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DOI: [https://doi.org/10.1016/s0895-7061\(98\)00162-9](https://doi.org/10.1016/s0895-7061(98)00162-9)

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Journal Article

Published Version

Originally published at:

Suter, P M; Locher, R; Hasler, E; Vetter, W (1998). Is there a role for the ob gene product leptin in essential hypertension? *American Journal of Hypertension*, 11(11):1305-1311.

DOI: [https://doi.org/10.1016/s0895-7061\(98\)00162-9](https://doi.org/10.1016/s0895-7061(98)00162-9)

Is There a Role for the ob Gene Product Leptin in Essential Hypertension?

Paolo M. Suter, Rudolf Locher, Erik Häsler, and Wilhelm Vetter

In this study we wanted to evaluate the relationship between the ob gene product leptin and blood pressure, as well as plasma renin activity and plasma aldosterone levels. We studied 139 subjects with a mean \pm SD age of 50 ± 14 years and a body mass index of 26.5 ± 5.3 kg/m²; 110 subjects had essential hypertension and 29 were healthy nonhypertensive controls. Blood pressure was measured in resting conditions in the morning and blood was drawn for the determination of the plasma renin activity, aldosterone, and leptin levels. The mean blood pressure of the population was 155/97 mm Hg. The relationship between these parameters was studied by univariate regression analysis according to gender and, whenever indicated, adjusted for age and body mass. The mean \pm SEM plasma leptin level in the whole population was 9.5 ± 0.6 ng/mL (range, 1.1–43.3). Subjects with stage I hypertension had significantly higher plasma leptin levels than normotensive subjects. Systolic blood pressure correlated with the plasma leptin levels and the leptin levels adjusted for body weight in women ($r = 0.422$, $P < .01$) and nonhypertensive men ($r = 0.644$, $P = .03$) only.

Plasma renin activity ($r = 0.329$, $P = .03$) and aldosterone levels ($r = 0.342$, $P = .026$) correlated with the leptin concentration. A significant relationship between the peripheral expression of the ob gene product leptin and systolic blood pressure was found in women and nonhypertensive men. In view of the multiple functions of leptin a causal relationship is postulated and potential mechanisms may involve modulatory effects of leptin on neuropeptide Y, angiotensinogen gene expression, the modulation of the autonomous nervous system, or effects on the pituitary adrenal axis. Direct relationships between both plasma renin activity and aldosterone levels and leptin support the potential importance of the relationship between leptin and blood pressure. Our observation may be of future importance for the understanding of the link between the increase in blood pressure and increasing body weight. Am J Hypertens 1998;11:1305–1311 © 1998 American Journal of Hypertension, Ltd.

KEY WORDS: ob gene product, leptin, obesity, blood pressure, essential hypertension, renin, aldosterone.

The pathogenesis of essential hypertension is still not fully elucidated. An increased body weight and obesity are often associated with increased blood pressure and hypertension. Nevertheless, the pathophysiologic mechanisms of essential hypertension and the blood pressure rise in

obesity are not yet known and different mechanisms have been suggested.¹ Hormonal changes associated with obesity, especially hyperinsulinemia, have been suggested as an important pathophysiologic mechanism for the development of hypertension in obese subjects.^{1,2} Recently adipose tissue has been claimed to be a hormone-producing tissue and several hormones produced in the adipocytes have been identified, one of them being the ob gene product leptin.³ Leptin represents an adipocyte-derived plasma protein, which has been identified as the mutant gene product in ob/ob mice.

Leptin (from the greek word *leptos* meaning thin)

Received January 9, 1998. Accepted June 12, 1998.

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TABLE 1. AGE, ANTHROPOMETRIC CHARACTERISTICS, BLOOD PRESSURE, LEPTIN LEVELS, PLASMA RENIN ACTIVITY, AND ALDOSTERONE LEVELS IN THE STUDY POPULATION ACCORDING TO ANTIHYPERTENSIVE MEDICATION

Parameter	All Patients (n = 139)	Without Antihypertensive Medication (n = 62)	With Antihypertensive Medication (n = 77)	*P
Age (years)†	49 ± 14	43 ± 2	54 ± 1	.000
Gender (m/f)	75/64	30/32	45/32	.20‡
Body weight (kg)†	75 ± 1	68.8 ± 2	78.7 ± 1.8	.81
Height (m)†	1.68 ± 0.1	1.68 ± 0.1	1.67 ± 0.1	.32
Body mass index (BMI; kg/m ²)	26.5 ± 0.5	24.4 ± 0.6	28.3 ± 0.6	.000
Systolic pressure (mm Hg)	156 ± 3	142 ± 4	167 ± 3	.000
Diastolic pressure (mm Hg)	97 ± 1	89 ± 2	102 ± 2	.000
Heart rate (beats/min)	73 ± 1	71 ± 2	75 ± 2	.13
Serum leptin (ng/mL)	9.5 ± 0.6	8.67 ± 0.96	10.28 ± 0.85	.21
Serum leptin/kg body weight (ng/mL/kg)	0.13 ± 0.007	0.12 ± 0.01	0.13 ± 0.01	.47
Serum leptin/BMI (ng/mL)	0.34 ± 0.02	0.34 ± 0.03	0.36 ± 0.03	.66
Plasma renin activity (μg/L/h)§	1.96 ± 0.4	1.06 ± 0.74	2.34 ± 0.47	.15
Plasma aldosterone (pmol/L)§	206 ± 16	205 ± 31	207 ± 19	.97

* P or the difference with or without medication.

† Mean ± SD (all other, mean ± SEM).

‡ by χ^2 statistics.

§ Only 105 subjects.

represents a 16-kDA protein secreted from the adipose tissue cells. The circulating levels of leptin reflect the white adipose tissue mass and, accordingly, there is a rather good correlation between absolute body weight or fat mass and circulating leptin levels. This adipose tissue hormone may play a role in the regulation of food intake and energy expenditure by its action on central nervous system networks, including the modulation of the autonomous nervous system or interaction with specific neurotransmitters.^{4,5} Although presently leptin's major role seems to be in the regulation of food intake and energy metabolism, recent evidence suggests that this hormone may extend its effects and functions well beyond these aspects of body weight regulation to include other organ systems such as kidney, lung, testis, prostate, bone marrow, as well as the cardiovascular system.^{4,6-11} Due to these multiple effects of leptin it is conceivable that this hormone may directly or indirectly interfere with the regulation of blood pressure and thus hypertension.

The discovery and description of the ob gene may for the first time provide a molecular device to understand the pathophysiologic basis of obesity and also the associated metabolic disorders such as hypertension. In view of these new findings and concepts, in this study we examined the possible associations between systolic and diastolic blood pressure, blood pressure regulatory hormones (renin and aldosterone), and serum leptin concentrations in normal controls and hypertensive subjects.

SUBJECTS AND METHODS

One hundred thirty-nine subjects with a mean (\pm SD) age of 49.5 ± 13.8 years and a mean (\pm SD) body mass index (BMI) of 26.5 ± 5.3 kg/m² participated in the study. The mean body weight distribution of the population corresponds to $120\% \pm 2\%$ of the Metropolitan Life Insurance Ideal Body Weight. The gender distribution of male to female (m/f) was equally distributed for the whole population (75/64). Twenty-nine subjects were healthy controls (m/f = 13/16) recruited from the hospital staff; 110 subjects were consecutive admissions (m/f = 62/48) to the Medical Policlinic at the University Hospital of Zürich. Seventy-seven (56%) subjects were taking antihypertensive medication. The blood pressure, antihypertensive medication, and selected biochemical and anthropometric characteristics of the study population are summarized in Table 1. The admission diagnosis or one of the major diagnoses of all subjects in the patient group was an elevated blood pressure (ICD Code 401). Upon arrival in the hospital the usual medical workup was done and resting blood pressure was measured in a sitting position after at least a 10-min rest using a mercury sphygmomanometer; the heart rate was recorded at the same time. Height and weight were measured and the BMI computed (BMI, weight [kg] divided by height [meters] squared). Blood was drawn in the morning after 10-12 h fasting for a routine laboratory analysis (electrolytes, kidney and

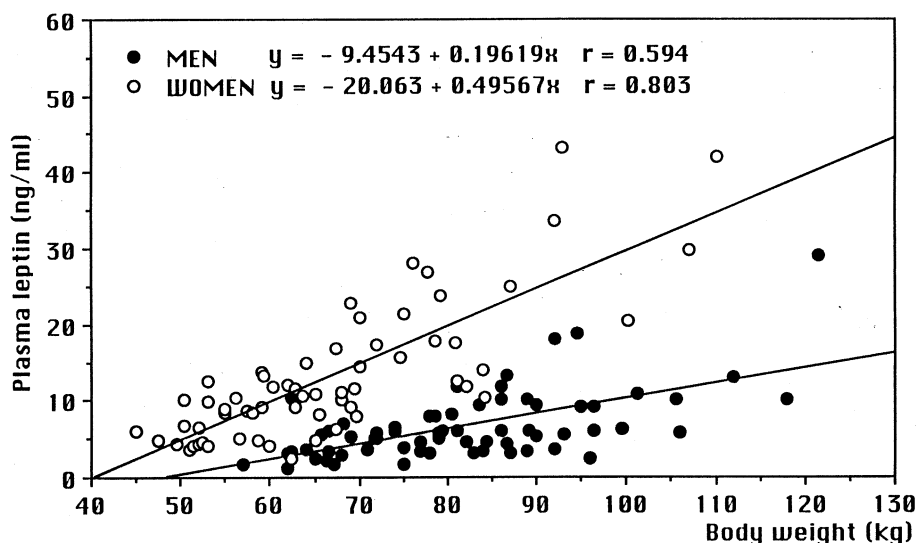


FIGURE 1. Relationship between body weight (kg) and plasma leptin levels (ng/mL) in men and women.

liver function, and white and red blood cells) and plasma was collected for the leptin assay. In a subgroup of subjects ($n = 106$) blood was drawn after the subjects lay supine with an indwelling catheter for 30 min for the determination of plasma renin activity and plasma aldosterone levels. The only exclusion criteria were reduction dieting, overfeeding, or severe illness.

Leptin Radioimmunoassay (RIA) The plasma leptin levels were determined by radioimmunoassay (RIA, LINCO Research Inc., St. Charles, MO). In these kits antibodies were raised against highly purified human leptin and both the standard and tracer prepared with human leptin. All samples were assayed in duplicate and the reliability tested. The assay variability was tested and was found to be in the range of 0.95%–1.2%.

Other Biochemical Determinations Fasting plasma glucose was determined using standard laboratory tests. Thyroid function was assessed by the measurement of circulating thyroid stimulating hormone (TSH) levels. Quantitative determination of plasma renin activity (PRA) was done by the radioimmunoassay of generated angiotensin I (GammaCoat Plasma Renin Activity ^{125}I RIA Kit, Incstar Corporation, Stillwater, MN) and plasma aldosterone levels were determined by a radioimmunoassay.¹²

Statistical Methods The normality of the data was confirmed by the Shapiro-Wilk W test. The potential relations between the variables of interest were tested by univariate regression analysis. All statistical tests are two-tailed and a $P < .05$ was regarded as statistically significant. All values are expressed as mean \pm SEM, unless otherwise stated. Because some parameters of interest were not normally distributed, selected analyses were done based upon a natural log transformation of the measured values. The statistical anal-

ysis were done with the JMP 2.05 Program (SAS Institute Inc., Cary, NC) and the StatView Program (Abacus Concepts, Berkeley, CA). Many factors may affect plasma leptin levels; however, body weight seems to be of major importance. Because the plasma leptin levels reflect mainly the white adipose tissue mass per body weight, the measured plasma leptin levels were adjusted for absolute body weight (kg) or BMI whenever indicated. Because women show higher leptin levels for a certain adipose tissue mass or body weight, selected analyses have been made separately by gender.¹³

RESULTS

The ob gene product was expressed in all subjects, and the mean (\pm SEM) plasma leptin level in the population was 9.5 ± 0.6 ng/mL (range, 1.1 to 43.3). Women had significantly higher leptin levels than men (12.0 ± 0.95 ng/mL *v* 6.65 ± 0.78 ng/mL, $P < .001$); in both gender groups as well as the whole population the plasma leptin values were normally distributed. The gender difference in plasma leptin levels was found in subjects with a body mass index (BMI, kg/m^2) ≤ 25 kg/m^2 and ≥ 25 kg/m^2 . The relationship between body weight and plasma leptin levels according to gender in the population is shown in Figure 1.

The mean systolic and diastolic blood pressures of the whole population were 155 ± 3 mm Hg and 97 ± 1 mm Hg, respectively. The systolic blood pressure correlated with the BMI in the subjects without anti-hypertensive medication ($r = 0.514$, $P < .0001$; adjusted for age); the corresponding values for the diastolic blood pressure were $r = 0.462$ and $P < .001$, respectively. Sixty-seven percent of the subjects showed a systolic blood pressure ≥ 140 mm Hg, and 66% of the subjects had a diastolic pressure ≥ 90 mm

TABLE 2. SERUM LEPTIN LEVELS \pm SEM IN THE WHOLE POPULATION ACCORDING TO BLOOD PRESSURE STATUS USING THE U.S.-JOINT NATIONAL COMMITTEE CLASSIFICATION CRITERIA¹⁴

	n	Serum Leptin (ng/mL)	Serum Leptin (ng/mL/[kg body weight])
Systolic blood pressure			
Normal	23	6.7 \pm 1.6	0.11 \pm 0.02
High normal	14	9.7 \pm 2.0	0.12 \pm 0.02
Stage I	33	10.1 \pm 1.3	0.14 \pm 0.01
Stage II	25	11.7 \pm 1.5	0.13 \pm 0.02
Stage III	23	9.6 \pm 1.6	0.13 \pm 0.02
Stage IV	8	11.5 \pm 2.6	0.17 \pm 0.03
Diastolic blood pressure			
Normal	31	7.9 \pm 1.4	0.11 \pm 0.01
High normal	4	5.9 \pm 3.8	0.11 \pm 0.04
Stage I	33	10.1 \pm 1.3	0.13 \pm 0.01
Stage II	24	10.9 \pm 1.5	0.14 \pm 0.02
Stage III	24	10.5 \pm 1.6	0.13 \pm 0.02
Stage IV	10	11.6 \pm 2.43	0.15 \pm 0.03

Hg. Plasma leptin levels in subjects less than or greater than the latter systolic cutoff were $8.3 \pm 1.2/10.5 \pm 0.8$ ng/mL ($P = .1$ for the difference). The corresponding values for the diastolic cutoff were $8.1 \pm 1.2/10.7 \pm 0.8$ ng/mL ($P = .07$), respectively. Plasma leptin levels \pm SEM in the entire population according to systolic and diastolic blood pressure status using the U.S.-Joint National Committee criteria¹⁴ are summarized in Table 2 (ANOVA for nonsignificant trend). The male/female ratio in the different blood pressure groups was identical in all stages of hypertension (χ^2 , ns).

Plasma leptin levels were significantly higher in stage I hypertensives than in subjects with normal blood pressure (10.1 ± 0.98 ng/mL *v* 6.7 ± 1.2 ng/mL, $P = .03$); adjusting the leptin levels for body weight (kg) or body mass index (kg/m²) led to a loss of the statistical significance of the difference; however, a lower plasma leptin concentration in the nonhypertensive subjects was still evident (0.13 ± 0.01 ng/mL *v* 0.14 ± 0.01 ng/mL).

There was no correlation between leptin and the systolic ($r = 0.158$, $P = .07$) and diastolic ($r = 0.165$, $P = .06$) blood pressure in the whole population (ie, including subjects taking antihypertensive medication). The univariate correlation coefficient (r) between plasma leptin levels and systolic and diastolic blood pressure for the population, as well as in different subgroups of the population according to gender and hypertension status, is summarized in Table 3. The relationship was found to be significant in women and nonhypertensive men only. There was no difference in leptin levels in subjects according to the presence of antihypertensive therapy.

TABLE 3. UNIVARIATE CORRELATIONS (r , ADJUSTED FOR AGE) BETWEEN TOTAL PLASMA LEPTIN, ADJUSTED FOR BODY WEIGHT, AND BP (SYSTOLIC/DIASTOLIC) FOR THE WHOLE POPULATION AND SUBGROUPS, ACCORDING TO GENDER AND BP MEDICATION

Group/Subgroup	r With Total Leptin	r With Leptin/kg Body Weight*
Whole population	0.115/0.106	0.100/0.050
Without medication†	0.322‡/0.200	0.264§/0.122
Hypertensives	0.056/0.060	0.078/0.018
Normotensive controls	0.329#/0.220	0.149/0.203
Men		
All	0.089/0.119	0.000/0.014
Without medication	0.230§/0.219	0.210§/0.146
Hypertensives	-0.144/-0.209	-0.109/-0.165
Normotensive controls	0.644§/0.291	0.631§/0.258
Women		
All	0.317‡/0.330‡	0.361**/0.343‡
Without medication	0.422‡/0.254	0.401§/0.224
Hypertensives	0.150/0.300#	0.233/0.348#
Normotensive controls	0.116/0.177	0.127/0.240

* Plasma leptin levels divided by body weight (see Subjects and Methods section); † The group without medication includes healthy controls and hypertensive patients without medication; ‡ $P < .01$; § $P < .05$; # $P < .05$; ** $P < .001$.

The plasma renin activity (PRA) did not correlate with plasma leptin levels in the whole population ($r = 0.054$, $P = .53$). In the whole population plasma aldosterone levels correlated positively with plasma leptin levels ($r = 0.196$, $P = .04$). Limiting the analysis to subjects without antihypertensive medication or without any medication influencing the renin-angiotensin-aldosterone system ($n = 42$) showed a positive relation for the PRA ($r = 0.329$, $P = .03$) as well as aldosterone levels ($r = 0.342$, $P = .026$) with increasing plasma leptin levels (Fig. 2).

Heart rate correlated significantly with plasma leptin levels in the whole population ($r = 0.224$, $P = .01$) independently of gender. In subjects without any antihypertensive medication this relationship was $r = 0.372$ ($P = .008$). No relationship was found between age and plasma leptin levels.

DISCUSSION

Our data show a positive relationship between systolic blood pressure and plasma leptin concentration. This relationship was found to be significant in women and nonhypertensive men only.

Several lines of evidence based on our descriptive data suggest a potential role of the ob gene product leptin in the regulation of blood pressure or in the pathogenesis of essential hypertension. First, leptin levels (adjusted for adipose tissue mass or body mass)

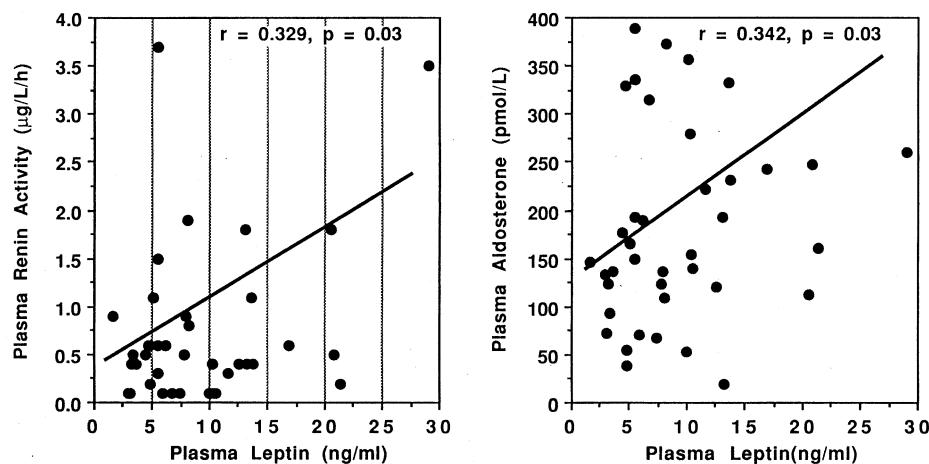


FIGURE 2. Relationship between plasma leptin levels and plasma renin activity and plasma aldosterone levels.

correlated with systolic blood pressure in women and in nonhypertensive men. The relationship was not significant for diastolic blood pressure. This relationship was independent of age and body weight. Second, serum leptin levels correlated with plasma renin activity (PRA) and aldosterone plasma levels (Fig. 2). Third, there was a close relationship between heart frequency and plasma leptin levels, which is in agreement with modulatory effects of leptin on the sympathetic nervous system. This constellation of findings in our population suggests a role for the ob gene product in blood pressure regulation. The described relationships were statistically not very strong, which may be due to the heterogeneity of our study population or the possibility that leptin only has a minor role in the pathogenesis of hypertension.

Our findings are in agreement with a recent study of the metabolic significance of leptin in humans, where a relationship between elevated systolic and diastolic blood pressure has been described in men.¹⁵ Interestingly, in this study no relationship was found for women. These authors suggested that the lack of a relationship between blood pressure and leptin levels in women is in agreement with the findings that leptin is associated with insulin resistance only in men and that insulin resistance is associated with an elevated blood pressure.

There are several lines of evidence that may support our hypothesis that leptin may play a role in blood pressure regulation. An increased body weight and obesity are associated with increased blood pressure. Serum insulin levels correlate with serum leptin levels¹⁶ and it may be hypothesized that these two hormones may interact and modulate the effects of each other and contribute to a common mechanism leading to hypertension.^{2,17} Because we did not measure fasting insulin levels in our patients no statement regarding the interaction between the two hormones of interest can be made.

The importance of the classical renin-angiotensin system (RAS) in the regulation of blood pressure is well known and established.¹⁸ Several lines of evidence suggest that the angiotensinogen (AGT) gene is expressed in different tissues, including the adipose tissue.^{19,20} Accordingly, adipose tissue may contribute to the regulation of blood pressure, as AGT represents the substrate from which the hypertensive hormone angiotensin II is formed and adipocytes have been shown to form angiotensin-I and angiotensin-II.^{19,21,22} It has been reported that in hypertensive animals the AGT gene shows a higher expression in adipose tissue than in normotensive controls, independent of body weight. Further it was shown that the AGT is elevated in adipose tissue from obese ob/ob and db/db mice.²³ The AGT expression in adipose tissue is regulated by different factors and was shown to decrease during fasting and was restored by refeeding, situations that are parallel to a decrease and increase of the blood pressure, respectively. Insulin has been shown to increase AGT mRNA content in adipocytes.²³ Recently it has been suggested that the ob gene product leptin may contribute to the up-regulation of this gene in adipocytes and thus may eventually contribute to the pathogenesis of hypertension.²¹⁻²⁵ These findings may suggest that the relationship between blood pressure and leptin levels may be of pathophysiologic importance. However, as summarized in Figure 3, the role of leptin may be of only secondary, indirect importance by modulating other endocrine factors of blood pressure regulation such as stimulation of the production of angiotensinogen in adipose tissue.

An increase in body weight or obesity has been found to result in an activation of the sympathetic nervous system, which is also reflected in higher epinephrine and norepinephrine plasma levels in obese subjects.^{2,26} Leptin interacts with specific receptors in the hypothalamus and has been reported to decrease

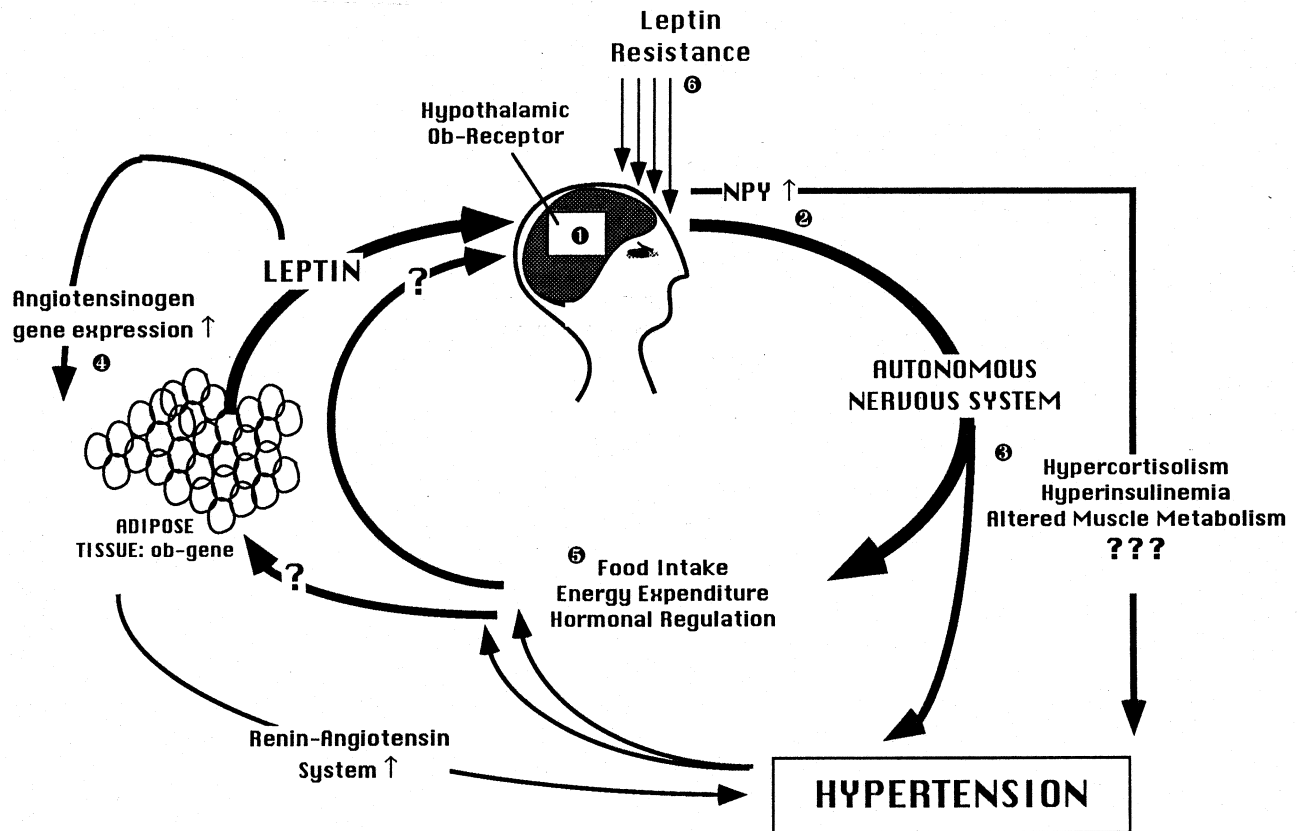


FIGURE 3. A hypothetical model of the role of the ob gene product leptin in blood pressure regulation.

the levels of neuropeptide Y (NPY).^{5,9,27,28} It has been hypothesized that the suppression of NPY by leptin leads to an activation of the sympathetic nervous system.¹⁵ The latter hypothesis seems attractive but remains to be proved. NPY has many different central and peripheral cardiovascular effects that may directly or indirectly affect blood pressure.²⁹ Hypercortisolism may also contribute to the pathogenesis of higher blood pressure, as hyperleptinemia may also lead to an increase in basal plasma ACTH and corticosterone levels in certain experimental conditions.³⁰ In obese subjects, therefore, two mechanisms may lead to increased blood pressure and both may be related to increased leptin levels in obese subjects. The increased activity of the sympathetic nervous system in obesity and increased angiotensin I and II production at the level of the adipocyte may lead to increased vasoconstrictory stimulus and thus hypertension.

Further, leptin may be of crucial importance in the regulation of fuel homeostasis,¹⁶ and the proportion of oxidation of the different energy substrates may affect the regulation of vascular tone and thus affect blood pressure. Another possible mechanism for the potential effects of leptin on the regulation of blood pressure may be through the effects on neural networks, which

may interfere with regulatory systems of blood pressure in the central nervous system. Many effects of the ob gene product seem to be mediated by the modulation of the sympathetic nervous system or by modulation of the central nervous system output.²⁷ In an animal model using Sprague-Dawley rats the chronic infusion of leptin led to a reversible increase in arterial pressure.³¹ The potential mechanisms and interrelations are summarized in Figure 3.

Our data suggest a relationship between the peripheral expression of the ob gene product leptin and systolic blood pressure in women and nonhypertensive men. Whether this association is independent from other factors (especially other hormones, such as insulin) is unknown and our data do not permit us to formulate defined mechanisms for the leptin-blood pressure interaction. It is not possible to give a final answer to the question formulated in the title of this paper. In view of the low-level correlations in this study and the known relative importance of other hormones and mediators in the regulation of blood pressure, the most likely answer would be "not much." Nevertheless, our observation may be of future importance for the understanding of the link between the increase in blood pressure and increasing body weight.

ACKNOWLEDGEMENTS

The assistance and help in the determination of plasma renin, aldosterone, and leptin concentrations by Mrs. Küffer and Mrs. Meier, respectively, is greatly appreciated.

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