

Mechanisms of Sympathetic Activation in Obesity-Related Hypertension

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Obesity prevalence is soaring in industrialized countries and progressively increasing in the developing world. Altered patterns of nutrition and reduction in work-related energy expenditure have led to obesity becoming a truly global health issue. The central thermodynamic formulation for the origins of obesity, a mismatched energy balance equation, with an excess of dietary calorie intake over body energy expenditure, is a first step in the understanding of this phenomenon but leaves the diverse causal issues unexplored.

Dietary calorie intake is modified by multiple social, economic, and cultural issues. Similarly, the reduction in energy expenditure in recent decades has complex origins, deriving from demographic and social change, which includes third-world transition from a labor-intensive agricultural economy to an industrial base, the introduction of household labor-saving devices, the popularity of transportation modes not reliant on physical effort, and from changed recreational habits, particularly in childhood (computer games instead of physical games). The prevalence of childhood obesity is escalating, having whimsically but not entirely unrealistically been attributed to “potato chips and computer chips.”

Obesity and hypertension are intimately associated, and both very commonly coexist in individual patients with insulin resistance, hyperinsulinemia, and hyperlipidemia, this clustering of adverse health factors¹ being designated the metabolic syndrome. The pathophysiological mechanisms by which obesity leads to hypertension remain uncertain. Understanding these processes might, perhaps, provide a more rational basis for drug treatment of obesity-related hypertension. Attempts at reduction in body weight, although pivotal in the treatment of obesity-related hypertension, more often than not fail, so that antihypertensive drug therapy is often needed.

This review analyses the proposition that obesity is characterized by activation of the sympathetic nervous system and that obesity-related hypertension is, in fact, neurogenic, being initiated and sustained by neural mechanisms. At one time, this idea would have been held to fly in the face of both reason and empirical evidence, because the sympathetic nervous system is thermogenic and promotes negative energy balance and weight loss,² and in earlier experimental models of obesity, sympathetic nervous activity was found to be suppressed.³ Consideration of these earlier and very influen-

tial experimental models of obesity, many of which involved brain lesions inhibiting both sympathetic nervous outflow and satiety, will now be the starting point for this review.

Hypothalamic Models of Experimental Obesity

Ventromedial hypothalamic injury in rats can cause obesity either with or without hyperphagia.^{3,4} The observation that hypothalamic ablation can cause obesity without overeating, but associated with sympathetic nervous suppression, led Bray et al³ to propose that the sympathetic nervous system underactivity commonly present in animal models of obesity caused failed stimulation of thermogenesis and provided a metabolic basis for weight gain and obesity. Young and MacDonald, in their thoughtful review,⁵ extended this idea to incorporate an importance for reduced secretion of adrenaline from the adrenal medulla in experimental models of obesity as an additional basis for positive energy balance. Reduced sympathetic nervous activity has been emphasized as a potential mechanism of weight gain also in humans.⁶ This is in accordance with the apparent importance of the sympathetic nervous system in virtually all of the individual components of daily energy expenditure, including resting metabolic rate, energy expenditure related to physical activity, the thermic effect of food, and in cold-induced thermogenesis.⁷

Short-Term Overfeeding in Animals and Experimental Models of Obesity Caused by Overeating

In a body of elegant research contemporary with these studies of experimental hypothalamic obesity, Landsberg and Young² demonstrated that short-term overfeeding of rats activated the sympathetic nervous system. Sympathetic stimulation by overeating seems to occur also in humans.⁸ Many studies of experimental obesity, where overfeeding was used as the mechanism for causing weight gain and obesity, followed the Landsberg and Young² discovery. In contrast with hypothalamic obesity, this is a technique quite clearly congruent with the human condition.

Overfeeding in rats,² dogs,^{9,10} and rabbits¹¹ consistently produces changes in body weight, sympathetic nervous activity, and blood pressure. Despite the species differences and

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differences between studies in the form of dietary loading (namely, chow-fed, high fat, or glucose-enriched), the common response was rapid weight gain, sympathetic nervous activation, and blood pressure elevation.⁹⁻¹¹ The contrast with hypothalamic forms of experimental obesity was striking in the directionally opposite changes in sympathetic nervous system activity. Drawing on these and other observations, in a highly influential review, Landsberg¹² postulated that overeating initiates thermogenesis by stimulation of the sympathetic nervous system and that the sympathetic activation seen in experimental obesity represents an adaptive response to overeating, helping to stabilize body weight through stimulating thermogenesis. This is achieved, however, at the price of sympathetic nervous activation in the kidneys and vasculature secondarily elevating blood pressure. How well does this hypothesis conform to the findings in human obesity?

Sympathetic Activity in Human Obesity and Obesity-Related Hypertension

Initially there was a high level of disagreement concerning the state of sympathetic nervous system function in human obesity, with a substantial number of earlier studies using norepinephrine urinary excretion and plasma concentration measurements supporting the proposition deriving from hypothalamic models of obesity that sympathetic nervous activity in obesity is low.^{5,6} Application of the more specific methodology of sympathetic nerve recording and isotope dilution measurement of norepinephrine spillover to plasma reversed this earlier position.

The Pattern of Regional Sympathetic Activation in Human Obesity With Normal Blood Pressure

In obese people with normal blood pressure, a summary statement, based on studies using the newer methodology, is that the sympathetic outflows to the kidneys and skeletal muscle vasculature are activated, often 2- to 3-fold, and the sympathetic outflow to skin and the hepatomesenteric circulation and the adrenal medullary secretion of epinephrine are normal, whereas the sympathetic outflow to the heart is reduced, with cardiac norepinephrine spillover being only 40% to 50% of that found in healthy, lean people.^{7,13-15} These measurements of sympathetic activity have been typically made at rest, during the morning. Comparisons of reactive and diurnal influences on the sympathetic nervous system in lean and obese people might be relevant but have not been made to date.

The regional heterogeneity of sympathetic nervous activation noted in the obese is in keeping with what is seen in a variety of physiological and pathological conditions, in which stimulation of the sympathetic outflow to one organ may be accompanied by normal or reduced sympathetic tone in others.¹⁶ The cardiac sympathetic inhibition seen in human obesity contrasts with the unchanged¹⁷ or activated² cardiac sympathetic outflow seen with overfeeding in experimental animals. Although in experimental overfeeding an increase in heart rate is seen, variably attributable to vagal withdrawal¹⁷ or sympathetic activation,² the heart rate is typically normal in human obesity.⁷

It is possible, but not tested to date, that cardiac sympathetic tone is reflexly depressed in human obesity in response to circulatory overloading¹⁸ brought on by high renal sympathetic

Obesity-Related Hypertension A Neurogenic Hypertension Variant

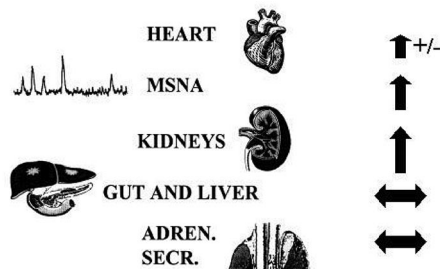


Figure 1. The sympathetic outflows to the kidneys and skeletal muscle vasculature are activated in obesity-related hypertension, whereas that to the heart is increased only marginally (in contrast to the reduced cardiac sympathetic tone present in normotensive obesity and the marked activation of the cardiac sympathetic outflow commonly present in lean patients with essential hypertension). In obesity-related hypertension, adrenal medullary secretion of adrenaline is normal, as is hepatomesenteric sympathetic tone.

nervous activity and sodium retention.¹⁹ With microneurography, the change in sympathetic nerve firing in obesity is seen to be an increase in multiunit (burst) firing frequency,¹³⁻¹⁵ with recruitment of actively firing individual fibers. Whether there are salvoes of multiple firing of single fibers within a single heart period, as is seen in cardiac failure and panic disorder, for example, is not known. Among the indices of overweight and body adipose tissue distribution, it is visceral adiposity that is most closely related with sympathetic overactivity. Among the obese, the whole body norepinephrine spillover rate is quantitatively linked to waist circumference.²⁰ Sympathetic nerve firing rates measured by microneurography have been reported to be 55% higher in men with elevated abdominal visceral fat than in men with subcutaneous obesity only, in whom muscle sympathetic nerve activity is no higher than in lean men.^{21,22}

Sympathetic Activity in Hypertensive Obese: Is Obesity-Related Hypertension Neurogenic?

Obesity related hypertension, as for essential hypertension in lean people,²³ seems to have an important neurogenic component, being characterized by activation of the sympathetic outflows to the kidneys and skeletal muscle vasculature and an absence of the suppression of the cardiac sympathetic outflow seen in the normotensive obese (Figure 1).^{13-15,24,25} There is, however, a problem with this formulation, considered in more detail later in this review. In short, this is that in patients with obesity-related hypertension, there is apparently no greater renal sympathetic activation than in the obese subjects whose blood pressure lies within the reference range; mean renal norepinephrine spillover rates are similarly 2- to 3- fold elevated.²⁵

Sympathetic Nervous Activity in the Metabolic Syndrome

Overweight, hypertension, insulin resistance, hyperinsulinemia, and hyperlipidemia very commonly coexist in individual patients, both women and men, with this clustering of adverse

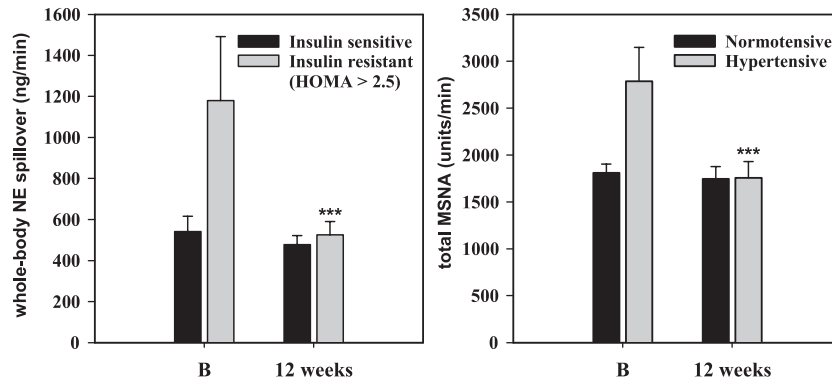


Figure 2. Sympathetic activity at baseline (B) and after a 12-week hypocaloric diet, stratified by insulin resistance (left) and hypertensive status (right). Insulin-resistant ($n=10$) and insulin-sensitive ($n=9$) subjects were defined as homeostasis model assessment index of ≥ 2.5 and < 2.5 , respectively. Hypertensive ($n=10$) and normotensive ($n=7$) subjects were defined as those with a supine resting blood pressure of $\geq 130/85$ mm Hg and $< 130/85$ mm Hg, respectively. Sympathetic nervous system activity was higher in obese people with insulin resistance and with elevated blood pressure. Data are shown as the mean \pm SEM. *** $P < 0.001$ vs baseline values. NE indicates norepinephrine; MSNA, muscle sympathetic nerve activity (from Reference 28).

health factors constituting the metabolic syndrome.¹ Disagreement exists over diagnostic criteria, based primarily on which individual elements must be present, and in what combinations, for diagnosis. For example, does the concurrence of hypertension, insulin resistance, hyperinsulinemia, and hyperlipidemia without obesity qualify? Presumably overweight is the prime mover and must be present for diagnosis. Given existing uncertainty over the nature of the pathophysiological mechanisms linking the individual components, that the syndrome is a discrete entity at all is challenged.²⁶

Paradoxically, research on the sympathetic nervous system in obesity and in the metabolic syndrome has run parallel paths, with surprisingly little cross-citation. The findings in the metabolic syndrome are, as for obesity, very much as would be expected: elevated whole body norepinephrine spillover accompanied by increased muscle sympathetic nerve activity (including single fiber firing).^{15,27–29} Sympathetic activity does increase with increasing numbers of components of the metabolic syndrome; specifically, muscle-sympathetic nerve firing in metabolic syndrome patients with hypertension is higher than in metabolic syndrome patients with normal blood pressure (Figure 2).^{15,27–29}

Causes of Sympathetic Nervous Activation in Obesity

The presence of regionalized sympathetic nervous activation in human obesity is now established beyond question, but its mechanism remains elusive. The list of possible mechanisms is long, but for none is the supporting evidence totally persuasive. Does the sympathetic activation represent an ongoing response to continuing overfeeding, which is suggested by the experimental models, or perhaps it is driven by the pathophysiological and clinical changes which accompany obesity once it has developed, including hyperinsulinemia, high plasma leptin levels, and obstructive sleep apnea?

Hyperinsulinemia

The original formulation by Landsberg,¹² based on the observation originating from his work with Young² that overfeeding in rats activates the sympathetic nervous system and elevates

blood pressure, was that the insulin response to increased dietary energy intake was the prime mover in the following cascade: overfeeding, hyperinsulinemia, sympathetic nervous activation, thermogenesis, and hypertension. More recent thinking might shift the emphasis, attributing the hyperinsulinemia in obesity to the accompanying insulin resistance rather than specifically to an overfeeding response.

The logical force of the Landsberg¹² argument led to a series of studies testing whether insulin, in fact, does activate the sympathetic nervous system. With infusion of insulin in humans to acutely produce hyperinsulinemia and clamping of blood glucose concentrations to avoid hypoglycemia, activation of the sympathetic nervous outflow to the skeletal muscle vasculature is seen with microneurography.³⁰ This effect of insulin is mediated through the central nervous system (CNS), either as a reflex response to vasodilatation or as a direct effect of insulin on forebrain areas regulating sympathetic outflow.³¹ Although fasting serum insulin concentrations are higher in the obese, we have reported previously that serum insulin and renal noradrenaline spillover values are not quantitatively related overall,⁷ arguing against hyperinsulinemia per se causing the elevated renal sympathetic nervous activity. Furthermore, euglycemic insulin infusion in humans (lean hypertensive patients were studied) does not seem to activate the renal sympathetic nerves.³² Because obesity is accompanied by high rates of norepinephrine spillover from the kidneys, it does seem that the increased CNS sympathetic nervous outflow in obesity involves mechanisms other than hyperinsulinemia.

In attempts to interpret the linkage between sympathetic nervous activation and hyperinsulinemia in obesity, a contrary viewpoint is now gaining favor. Considered below, this is that the hyperinsulinemia is a secondary phenomena, driven by sympathetic activation and resulting from neural vasoconstriction lowering skeletal muscle blood flow and reducing glucose delivery to muscle.^{33,34}

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA), common in obesity, has been championed as the major, perhaps even exclusive cause of the

sympathetic nervous activation in obesity.³⁵ Apneic episodes at night are accompanied by intense sympathetic nervous activation, elegantly documented by Narkiewicz et al³⁵ and Somers et al³⁶ using microneurography. These authors suggest that, with time, this episodic nocturnal sympathetic stimulation evolves into ongoing, daytime sympathetic nervous activation.

It now seems probable that OSA is, in fact, one causal mechanism of sympathetic activation in obesity. In support of this idea, an intriguing recent article describes some elevation of sympathetic tone even in lean men with OSA,³⁷ perhaps allowing a disentangling of an independent but usually combined influence of obesity and OSA. Sympathetic activity in lean men with OSA was elevated, similar to that in obese men without OSA, but materially less than in men with both OSA and obesity, in whom there seemed to be an equal and additive effect attributable to both OSA and to obesity. Clearly, OSA contributes to but is not the exclusive cause of sympathetic activation in obesity.

It should be added that there are, however, 2 points of dissonance with this story. The first is that no mechanism has yet been proposed by which nocturnal sympathetic stimulation during apneic episodes can be generalized to round-the-clock sympathetic activation. The second is that the reversal of OSA with continuous positive airway pressure therapy does not lower sympathetic nervous system activity.^{38,39} Mills et al,³⁸ in a recent comprehensive study of OSA patients with the metabolic syndrome, demonstrated no influence of continuous positive airway pressure on sympathetic activity, assessed by measurement of the appearance rate of norepinephrine in plasma.

High Plasma Leptin Concentration

It has been proposed that the sympathetic nervous activation of obesity might be driven by high plasma levels of leptin. Leptin, a 16-kDa protein derived principally from adipose tissue, has been implicated in body weight homeostasis. Plasma leptin concentrations are elevated in human obesity.⁴⁰ The observation that in humans plasma leptin levels and body weight are closely linked suggested that perhaps resistance to the anorexic effects of leptin develops as its plasma concentration rises.⁴⁰ It proved easy to induce leptin resistance experimentally. An early study demonstrated experimentally that substantially more leptin needed to be administered to diet-induced obese mice to cause significant feeding inhibition than was required for a comparable effect in their lean, standard chow-fed counterparts.⁴¹ Leptin increases the expression of pro-opiomelanocortin, which is potently anorexigenic, in neurons of the arcuate nucleus of the mediobasal hypothalamus. Variants of brain leptin resistance include failure of pro-opiomelanocortin expression and antagonism of brain melanocortin receptors by Agouti-related protein.⁴² Importantly, brain leptin resistance of this type can be selective, such that the effect of leptin on appetite is inhibited, whereas that on sympathetic activity, including that in the kidneys, is preserved.⁴³

With intravenous infusion of leptin in rats, activation of the sympathetic outflows to the kidneys and hind limb vasculature is seen,⁴⁴ as well as stimulation of epinephrine secretion

by the adrenal medulla, with an increase in heart rate, suggesting that the cardiac sympathetic nerves are stimulated. These effects have some parallel in the pattern of sympathetic nervous change seen in human obesity,^{7,13–15,25} perhaps suggesting that leptin stimulation of the sympathetic nervous system may be the underlying explanation, but it should be emphasized that in human obesity epinephrine secretion rates are normal, and the cardiac sympathetic outflow is not stimulated.^{7,45,46}

No totally definitive leptin administration studies, with quantification of sympathetic nervous activity during leptin dosing, have been performed in humans. In one study, subcutaneously administered leptin was apparently without effect on sympathetic activity.⁴⁷ More recently, twice daily subcutaneous leptin administration during dietary calorie restriction was demonstrated to abolish the sympathetic inhibition, which otherwise occurs in the cardiac sympathetic outflow (estimated from the degree of heart rate slowing with β -adrenergic blockade) on a low-calorie diet.⁴⁸ The urinary excretion of norepinephrine, however, was not altered by leptin. Testing of whether pharmacological blockade of leptin reduces sympathetic activity in obesity is not technically possible, given the unavailability of an appropriate antagonist. In the absence of leptin antagonists, measurement of sympathetic activity in the obesity accompanying leptin deficiency syndromes⁴⁹ might provide useful, alternative information, but this has not been done to date.

Our own observations in cross-sectional studies, and those of others, where sympathetic nervous activity and leptin plasma concentration and kinetics are measured concurrently, provide limited but inconclusive support for the idea that high plasma leptin concentrations in obesity drives the sympathetic activation that is present. These studies typically find plasma leptin concentrations in lean and obese normotensive men to be correlated with measures of whole body and regional sympathetic activity in some outflows (kidneys and skeletal muscle vasculature) but not strongly so.^{45,46,50} The study by Masuo et al^{51–53} of shipyard workers in Osaka, Japan, is also pertinent. In this investigation of the emergence of the pathophysiological markers accompanying developing obesity-related hypertension, in men followed for 10 years, the authors found that sympathetic nervous activation unequivocally preceded elevation in plasma leptin concentration. In short, unlike in some rodent models of obesity, in human obesity the case for leptin driving the sympathetic activation present is not strong.

Surprisingly, release of leptin from the brain has been reported in humans,^{46,54} as has leptin expression in human^{55,56} and rat⁵⁷ brains. In human obesity, leptin overflow into the internal jugular veins is increased, accompanied by increased CNS turnover of serotonin.⁴⁶ This is noteworthy in that it suggests a functional coupling in human obesity, perhaps as an adaptive response, albeit futile, of 2 brain systems known to cause satiety.

Postscripts to this finding of leptin expression in the brain are the recent report, from the discoverer of leptin, that leptin has neurotrophic properties, well demonstrated in the hypothalamus,⁵⁸ and the observation that in depressive illness there is markedly reduced hypothalamic expression of leptin

and leptin overflow from the brain.⁵⁶ Patients with depressive illness had been suspected of having a loss of brain neurotrophic support. Clearly there is much more to the “adipocyte hormone” than originally envisaged!

Other Neural Mechanisms?

It has been suggested that the sympathetic activation of obesity might originate from reduced gain of the arterial baroreflex. Because decreased arterial baroreflex sensitivity is present in both central and peripheral obesity⁵⁹ and sympathetic activation is present only in the former, the proposition is unlikely. A second obstacle to accepting that obesity-related sympathetic activation is because of diminished central baroreflex restraint of sympathetic tone is the generally, although admittedly not universally, held view that the arterial baroreflex modifies short-term fluctuations in sympathetic tone but does not determine prevailing, static sympathetic activity.

In end-stage renal disease, afferent nerves from the kidneys stimulate central sympathetic outflow.⁶⁰ Might such a process be operating in some patients with obesity? Although the mechanisms are unclear, obesity has emerged as a major community cause of renal disease and failure.⁶¹ Clearly this line of reasoning, that renal afferents might increase central sympathetic outflow in obesity, is at present speculative.

Renin–Angiotensin Sympathetic Stimulation in Obesity?

Interaction between the renin–angiotensin system and the sympathetic nervous system has traditionally been regarded as bidirectional. The contribution of the renal sympathetic nerves to renal renin release, one component of this proposed synergy, is clear. The other element, facilitation of the sympathetic nervous system by angiotensin, has a long research pedigree, dating back 40 years to the observations of Dickinson⁶² and Bickerton and Buckley,⁶³ but remains disputed.⁶⁴ A subset of patients with essential hypertension, the so-called “high renin essential hypertensives,” do have elevated rates of renal renin release²³ and high plasma angiotensin II concentration, but because this high-renin phenotype is not particularly associated with obesity (perhaps surprising given the documented activation of the renal sympathetic outflow in obesity), it would seem to be unlikely that the renin–angiotensin system is driving the sympathetic activation of human obesity. In contrast to this interpretation, a recent report documents substantial sympathetic inhibition by angiotensin receptor blockade in obesity-related hypertension,⁶⁵ which is not produced by angiotensin receptor blockers in lean men with normal⁶⁶ or elevated blood pressure.⁶⁴ Clearly, the matter remains unsettled.

Lifestyle Influences Activating the Sympathetic Nervous System in Obesity?

Largely unexplored as possible causes of sympathetic activation in obesity are the lifestyle factors of chronic mental stress and lack of exercise. A very recent report from the Whitehall II Study convincingly incriminates occupational stress in the development of the metabolic syndrome.⁶⁷ Exercise training lowers sympathetic activity, with preferential inhibition of the

renal sympathetic outflow.⁶⁸ Again, whether these observations perhaps suggest an importance, in the sympathetic activation of obesity, for chronic mental stress and sedentary lifestyle is largely speculative.

Consequences of Sympathetic Activation in Obesity

Hypertension

Activation of the sympathetic nervous outflows to the kidneys, heart, and skeletal muscle vasculature is a now very well-documented pathophysiological finding in lean young and middle-aged patients with essential hypertension.²³ Their hypertension is conceived as being “neurogenic,” initiated and sustained by the increased sympathetic nervous cardiovascular drive. It is probable that obesity-related hypertension also has an important neurogenic component,^{13,15,25,50} mediated by activation of the sympathetic outflows to the skeletal muscle vasculature and, in particular, the kidneys.

A large number of studies, reviewed by Di Bona,¹⁹ have demonstrated the importance of the renal sympathetic nerves in the development of hypertension in various experimental models, including experimental obesity.^{9,10} The neurogenic hypothesis of human obesity-related hypertension emphasizes activation of the renal sympathetic outflow as the prime mover in the blood pressure elevation. This is supported by evidence from the investigation of obesity-related hypertension caused by overfeeding in dogs, where sympathetic activation occurs, accompanied by impaired renal pressure natriuresis, increased secretion of renin, and retention of sodium despite increases in glomerular filtration rate and renal plasma flow.^{9,69}

It is probable that in human obesity-related hypertension, also the renin–angiotensin system contributes to the blood pressure elevation, although plasma renin activity and plasma angiotensin concentration typically are normal⁷⁰ or only minimally elevated.⁷¹ From high renal sympathetic activity, which increases renal renin secretion in human hypertension,⁷² and the well-documented production of angiotensin in adipose tissue,^{73,74} high plasma angiotensin values might have been anticipated. Perhaps the renin–angiotensin system activity is “inappropriately normal,”⁷¹ given that human obesity is characterized by circulatory overloading from renal sodium retention.¹⁸

In patients with obesity-related hypertension, there is a comparable, not greater, increase in renal sympathetic outflow to that present in obese people whose blood pressure lies within the reference range.²⁵ These results do present a paradox. The higher renal sympathetic nervous activity in the obese thus may be important in the development of their hypertension, but it would seem to be a necessary rather than a sufficient cause. There is, however, another possible interpretation, which hypothetically places the normotensive obese at the lower end of blood pressure distribution before their weight gain. Accordingly, the higher renal sympathetic tone in the normotensive obese might influence their blood pressure, which, although “normal,” is higher than would have been the case in the absence of renal sympathetic activation. Blood pressure does tend to fall with weight loss and the

accompanying lowered sympathetic activity in all obese people regardless of their starting blood pressure.

Despite this equivocation, there has been a search for genetic influences that might tip the balance, determining whether the development of obesity leads to hypertension. Of potential modifiers, perhaps most convincingly demonstrated is the β 2-adrenoceptor genotype.⁷⁵ In a cohort of Japanese men studied longitudinally, the development of new hypertension with weight gain was substantially more common with the Gly16 allele. This allele is characterized by an increase in agonist-induced adrenoceptor desensitization.⁷⁶ The predisposition to hypertension development might possibly involve, under the existing conditions of increased sympathetic nervous activity, progressive reduction in β 2-adrenergic mediation of vascular dilatation, which would represent the blunting of a potentially antihypertensive mechanism.

Insulin Resistance

The linkage between sympathetic nervous activation and hyperinsulinemia in obesity has 3 possible mechanisms. We have argued earlier in this review against the first, that hyperinsulinemia causes the sympathetic activation. A contrary viewpoint now gaining favor, considered in detail below, is that the hyperinsulinemia is a secondary phenomenon, driven by sympathetic activation and resulting from neural vasoconstriction lowering skeletal muscle blood flow and reducing glucose delivery to muscle.^{33,34} A third suggested basis for the link is that it is insulin resistance in a tissue that is actually determining local blood flow in obesity through insulin resistance lowering the regional metabolic rate with blood flow adjusting downward in parallel with the lowered tissue metabolic needs. This latter explanation does, however, seem to be unlikely, because organ-specific oxygen use is often increased, rather than reduced, in obesity.⁷

What is the evidence that sympathetic mediated vasoconstriction in skeletal muscle causes the insulin resistance of obesity, lowering skeletal muscle blood flow and reducing glucose delivery to muscle? Sympathetic activation induced by lower body negative pressure,⁷⁷ which increased forearm norepinephrine spillover by 60%, significantly lowered insulin-mediated muscle glucose uptake and insulin sensitivity measure by euglycemic clamp. Similarly, with reflex sympathetic activation accompanying unloading of cardiopulmonary receptors by bilateral thigh cuff inflation,⁷⁸ both forearm blood flow and glucose use were reduced. Within this conceptual framework, it is a particularly telling observation that, in contrast with these 2 examples, insulin-induced glucose use is increased with the sympathetic activation of acute mental stress^{79,80} during which, unlike with the other 2 stimuli, skeletal muscle blood flow increases because of the vasodilator action of epinephrine and regional sympathetic withdrawal in the limbs.

Whether skeletal muscle blood flow is reduced in human obesity and contributes to the insulin resistance present has been disputed. Baron et al³³ attributed the reduction in insulin sensitivity postprandially in obese people to the reduction in limb blood flow that occurs. Earlier reports described increased skeletal muscle blood flow at rest in obesity,^{81,82} but 2 recent studies do document flow to be reduced.^{83,84} Ribeiro et al⁸⁴ noted that forearm blood flow was lower in obese than

lean women and lowered in proportion to increases in muscle sympathetic nerve activity.

Based on this reasoning, reduced skeletal muscle blood flow in obesity hypertension resulting from neural vasoconstriction may possibly be the primary cause of the insulin resistance and the attendant hyperinsulinemia.^{33,34,85} A 10-year, longitudinal study of shipyard workers in Osaka by Masuo et al⁵¹⁻⁵³ supports this position. By investigating the chronology of the emergence of the pathophysiological markers accompanying developing obesity-related hypertension,⁵¹⁻⁵³ the authors hoped to establish which might be the prime mover in elevating blood pressure. Sympathetic nervous activation clearly preceded elevation in serum insulin and perhaps caused it.

Also relevant is the observation that the centrally acting imidazoline agents, moxonidine and rilmenidine, which inhibit sympathetic outflow to the skeletal muscle vasculature, reduce insulin resistance, an effect presumably attributable to a removal of neural vasoconstriction not seen with other antihypertensive drugs.^{86,87} Inhibition of sympathetically mediated lipolysis is an additional possible mechanism by which this drug class might increase insulin sensitivity. Free fatty acids in plasma and skeletal muscle impair insulin-mediated glucose disposal.^{88,89}

Thermogenesis

The hypothesis for the development of obesity-related hypertension formulated by Landsberg¹² suggests that increased thermogenesis, mediated by sympathetic nervous activation, should be present in obese people. The responses to pharmacological inhibition of CNS sympathetic outflow or to β -adrenoceptor blockade suggest an important role of the sympathetic nervous system in many components of daily energy expenditure, including resting metabolic rate.

Splanchnic oxygen consumption is elevated in obesity, and in the kidneys this is proportional to sympathetic activity.⁷ The important caveat is that this increased oxygen consumption has not been demonstrated to be in excess of that expected from the higher organ and whole body mass, which would be a prerequisite for concluding that sympathetically mediated thermogenesis had been demonstrated.

Obesity?

It is highly paradoxical that sympathetic nervous activation might be thought to predispose to the development of obesity, but empirical evidence from 2 sources, longitudinal epidemiological studies in Tecumseh, Mich,⁹⁰ and Osaka,⁵³ does suggest this. In both studies, the presence of higher sympathetic activation at entry predicted the subsequent development of obesity. This intriguing concept is controversial but certainly has not been discredited. Mechanisms suggested for the link are 2-fold: first, through higher sympathetic activity causing insulin resistance and hyperinsulinemia, thereby predisposing to weight gain, or, second, by causing desensitization of β -adrenoceptors impairing thermogenesis.^{53,85}

Renal Disease?

Obesity contributes to the development and progression of renal disease,⁶¹ an effect independent of the presence of type II diabetes. Renal pathophysiology present in obesity includes

impairment of renal pressure natriuresis, elevation in intrarenal pressure, and glomerular hyperfiltration.⁹¹ Nephron loss and progressive renal disease develop in some patients, which can progress to renal failure.⁶¹ Whether the high renal sympathetic activity present in obesity contributes to the development of renal disease is unknown.

Effect of Treatments on Sympathetic Activity in Obesity

Therapies aimed at reducing weight in the obese and blood pressure in those with obesity-related hypertension commonly modify sympathetic nervous activity. In some cases, this is their principal mode of action. In others, where the existing sympathetic activation is accentuated, the response is potentially adverse.

Weight Loss

There is continuing uncertainty as to whether, with eucaloric maintenance of previously lost weight, sympathetic activity and blood pressure remain reduced.^{92,93} Laaksonen et al⁹² found that on a very low-calorie diet, blood pressure fell early but that this blood pressure reduction was not sustained during eucaloric maintenance of the substantially lowered weight. This finding, disappointing in its clinical implications, is discordant with the many population studies linking blood pressure to obesity, which provide the logical underpinning for the recommendation that weight loss be the starting point in the treatment of obesity-related hypertension. Perhaps for blood pressure in the obese, current energy balance might be the prime mover, having a dominant influence on sympathetic tone and blood pressure, as observed by Landsberg and Young² in overfed and underfed rats, sometimes overriding any direct effect of body weight on blood pressure.

Dietary Calorie Restriction

The notion just presented is in accordance with common clinical experience that blood pressure is often quickly lowered in overweight hypertensive patients when placed on a calorie-restricted diet before any material loss in weight. The explanation probably lies in the direct inhibition of sympathetic activity by calorie restriction first described in the Landsberg and Young² experiments and subsequently demonstrated also in humans.⁸

Exercise

Regular aerobic exercise, a desirable component in any weight loss program, lowers blood pressure,⁹⁴ achieving this in part through sympathetic nervous system inhibition. This sympathetic inhibition, in preferentially involving the renal sympathetic outflow,⁶⁸ is well placed to achieve an antihypertensive effect.

Drugs Promoting Weight Loss

The effects of the combined noradrenaline and serotonin reuptake blocker, sibutramine, on the sympathetic nervous system have been extensively studied. This was because at first it was thought that the drug stimulated thermogenesis through sympathetic nervous system augmentation, which

might confer cardiovascular risk. The safety of the drug now does seem to be established, although the small increases in heart rate and systolic blood pressure seen do remain of some concern. Recent measurements of muscle sympathetic activity exclude any drug-induced sympathetic nervous activation by sibutramine.

Antihypertensive Drugs

Most interest centers on the antiadrenergic antihypertensives, which potentially can target the neural pathophysiology elevating the blood pressure, but through an antithermogenic action might cause weight gain. β -Adrenergic blocking drugs are found in large trials to cause some weight gain,⁹⁵ perhaps 1 to 2 kg on average. The imidazoline binding agents, such as rilmenidine and moxonidine, which inhibit sympathetic outflow, might also be expected to increase weight, but surprisingly do not. Weight loss of 1 to 2 kg is typically seen, despite sympathetic inhibition,⁹⁵ perhaps because of the reduction in neurogenic vasoconstriction in skeletal muscle producing a favorable effect on insulin resistance and hyperinsulinemia.^{81,82} The evidence is conflicting concerning the capacity of renin-angiotensin system blockade to inhibit sympathetic activity.^{64,65} Any effect is materially less than seen with imidazoline binding agents.

Summary

The sympathetic nervous system is activated in human obesity and in the analogous experimental obesity produced by overfeeding. The causes remain uncertain and may be multiple (Figure 3). The consequences include hypertension, probably attributable to activation of the sympathetic outflow to the kidneys, and, more disputed, insulin resistance. Should antihypertensive drug therapy in obesity hypertension specifically target the existing neural pathophysiology? Such an approach can be advocated on theoretical grounds, but at present there is little empirical evidence to support it. Perhaps more important is the requirement that chosen antihypertensives do not cause weight gain or increase insulin resistance.

Perspectives

β 3-Adrenergic Agonists as Weight Loss Drugs?

There has been a long-held expectation that drugs of the β 3-agonist class, through stimulation of thermogenesis, would prove to be valuable weight loss agents. This high expectation was based in part on the belief that sympathetic nervous system activity was low in human obesity and that administration of the β 3-adrenergic agonist would "correct" this. Because it is now clear that human obesity is not characterized by sympathetic nervous underactivity, the logic underpinning the development of this drug class is weakened.

Effectiveness of Leptin Treatment of Obesity?

High hopes were held at first for leptin or leptin agonists as weight loss agents. A large trial of injectable leptin failed to cause weight loss,⁹⁶ perhaps attributable to leptin resistance or to failure of leptin to have the primary role in the control of adipose tissue mass in humans, which might have been anticipated from studies in rodents.

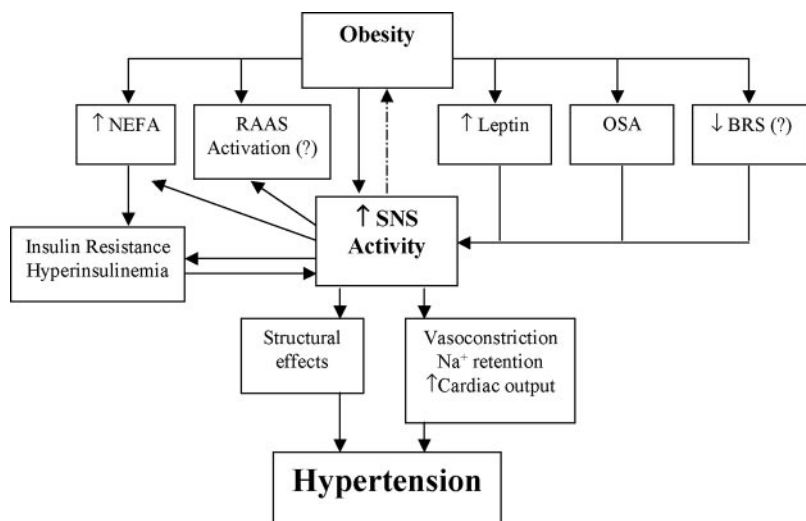


Figure 3. Potential pathophysiological mechanisms by which obesity may contribute to hypertension. Some of the putative mechanisms and interrelationships between the variables are provided in the text. NEFA indicates nonesterified fatty acids; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system; BRS, baroreflex sensitivity.

Is It Preferable That Antihypertensives Used in Obesity Hypertension Target the Existing Neural Pathophysiology?

Should centrally acting sympathetic suppressants, imidazoline binding agents such as rilmenidine and moxonidine, or perhaps β -adrenergic blockers be specifically prescribed in obesity-related hypertension to target the existing neural pathophysiology? The imidazoline binding agents produce the desired sympathetic inhibition in the skeletal muscle vasculature and kidneys.⁹⁷ Such an approach might be preferred on theoretical grounds, but at present there is little empirical evidence to support it.

Are There Other Grounds for Antihypertensive Drug Selection in Obesity Hypertension?

Although the comparative efficacies of all drug classes have not been evaluated to date, the published trials do not indicate a clear superiority for any particular class of antihypertensive.^{65,98,99} One report does describe greater blood pressure reduction in obese than lean hypertensive patients with combined α - and β -adrenergic blockade.¹⁰⁰ Others document elevated plasma and urinary aldosterone levels in obesity-related hypertension and efficacy of aldosterone receptor blockade in resistant obesity hypertension.^{101,102} Key considerations are whether the chosen drug might have adverse effects in obesity, causing weight gain (β -adrenergic blockers can do this), or promoting the development of diabetes (which β -blockers and diuretics can do) or have specific benefits, increasing insulin sensitivity (unequivocally demonstrated only with imidazoline binding agents⁸⁶) or reducing the onset of new diabetes (demonstrated with renin-angiotensin blockade).¹⁰³ The latter highly desirable property has been attributed to angiotensin-converting enzyme inhibitors and angiotensin receptor blockers promoting adipogenesis,^{71,104} producing smaller, more insulin-sensitive adipocytes.

Is Blood Pressure Reduction Sustained During Eucaloric Maintenance of Goal Weight?

There is evidence that with eucaloric weight maintenance, after previous loss of weight, sympathetic activity and blood pressure are reduced less than during the phase of negative energy balance.⁹³ Blood pressure drifting up in the clinic,

after goal weight is reached and dietary restriction is liberalized, might be because of this. To maintain blood pressure control, addition of an aerobic exercise program or antihypertensive medication might be needed.

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