

Role of sympathetic nervous system and neuropeptides in obesity hypertension

JE Hall, MW Brands, DA Hildebrandt, J Kuo, S Fitzgerald

Abstract

Obesity is the most common cause of human essential hypertension in most industrialized countries. Although the precise mechanisms of obesity hypertension are not fully understood, considerable evidence suggests that excess renal sodium reabsorption and a hypertensive shift of pressure natriuresis play a major role. Sympathetic activation appears to mediate at least part of the obesity-induced sodium retention and hypertension since adrenergic blockade or renal denervation markedly attenuates these changes. Recent observations suggest that leptin and its multiple interactions with neuropeptides in the hypothalamus may link excess weight gain with increased sympathetic activity. Leptin is produced mainly in adipocytes and is believed to regulate energy balance by acting on the hypothalamus to reduce food intake and to increase energy expenditure via sympathetic activation. Short-term administration of leptin into the cerebral ventricles increases renal sympathetic activity, and long-

term leptin infusion at rates that mimic plasma concentrations found in obesity raises arterial pressure and heart rate via adrenergic activation in non-obese rodents. Transgenic mice overexpressing leptin also develop hypertension. Acute studies suggest that the renal sympathetic effects of leptin may depend on interactions with other neurochemical pathways in the hypothalamus, including the melanocortin-4 receptor (MC4-R). However, the role of this pathway in mediating the long-term effects of leptin on blood pressure is unclear. Also, it is uncertain whether there is resistance to the chronic renal sympathetic and blood pressure effects of leptin in obese subjects. In addition, leptin also has other cardiovascular and renal actions, such as stimulation of nitric oxide formation and improvement of insulin sensitivity, which may tend to reduce blood pressure in some conditions. Although the role of these mechanisms in human obesity has not been elucidated, this remains a fruitful area for further investigation, especially in view of the current *epidemic* of obesity in most industrialized countries.

Keywords: Obesity; Leptin; Angiotensin; Kidney; Sodium excretion.

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Department of Physiology Biophysics – University of Mississippi Medical Center

Correspondência:

Dr. John E. Hall

Department of Physiology and Biophysics – University of Mississippi Medical Center – 2500 North State Street – Jackson, MS 39216-4505 – USA – Ph: (601) 984-1801 – Fax: (601) 984-1817 – E-mail: jehall@physiology.umsmed.edu

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Introduction

Approximately 30% to 35% of the adult population in the United States is at least 20% overweight, with a body mass index (BMI) greater than 27 kg/m²^{1,2}. In some groups, such as African American women older than age 45-50, the prevalence of obesity may be as high as 70% to 80%, coinciding with a 70% to 80% rate of hypertension³. Because cardiovascular morbidity and mortality increase substantially as BMI rises above 25 kg/m²^{4,5}, this level of BMI should perhaps be considered overweight. By this more stringent definition, over half of the adult population in the United States is overweight². Similar statistics exist for other industrialized countries, leading nutrition experts to declare an *epidemic* of obesity¹.

Obesity is a major cause of human essential hypertension

An important consequence of excess weight is increased blood pressure. Epidemiological studies indicate that hypertension is rare in lean populations, but common in overweight groups⁵. The relationship between obesity and hypertension cannot be attributed solely to genetic factors since it is observed in diverse populations throughout the world, and in populations of similar origin living in different locations⁵. Other cardiovascular risks associated with industrialization cannot fully explain this relationship because it has been observed in multiple studies of *primitive* non-industrialized societies⁵. Thus, obesity and hypertension appear to be inextricably linked. Risk estimates from the Framingham Heart Study suggest that approximately 78% of essential hypertension in men and 65% in women can be directly attributed to obesity⁶.

Experimental studies in animals and humans have reinforced the importance of obesity in causing hypertension by demonstrating a rise in blood pressure with weight gain due to a chronic high fat diet. Moreover, weight loss lowers blood pressure in normotensive and hypertensive subjects even when sodium intake is prevented from decreasing^{5,7}. The therapeutic value of weight loss in lowering blood pressure has been repeatedly demonstrated in multiple clinical studies.

Blood pressure and BMI are closely associated. Figure 1 shows a linear relationship between BMI and blood pressure in over 22,000 Korean subjects, most of whom were not overweight⁸. A similar relationship between BMI and blood pressure has been found in normotensive and hypertensive subjects in diverse groups of people, including those of West African origin, Caucasians and Asians⁵.

This close association between BMI and blood pressure is somewhat unexpected since BMI, although correlated with obesity, is not a direct

marker of adiposity. For example, older individuals with loss of skeletal muscle mass may have normal BMI despite increased adiposity. Measurement of BMI also does not take into account the distribution of body fat which appears to be an important risk factor for cardiovascular disease; hypertension and insulin resistance are more prevalent in subjects with central compared to lower body obesity⁹. The fact that there is a clear association between BMI and arterial pressure even in non-obese, lean populations, however, indicates that the effect of weight gain on blood pressure regulation may be more complex than can be explained simply by increasing adiposity.

Why are some obese people “normotensive”? The observation that some obese subjects are not hypertensive (according to the standard criteria of a systolic/diastolic blood pressure greater than 140/90) has been interpreted as evidence that there are large, genetically determined variations in the blood pressure responses to weight gain. This concept seems to be

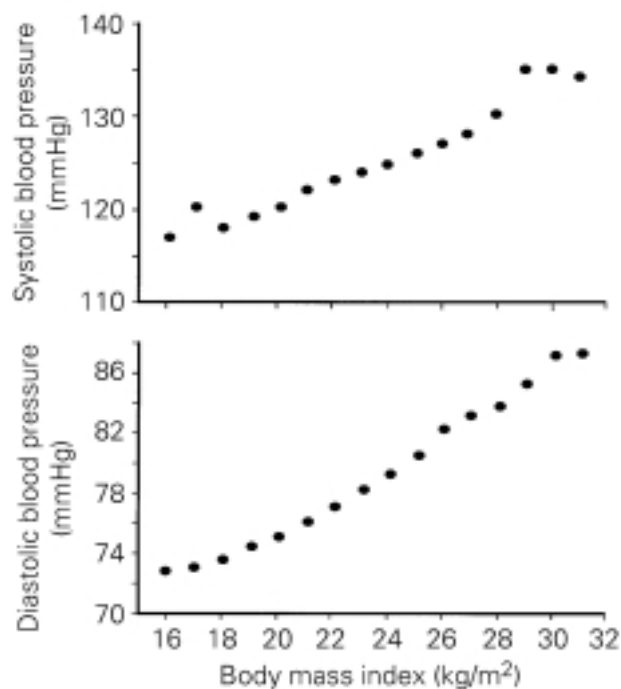


Figure 1 – Relationship between body mass index and mean systolic and diastolic blood pressure in 22,354 Korean subjects. (Redrawn from ref. 8).

consistent with the observation that some populations, such as the Pima Indians in the Southwestern United States, have a high prevalence of obesity but may not have corresponding high rates of hypertension until diabetic nephropathy occurs¹⁰. Similarly, obesity has been suggested to carry a greater risk of hypertension in Caucasian than African American females¹⁰.

Another explanation for the occasional dissociation between hypertension and obesity is that almost all individuals experience increased blood pressure with weight gain. However, baseline blood pressure (i.e., the blood pressure measured before weight gain) varies in different populations, due to genetic differences or to other factors that influence blood pressure regulation. Thus, a person with low baseline blood pressure may not be classified as *hypertensive* (greater than 140 mmHg/90 mmHg) even though arterial pressure and the risk for cardiovascular disease is higher than before the weight gain. On a population basis, weight gain shifts the frequency distribution so that a much greater fraction of obese subjects are hypertensive compared with lean subjects. Therefore, obese subjects with normal blood pressure (< 140 mmHg/90 mmHg) are hypertensive relative to their baseline blood pressure and perhaps should be considered for antihypertensive therapy. In fact, much of the population risk for cardiovascular disease occurs at blood pressures much lower than 140 mmHg/90 mmHg and obesity adds to this risk.

This explanation is supported by the finding that weight loss usually reduces blood pressure in normotensive as well as in hypertensive obese subjects⁵. Also, this is consistent with the observation that weight gain almost invariably increases blood pressure in humans and experimental animals¹¹. Thus, the observation that

some obese subjects are not hypertensive (based on the usual definition of hypertension) may be related mainly to their lower baseline blood pressure, rather than the absence of a rise in blood pressure with weight gain.

Animal models of obesity and their relevance to human obesity

Although various neurohumoral abnormalities have been proposed to mediate obesity hypertension, it has been difficult in human studies to separate changes that contribute to increased arterial pressure from changes that are secondary to hypertension. Experimental studies in animals allow a more mechanistic approach to the problem, but there are few animal models of obesity in which sequential changes in renal, cardiovascular, and endocrine functions have been examined during the development of hypertension before and after the suspected pressor systems have been inhibited.

There are many rodent models of genetic obesity and they have contributed to advances in our understanding of the molecular genetics of obesity. Unfortunately, the cardiovascular and renal changes in most of these genetic models have not been well characterized. Those that have been studied often do not mimic the cardiovascular, renal, and neurohumoral changes found in obese humans. For example, the Zucker fatty rat, a widely used model of genetic obesity, has decreased plasma renin activity¹², whereas obese humans often have increased plasma renin activity¹³. Also, increased sympathetic activity appears to play a significant role in causing hypertension in obese humans¹⁴, but not in Zucker fatty rats¹².

In contrast to genetic models of obesity, experimental animals fed high fat diets have many characteristics of

obese humans. For example, animals fed high fat diets until they become obese exhibit endocrine, renal, sympathetic, cardiovascular, and metabolic changes very similar to those found in obese humans¹⁵⁻¹⁷. These observations lend credence to the hypothesis that dietary factors, especially a high fat diet, play a major role in causing human obesity.

Mechanisms of obesity hypertension

Hemodynamic changes in obesity

Rapid weight gain causes increased regional blood flows, cardiac output, and arterial pressure in experimental animals and humans. In dogs placed on a high fat diet for five weeks with a constant intake of sodium, protein, and carbohydrates, there were parallel increases in body weight and blood pressure, with arterial pressure increasing 15 mmHg to 20 mmHg¹⁶ (Figure 2). This is similar to the modest changes in blood pressure observed in the first few weeks after rapid weight gain or weight loss in humans. A high fat diet in dogs also markedly raised heart rate and cardiac output, with little change in stroke volume. The rise in resting heart rate in obesity was due primarily to withdrawal of parasympathetic tone rather than increased sympathetic activity or increased intrinsic heart rate¹⁸. Total peripheral vascular resistance decreased during the high fat diet, but when indexed for body weight (total peripheral vascular resistance index) there was a slight increase¹⁶, similar to that observed in obese humans¹⁹.

Obesity increases regional blood flows and cardiac output. Studies in humans and experimental animals indicate that obesity is associated with extracellular volume expansion and

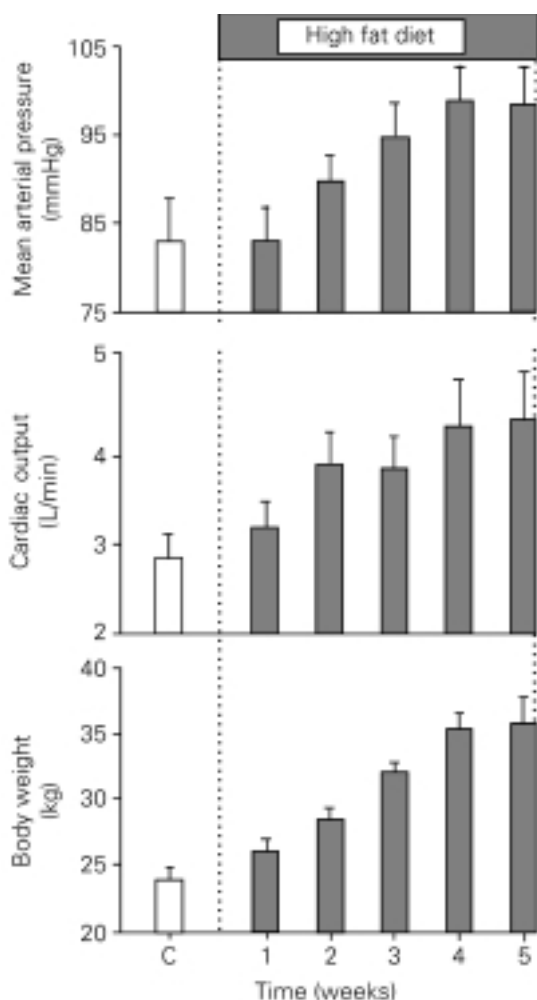


Figure 2 – Effects of 5 weeks of a high fat diet on mean arterial pressure, cardiac output, and body weight in dogs. C, Control. (Redrawn from ref. 16).

increased regional blood flows that summate to raise cardiac output. Part of the increased cardiac output observed with weight gain is due to additional blood flow required for the extra adipose tissue. However, blood flows in non-adipose tissue, including the heart, kidneys, gastrointestinal tract, and skeletal muscle, also increase with weight gain^{16,19,20}. The mechanisms responsible for increased regional blood flows have not been fully elucidated but are likely due, in part, to increased metabolic rate and local accumulation of local vasodilator metabolites and to growth of the organs and tissues in response to their increased metabolic demands.

Obesity causes cardiac hypertrophy and impaired systolic and diastolic function. Despite increased cardiac output, there is evidence for impaired cardiac systolic and diastolic function in obesity. In animals fed a high fat diet for 5 to 12 weeks, cardiac filling pressures are increased and diastolic dysfunction is evident even at this early stage of obesity²¹. Clinical studies also indicate that cardiac hypertrophy is more severe in obese than in lean subjects with comparable hypertension²². Furthermore, high sodium intake, which often occurs concurrently with high caloric intake, exacerbates obesity-induced cardiac hypertrophy²³.

Obesity impairs renal-pressure natriuresis and causes sodium retention

Abnormalities of kidney function, characterized by a hypertensive shift of pressure natriuresis, appear to play a central role in all forms of hypertension studied thus far²⁴. Obesity hypertension is no exception. Obese subjects require increased arterial pressure to maintain sodium balance, indicating impaired renal-pressure natriuresis²⁵. During five weeks of a high fat diet in dogs, there was marked sodium retention, much more than can be accounted for by the increased adipose tissue (Figure 3). Extracellular fluid and plasma volumes are also markedly elevated with dietary-induced obesity in experimental animals¹⁵ and in obese humans¹⁷. Sodium retention and volume expansion in obesity are not due to renal vasoconstriction or decreased glomerular filtration rate (GFR), as GFR and renal plasma flow are elevated in obese animals²² and humans¹⁹ compared with lean control subjects. Thus, in the early phases of the obesity, prior to glomerular injury and loss of nephron function, sodium retention is due mainly to increased renal tubular reabsorption (Figure 3).

The precise causes of increased tubular reabsorption and impaired pressure natriuresis are not completely clear but appear to be due to 1) activation of the renin-angiotensin system^{13,15}, 2) physical compression of the kidneys^{11,25}, and 3) increased renal sympathetic nerve activity^{14,25}. In this paper, we mainly discuss the role of the sympathetic nervous system.

Sympathetic activation contributes to hypertension in obese subjects

Two lines of evidence suggest that the sympathetic nervous system is a

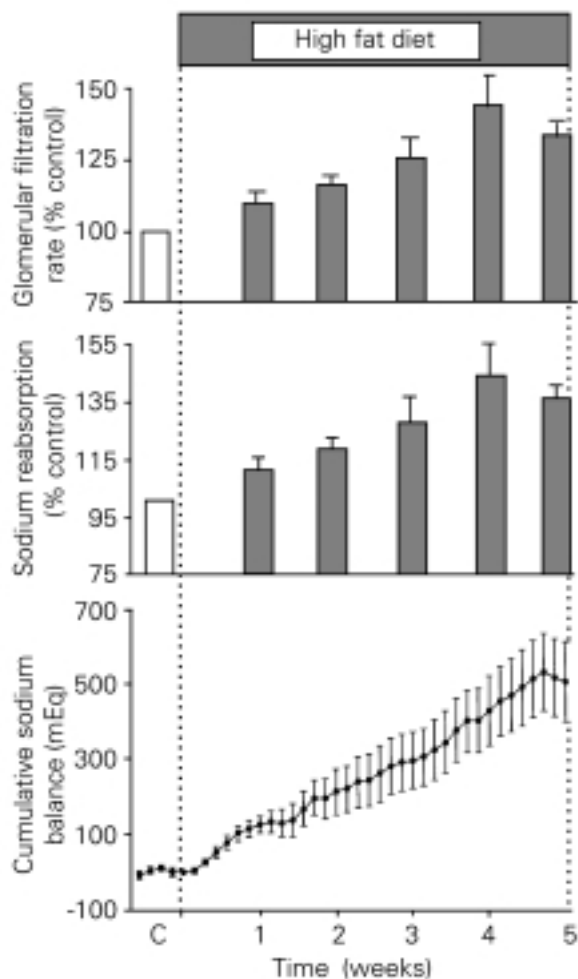


Figure 3 – Effects of 5 weeks of a high fat diet on glomerular filtration rate, renal sodium reabsorption, and cumulative sodium balance in dogs. C, Control. (Redrawn from ref. 16).

major factor in causing obesity-induced hypertension. First, direct and indirect methods suggest that sympathetic activity is higher in obese than in lean subjects. For example, high caloric intake increases norepinephrine turnover in peripheral tissues and raises resting plasma norepinephrine concentrations¹⁴. High caloric intake also amplifies the rise in plasma norepinephrine response to stimuli such as upright posture and isometric hand grip¹⁴. Obese hypertensive subjects also have increased sympathetic activity, measured directly with micro-neurographic methods, compared to lean subjects²⁶.

Second, pharmacologic blockade of adrenergic activity markedly blunts obesity hypertension. In dogs fed a high fat diet, combined α and β -adrenergic blockade lowered blood pressure to a much greater extent in obese than in lean dogs²⁷. Also, combined α and β -adrenergic blockade markedly attenuated the rise in blood pressure that occurred in dogs fed a high fat diet for 5 weeks. Clonidine, a drug that stimulates central α -2 receptors and reduces sympathetic activity, also markedly blunted the rise in blood pressure in dogs fed a high fat diet²⁸. Finally, combined α and β -adrenergic blockade for one month reduced blood

pressure more in obese compared to lean essential hypertensive patients²⁹. All of these findings support the conclusion that sympathetic activation plays a major role in mediating obesity hypertension.

Renal sympathetic nerves mediate sodium retention and hypertension in obesity. Sympathetic activation raises blood pressure and causes sodium retention in obesity mainly via the renal nerves. In dogs fed a high fat diet for five weeks, kidneys with intact renal nerves retained almost twice as much sodium as denervated kidneys. Also, bilateral renal denervation greatly attenuated sodium retention and hypertension in dogs fed a high fat diet (Figure 4)³⁰.

Mechanisms of sympathetic activation in obesity

Although it is clear that obesity increases renal tubular sodium reabsorption, impairs renal-pressure natriuresis, and causes hypertension, in part, by increasing renal sympathetic nerve activity, the mechanisms that increase renal sympathetic activity have not been fully elucidated. Potential mediators of sympathetic activation in obesity include: 1) renal afferent nerves, stimulated by increased intrarenal pressures and subsequent activation of renal mechanoreceptors, 2) hyperinsulinemia, 3) fatty acids, 4) angiotensin II (Ang II), and 5) hyperleptinemia.

Renal deafferentation does not attenuate obesity hypertension

Intrarenal pressures are markedly elevated in obesity, due in part to compression of the kidneys by extrarenal adipose tissue²⁵. Previous studies suggest that kidneys are richly

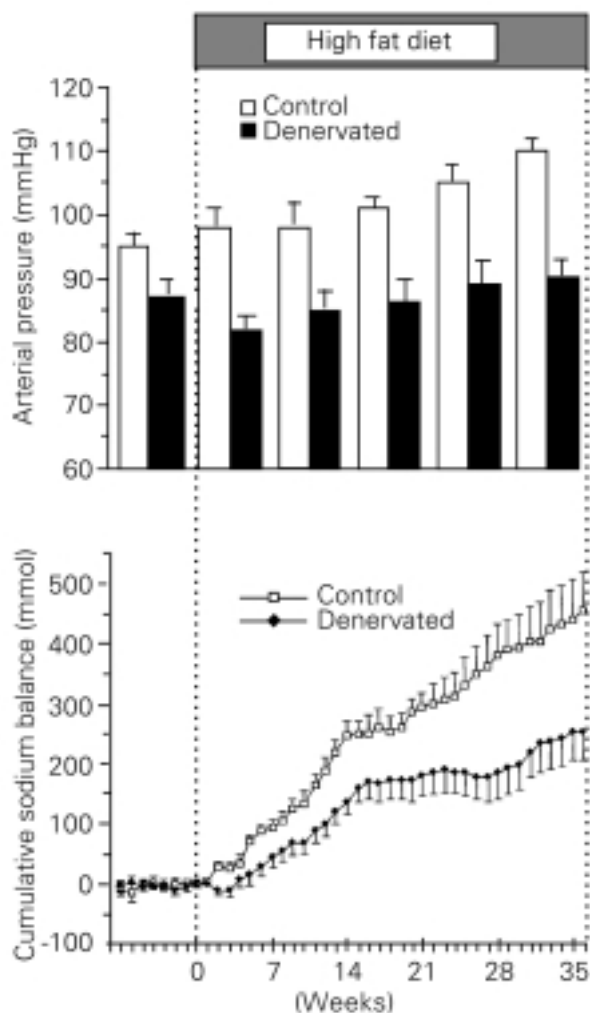


Figure 4 - Effects of 5 weeks of a high fat diet on mean arterial pressure and cumulative sodium balance in dogs with innervated kidneys (control) and bilaterally denervated kidneys (denervated). (Redrawn from ref. 30).

endowed with mechanoreceptors that can stimulate renal afferent nerves and thereby increase sympathetic activity when activated by increased intrarenal pressures. However, surgical removal of afferent fibers coming from the kidneys by dorsal root rhizotomies between T-10 and L-2 segments did not blunt the sodium retention or hypertension in dogs fed a high fat diet³¹. Thus, although the renal *efferent* sympathetic fibers contribute to sodium retention and hypertension, *afferent* pathways originating in the kidney do not appear to play a major role in stimulating sympathetic activity in obesity hypertension.

CNS effects of hyperinsulinemia cannot explain sodium retention and hypertension in obesity

Obesity is associated with glucose intolerance, fasting hyperinsulinemia, and an exaggerated insulin response to glucose loads³². The increased plasma insulin concentrations occur as a compensation for impaired metabolic effects of insulin, a condition known as *insulin resistance*. Not all tissues share in this insulin resistance, however, and hypertension has been suggested to be one of the unfortunate consequences of these increased levels of insulin.

Acute studies suggest that high insulin levels may cause modest sodium retention and increased sympathetic activity, and these observations have been extrapolated to infer that hyperinsulinemia may be an important cause of obesity hypertension through activation of the sympathetic nervous system.

However, there is little evidence that chronic hyperinsulinemia mediates obesity hypertension. In humans and dogs, neither acute nor chronic hyperinsulinemia, lasting for several weeks, caused a hypertensive shift of pressure natriuresis or increased arterial pressure³². In fact, insulin infusions at rates that raise plasma concentrations to levels found in obesity tend to reduce arterial pressure by causing peripheral vasodilation³². Insulin also did not potentiate the blood pressure or renal effects of other pressor substances such as norepinephrine or Ang II³². Moreover, hyperinsulinemia did not increase arterial pressure even in obese dogs that were resistant to the metabolic and vasodilator effects of insulin³³.

We also tested in dogs whether hyperinsulinemia could increase blood pressure through direct CNS effects by infusing insulin chronically into the cerebral circulation; our results provided no evidence that chronic, selective CNS hyperinsulinemia causes hypertension³⁴ (Figure 5). Thus, multiple studies indicate that increased insulin levels cannot explain sympathetic activation, increased renal tubular sodium reabsorption, shift of pressure natriuresis, or hypertension associated with obesity in humans or in dogs.

Do high levels of fatty acids contribute to increased renal sympathetic activity and hypertension in obesity?

Elevated levels of nonesterified fatty acids (NEFA) have been

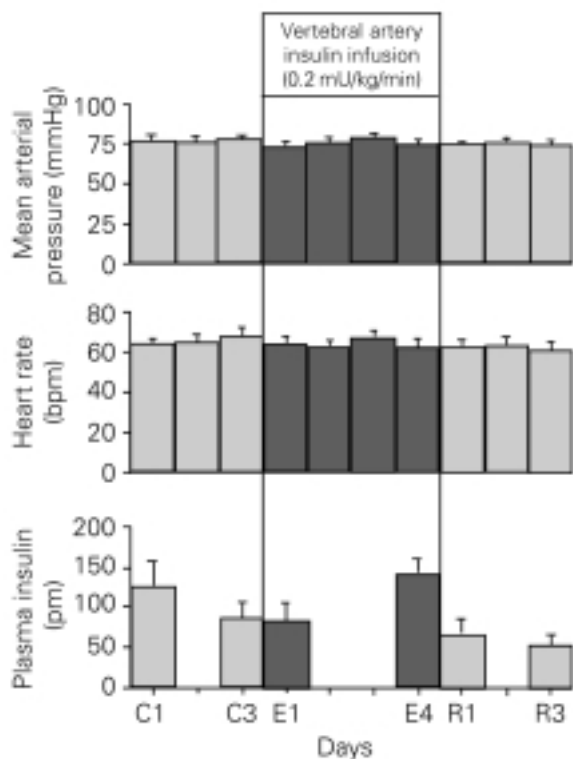


Figure 5 – Effects of 4 days of vertebral artery insulin infusion on mean arterial pressure, cardiac output, and total peripheral vascular resistance in dogs. C, Control; E, experimental; R, recovery. (Redrawn from ref. 34).

postulated to contribute to increased blood pressure in obese hypertensive subjects³⁵. Obese hypertensive patients have high fasting plasma NEFA concentrations, approximately double those of normotensive subjects, and raising NEFA acutely increases vascular reactivity to α -adrenergic agonists³⁵. High levels of NEFA also enhance reflex vasoconstrictor responses in the peripheral circulation³⁵.

In addition to enhancing the acute pressor responses to adrenergic stimuli, fatty acids have also been suggested to activate the sympathetic nervous system indirectly through afferent pathways originating in the liver. Grekin et al.³⁶ found that acute infusion of free fatty acids into the portal or systemic veins increased blood pressure and heart rate in rats, and that these effects were abolished by adrenergic blockade. Since portal vein infusion caused a greater rise in blood

pressure than systemic IV infusion, afferent pathways originating in the liver were postulated to activate the sympathetic nervous system in response to increased levels of fatty acids³⁶. However, we recently found that chronic infusion of a mixture of long-chain fatty acids for 7 days directly into the cerebral circulation³⁷, the portal vein (Hall JE, unpublished observations) or IV caused no significant changes in arterial pressure, systemic hemodynamics, or renal function in dogs. These observations provide no support for the hypothesis that fatty acids increase arterial pressure via hepatic afferent pathways.

Do the CNS effects of Ang II contribute to increased renal sympathetic activity and hypertension in obesity?

Plasma renin activity (PRA) is significantly increased in most obese

subjects despite marked sodium retention and increased extracellular fluid volume^{13,16}. Three additional observations suggest a role for Ang II in stimulating sodium reabsorption, shifting pressure natriuresis, and causing hypertension in obesity: 1) treatment with an Ang II antagonist blunted sodium retention, volume expansion, and increased arterial pressure associated with a chronic high fat diet in dogs³⁸; 2) angiotensin converting enzyme (ACE) inhibition attenuated hypertension in obese dogs³⁹; 3) ACE inhibitors were effective in reducing blood pressure in obese subjects, particularly in young patients⁴⁰.

Whether the effects of Ang II to raise blood pressure in obesity are due primarily to direct actions on the kidneys or to sympathetic activation is unclear. There is considerable evidence that Ang II has direct effects on the CNS. The physiologic role of Ang II in stimulating thirst is well established, but controversy remains regarding the physiologic importance of Ang II's role in regulating sympathetic activity. Part of this controversy relates to the paucity of data on the effects of long-term, physiologic increases in CNS levels of Ang II.

The observations of Hildebrandt et al.⁴¹ are consistent with a possible effect of physiological levels of Ang II on the CNS to chronically raise arterial pressure. Vertebral artery infusion of Ang II at a rate of only 0.5 ng/kg/min increased arterial pressure about 10 mmHg on the first day of infusion, and the rise in pressure was maintained for 7 days until the infusion was stopped. In contrast, IV infusion of Ang II at the same dose raised arterial pressure only about 4 mmHg on the first day. However, even this very low dose of intravenously infused Ang II raised arterial pressure by about 10 mmHg after 7 days of infusion. Thus, physiological levels of Ang II clearly have direct central effects that acutely

(for at least 24 hours) raise blood pressure. Whether these effects are important in maintaining chronic elevations in arterial pressure in obesity remains to be determined.

Does leptin link obesity and increased sympathetic activity?

The discovery of leptin and its effects on the central nervous system have provided another possible link between obesity and sympathetic activation⁴². Plasma levels of leptin, which is expressed mainly by adipocytes, rise in proportion to adiposity. Leptin from the plasma crosses the blood-brain barrier via a saturable transport system and acts on receptors in the lateral and medial regions of the hypothalamus to regulate energy balance by reducing appetite and by increasing energy expenditure through sympathetic stimulation (Figure 6). Although leptin's effects on energy balance have been extensively studied,

its effects on sympathetic activity and cardiovascular function are not as well understood.

Short-term effects of leptin on sympathetic activity and arterial pressure. Multiple studies have shown that acute intravenous or intracerebroventricular (ICV) infusions of leptin increase sympathetic activity in the kidneys, adrenals, and brown adipose tissue (BAT)^{43,44}. The acute effect of leptin on sympathetic activity is dose-dependent and occurs in the absence of changes in plasma insulin or glucose⁴⁴. Also, the increase in sympathetic activity is slow in onset and may not be fully developed even after 2-3 hours of leptin administration⁴³.

Despite an increase in sympathetic activity in several vascular beds, leptin administration for 2-3 hours often has little effect on arterial pressure^{43,44}, although small increases in arterial pressure have been observed in some studies when large doses of leptin are injected into the cerebral ventricles⁴⁵. The lack of an acute pressor effect of

leptin may be due to opposing depressor effects, such as stimulation of endothelial-derived nitric oxide⁴⁶, which offset the effects of increased sympathetic activity. Alternatively, the sympathetic stimulation caused by leptin may be too weak to cause marked peripheral vasoconstriction and acute increases in arterial pressure, but modest renal sympathetic stimulation could, over a period of several days, raise arterial pressure by causing increased renal tubular sodium reabsorption and volume expansion.

Role of neuropeptide-Y (NPY) in mediating effects of leptin.

Decreased NPY formation in the hypothalamus was initially believed to be the primary mediator of leptin's effects on satiety (see ref. 47 for review). Injection of NPY into the hypothalamus evokes virtually all of the features of leptin deficiency, including hyperphagia, reduced BAT thermogenesis, and obesity⁴⁷. NPY expression is also increased in the leptin-deficient ob/ob mouse and leptin repletion restores NPY expression to normal⁴⁷. The ob/ob phenotype appears to be mediated, in part, by increased NPY since ob/ob mice in which NPY expression has been knocked out (NPY^{-/-}) are substantially less obese than ob/ob mice with normal NPY expression. However, obesity in these mice is still severe, even in the absence of NPY expression, and they respond normally to the satiety effects of leptin indicating that leptin must also act on other targets to induce satiety⁴⁷.

Microinjection of large doses of NPY into the posterior hypothalamic nucleus or area postrema increases arterial pressure, whereas injection into the nucleus tractus solitarius or caudal ventrolateral medulla decreases blood pressure⁴⁸. Because leptin reduces NPY expression in the hypothalamus, the physiological significance of cardiovascular responses to NPY injections into the brain is difficult to assess.

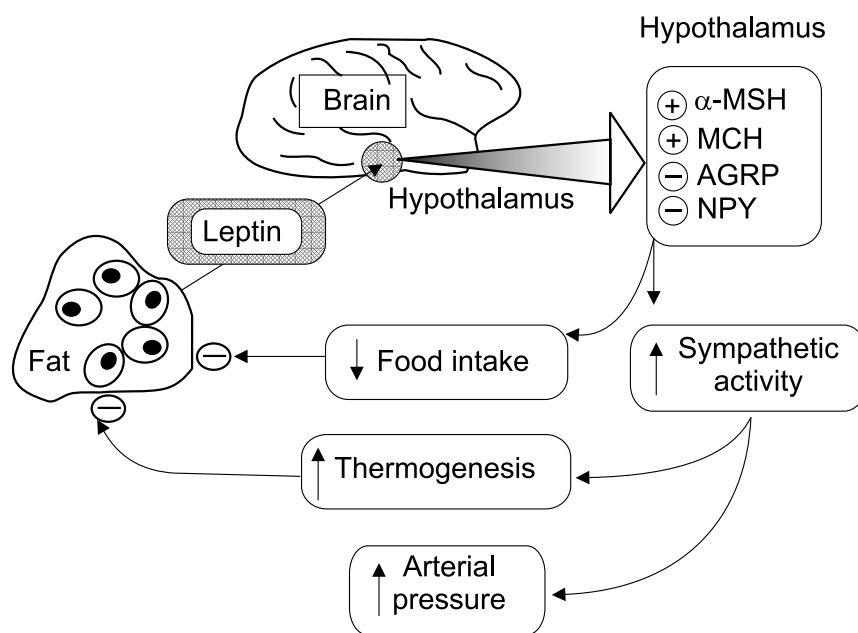


Figure 6 – Possible links between leptin and its effects on the hypothalamus, sympathetic activation, and hypertension. α -MSH, Melanocyte stimulating hormone; MCH, melanin-concentrating hormone; AGRP, agouti-related peptide; NPY, neuropeptide-Y.

Currently, there is little information on the role of NPY in mediating the acute or chronic effects of leptin on sympathetic activity and arterial pressure.

Role of melanocortin-4 receptors (MC4-R) in mediating cardiovascular and sympathetic stimulatory effects of leptin. Recent studies suggest that the proopiomelanocortin (POMC) pathway may interact with leptin to stimulate sympathetic activity and to regulate energy balance. Targeted deletion of the MC4-R induces obesity in rodents⁴⁹ and central administration of MC4-R agonists decreases feeding⁵⁰. The endogenous ligand for the MC4-R appears to be melanocyte stimulating hormone (α -MSH) produced from POMC precursors. Leptin increases expression of POMC in the arcuate nucleus⁵¹ and it is possible that a feedback pathway for control of appetite and sympathetic activity could operate as follows: increasing leptin, associated with obesity, would stimulate arcuate POMC expression and α -MSH which would then act elsewhere in the hypothalamus on MC4-R expressing neurons, causing decreased food intake and increased sympathetic activity. The MC4-R pathway, however, is not restricted to a single agonistic ligand, but also responds to other substances, such as the newly discovered agouti-related peptide (AGRP) which acts as an antagonist on this receptor.

Recent studies suggest that the MC4-R may be important in mediating leptin's acute effects on appetite and sympathetic activity. Treatment of rodents with an MC4-R antagonist attenuated the acute satiety-inducing action of leptin⁵⁰ and completely abolished the increased renal sympathetic activity associated with acute ICV leptin infusion in rats⁵². Surprisingly, MC4-R blockade did not prevent leptin-induced stimulation of sympathetic activity in BAT⁵². This finding suggests that the thermogenic effects of leptin

in BAT are not mediated via the MC4-R, whereas the effect of leptin to enhance renal sympathetic activity appears to depend on an intact MC4-R. These differing effects of MC4-R blockade on BAT and renal sympathetic activity also suggest that leptin may activate the sympathetic nervous system through multiple central pathways. However, the physiological role of the melanocortin system in mediating the effects of leptin on sympathetic activity and arterial pressure, especially in humans, remains to be determined.

Leptin may interact with other neurochemicals in the lateral hypothalamus. Recent studies suggest that the lateral hypothalamus releases an array of neurochemicals, such as the orexins, melanin-concentrating hormone (MCH), and hypocretin, that regulate appetite and energy homeostasis (see ref. 47 for review). However, their interactions with leptin in influencing appetite, sympathetic activity, thermogenesis, and arterial pressure are unknown.

Leptin and long-term control of arterial pressure. Although leptin has both pressor and depressor actions, and acute leptin administration has very little net effect on arterial pressure, chronic increases in leptin raise blood pressure in rodents. We demonstrated in non-obese Sprague-Dawley rats that IV or intracarotid artery infusion of leptin for 12 days, at rates that raise plasma concentration to levels (90 ng/ml-95 ng/ml) similar to those found in severe obesity, significantly increased mean arterial pressure and heart rate, measured 24 h/day using computerized methods (Figure 7)⁵³. The rise in arterial pressure was slow in onset and occurred despite a reduction in food intake that would tend to reduce arterial pressure. Transgenic mice overexpressing leptin also develop mild hypertension⁵⁴, comparable to that produced by chronic leptin infusions⁵³.

The mechanisms by which increased circulating leptin chronically raises arterial pressure and heart rate are not entirely clear, but are consistent with activation of the sympathetic nervous system. Also, we recently demonstrated that combined α and β -adrenergic blockade completely abolished the usual increases in arterial pressure and heart rate during 14 days of leptin infusion⁵⁵. In fact, after a α and β -adrenergic blockade, chronic leptin infusion reduced arterial pressure and heart rate, possibly due to decreased food intake and weight loss⁵⁵. Combined α and β -adrenergic blockade did not attenuate leptin-induced reductions in food intake or decreases in insulin and glucose levels. These observations indicate that increased adrenergic activity is essential for leptin-induced hypertension and tachycardia but does not play a major role in mediating the effects of leptin on insulin secretion or glucose homeostasis in non-obese rats.

Is obesity associated with resistance to leptin's actions on sympathetic activity and arterial pressure? The finding that increasing plasma leptin, to levels similar to those found in obesity, raises arterial pressure in non-obese rats is consistent with the hypothesis that leptin is an important link between obesity, sympathetic activity and hypertension. On the other hand, if obesity is associated with resistance to the effects of leptin on the hypothalamus, and therefore resistance to the effects of leptin on satiety and sympathetic activity, elevated leptin concentrations might cause minimal stimulation of sympathetic activity in obese subjects.

The fact that most obese human subjects have very high circulating leptin and continue to overeat is consistent with at least three possibilities: 1) that obese subjects are resistant to the effects of leptin on the hypothalamus, 2) that there is poor transport of leptin across the blood-brain barrier in some subjects,

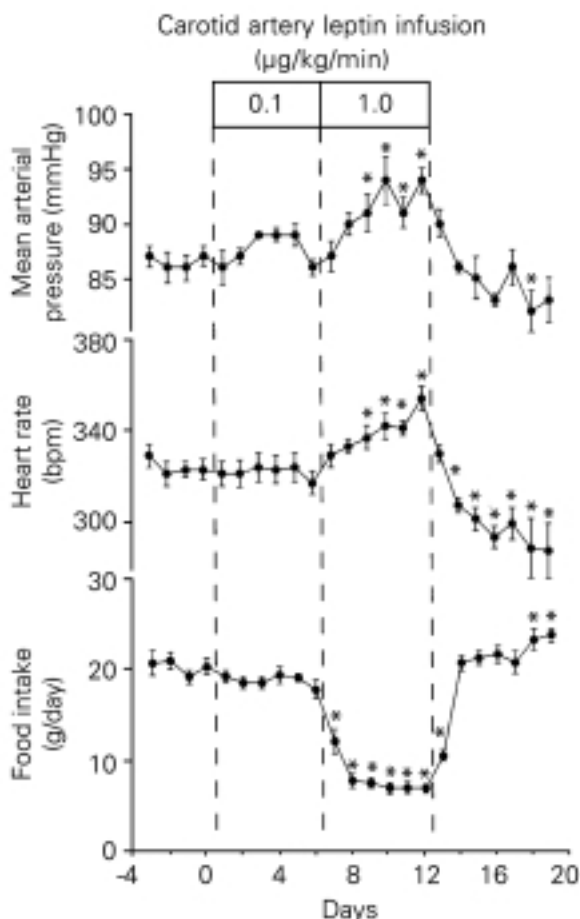


Figure 7 – Effect of bilateral carotid artery infusion of leptin at 0.1 $\mu\text{g}/\text{kg}/\text{min}$ (5 days) and 1.0 $\mu\text{g}/\text{kg}/\text{min}$ (7 days) on mean arterial pressure, heart rate, and daily food intake in conscious normal Sprague-Dawley rats. * $p < 0.05$ compared to control. (Redrawn from ref. 53).

or 3) that other factors override the chronic effects of leptin on the hypothalamus in obese subjects. There is some support for each of these possibilities. For example, diet-induced obesity in rodents is associated with impaired transport of leptin across the blood-brain barrier, and mice fed a high fat diet exhibit resistance to the satiety effects of centrally, but not peripherally, administered leptin⁵⁶. Also, acute ICV leptin administration increased lumbar sympathetic activity in non-obese rats, but had minimal effects in obese rats fed a high fat diet⁵⁷.

These observations are consistent with the hypothesis that obesity induces

resistance to the acute effects of leptin on sympathetic activity. However, another explanation is that basal sympathetic activity is already elevated in obese rats, due to high circulating leptin, and therefore further increases in leptin (above physiological levels) may not cause greater sympathetic stimulation. Also, it is important to note that the renal (rather than muscle) sympathetic nerves mediate the long-term effects of sympathetic activation to raise blood pressure in obesity³⁰. Whether diet-induced obesity attenuates the renal sympathetic responses to leptin is unknown. Nor have the long-term effects of leptin on blood pressure

and heart rate been studied in obese compared to lean subjects. Thus, a major issue that remains unresolved is whether there is resistance to the effects of leptin on renal sympathetic activity and, therefore, whether leptin contributes to increased blood pressure in obese subjects.

Leptin and human essential hypertension. Because obesity plays a major role in contributing to human essential hypertension, it is not surprising that plasma leptin concentrations are often elevated in hypertensive patients, or that leptin and blood pressure are correlated. Hirose et al.⁵⁸ found that serum leptin levels were highly correlated with mean arterial pressure and BMI in male Japanese adolescents. Moreover, heart rate was also correlated with serum leptin even after adjustment for age and BMI. Suter et al.⁵⁹ also found that systolic blood pressure correlated with plasma leptin after adjustment for BMI in women and in nonhypertensive men, but not in hypertensive men. Most of the data suggest that the correlation between leptin and blood pressure in hypertensive men is related mainly to the correlation between adiposity and blood pressure.

Not all studies, however, have shown a close relationship between leptin and hypertension. For example, genetic markers at the leptin locus are not significantly linked to hypertension in African Americans⁶⁰. This finding does not imply that leptin is unimportant in linking obesity and hypertension in African Americans, but merely that genetic abnormalities of leptin expression are not associated with essential hypertension. This is perhaps not surprising since a deficiency of leptin production rarely causes obesity in humans.

The complexity of the relationships between leptin and long-term blood pressure regulation is further illustrated by the finding that lower body obesity causes greater increases in leptin than

visceral obesity, even though visceral obesity is more closely associated with hypertension. Also, leptin levels are greater in women than men when compared at the same BMI, even though blood pressure is slightly higher in men. These observations, at the very least, indicate that other factors besides leptin contribute to obesity hypertension. However, the multiple interactions of leptin with other neurochemicals in the hypothalamus, as well as the peripheral metabolic, cardiovascular, and renal actions of leptin, are just beginning to be investigated and will require additional long-term studies before their significance in human obesity and their cardiovascular consequences can be fully appreciated.

It is important also to keep in mind that activation of the sympathetic nervous system is only one of the mechanisms by which obesity elevates blood pressure (Figure 8). Activation of the renin-angiotensin system as well as physical compression of the kidney may also be important factors in linking obesity to hypertension^{11,25}. In view

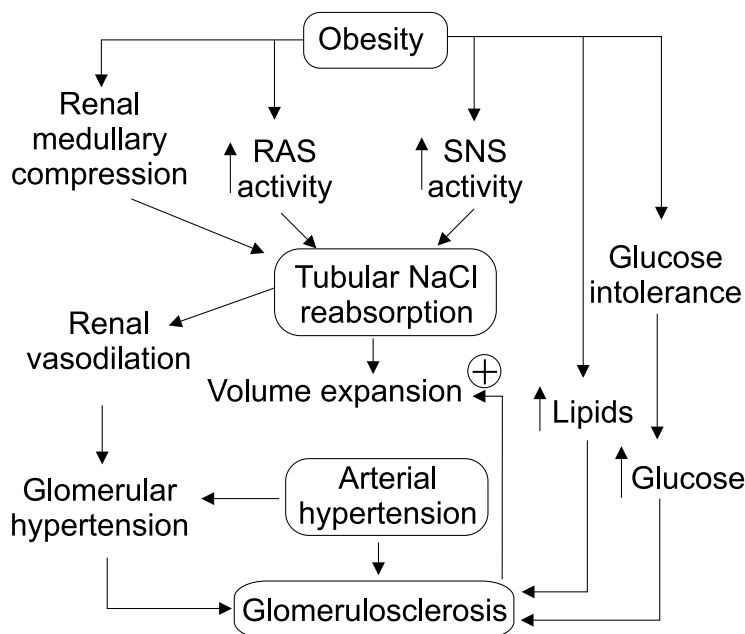


Figure 8 – Summary of mechanisms by which obesity may cause hypertension and glomerulosclerosis by activation of the renin-angiotensin (RAS) and sympathetic nervous systems (SNS), metabolic abnormalities, and compression of the renal medulla.

of the fact that obesity accounts for at least 75% of human essential hypertension, it is clear that unraveling the mechanisms by which weight gain

raises blood pressure and alters kidney function will provide the key to understanding human essential hypertension.

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