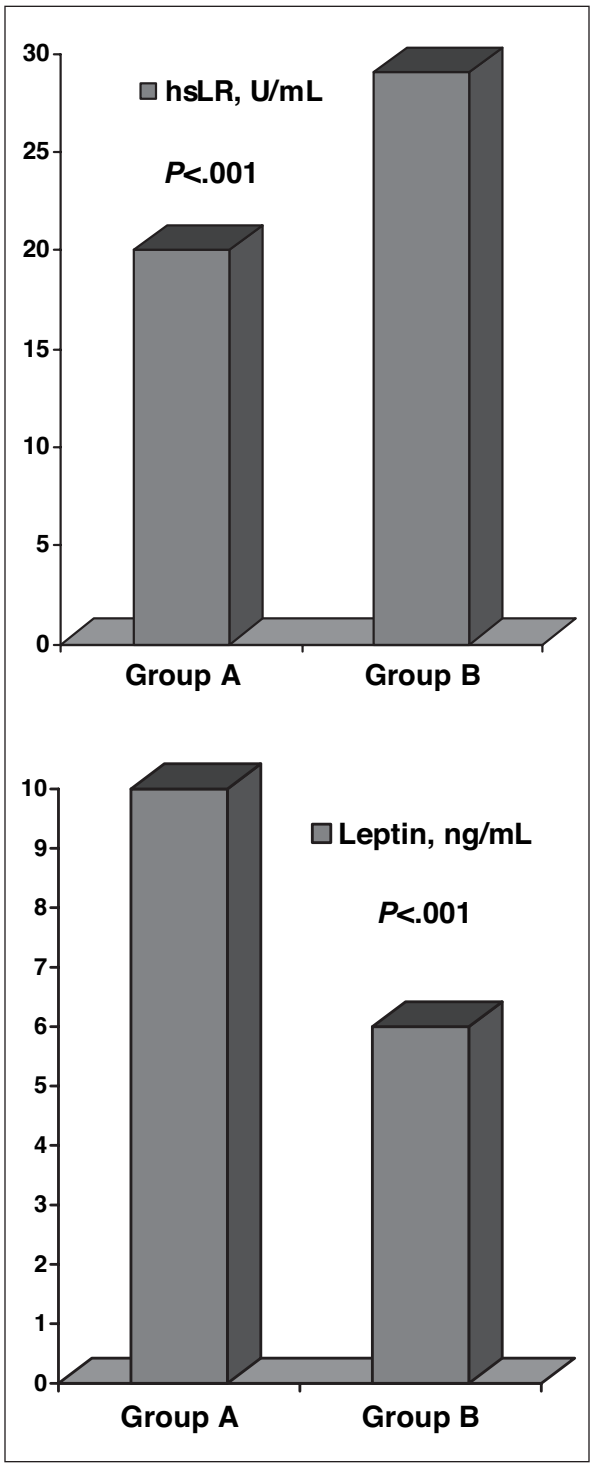

Figure. Plasma human soluble leptin receptor (hsLR) levels (top) and leptin levels (bottom) in healthy offspring of hypertensive parents (group A) and healthy offspring of healthy parents (group B).

hypertension[28] and/or coronary artery disease.[29,30] The combination of high leptin levels and increased systolic or diastolic BP is strongly associated with a rise in hemorrhagic stroke in males.[31]

Experimental pathophysiologic data have shown that leptin binding sites have been found in brain regions that are important in cardiovascular control; there is reason to suspect that leptin may affect cardiovascular function partly through its effects on the central nervous system. Current hypotheses suggest that leptin may have a balanced effect on BP, with central stimulation through sympathetic activation and a local depressor effect attributable to local nitric oxide (NO) release.[32,33] The regulatory effects of leptin on vascular tone and BP have been examined by intracerebroventricular and IV administration of leptin, demonstrating central as well as peripheral actions of the hormone. In addition to its central neurohormonal sympathetic excitation, which significantly increases the sympathetic outflow to kidneys, adipose tissue, skeletal vasculature, and adrenal medulla in rodents, leptin may exert direct peripheral vascular actions on certain vasoactive mediators such as NO and endothelin-1. Leptin has been shown to directly induce vasorelaxation through NO-dependent as well as NO-independent mechanisms. So while the enhanced sympathetic nervous activation is expected to increase vascular tone and BP, leptin has been shown to elicit peripheral vascular relaxation when sympathetic control is removed.[20,32–35] Recent data in patients with essential hypertension have shown an inverse relation between BP and vascular activity of NO.[36] The reduction of hsLR concentration plus the significantly enhanced plasma leptin levels in healthy offspring of hypertensive parents may lead to endothelial dysfunction and impaired vasorelaxant activity of leptin, which consequently could lead to derangement of the hypothesized leptin homeostasis.

In the clinical setting, the most common leptin abnormality in patients is receptor insensitivity, leading to secondary circulating leptin excess and peripheral leptin resistance.[37] A good analogy for this condition is type 1 vs type 2 diabetes mellitus, where increasing levels of insulin are necessary in type 2 diabetes to control blood glucose because of insulin resistance. Indeed, in the commonest clinical settings of leptin resistance or leptin receptor insensitivity, there is concurrent insulin resistance or insulin receptor insensitivity. In these settings circulating leptin level is elevated. Serum leptin levels have been shown to be an independent predictor of cardiovascular morbidity and mortality in these conditions. Leptin levels therefore serve as a marker for the degree of receptor resistance and the underlying severity of the metabolic derangement.[38] This can explain our

findings that enhanced leptin plasma levels can be associated with leptin resistance, and consequently a decreased hsLR concentration.

The mechanisms of leptin plasma elevation in healthy offspring of hypertensive parents are not clear. Possible mechanisms include: (1) a difference in fat mass between the healthy offspring of hypertensive parents and healthy offspring of healthy parents despite the matching BMI; (2) a difference in the signaling of fat-cell kinetics between the 2 groups; or (3) a compensation to leptin resistance in healthy offspring of hypertensive parents.

One limitation of our study is that we have not evaluated plasma insulin levels and insulin resistance in our study population; accumulating evidence has suggested a close interaction between hyperleptinemia and hyperinsulinemia. It is also well known that leptin exerts its effect by using tissue receptors, while the role of soluble receptors is not completely clarified; this is another limitation of our study.

The limitations of BMI for estimating body fat are known, and it is possible that more accurate measures of adipose tissue mass might be necessary to categorically exclude obesity as a common antecedent. A simple waist measurement might be a better approach. Studies that were conducted with the use of alternate methods, however, such as abdominal subcutaneous tissue biopsies or computed tomographic scan, have shown correlations with leptin levels similar to those found in our study or previous studies.[39–41] To our knowledge, this is the first time that a decreased concentration of hsLR has been identified in healthy offspring of hypertensive parents.

CONCLUSIONS

Our findings suggest that healthy offspring of hypertensive parents have significantly elevated plasma leptin levels and a significantly decreased concentration of hsLR compared with healthy offspring of healthy parents. Further studies are necessary to confirm these observations, but they support the practice of examining children and young adults for cardiovascular risk as a basis for prevention of adult heart disorders.

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