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Editorial

Diet, Obesity and Hypertension: An Hypothesis Involving Insulin, the Sympathetic Nervous System, and Adaptive Thermogenesis

LEWIS LANDSBERG

From Harvard Medical School and the Dana-Thorndike Laboratories, Department of Medicine, Beth Israel Hospital, Boston, MA 02215

The association of obesity and hypertension is well recognized. Although the frequency of hypertension in obese subjects varies depending upon the age, race, and sex of the population studied, as well as the definitions employed for 'hypertension' and 'obesity', several reports suggest that as many as 50 to 60 per cent of overweight people have high blood pressure [1, 2]. Hypertension, more importantly, is probably the major factor accounting for increased cardiovascular disease in the obese [3, 4]. Despite the importance of the clinical problem, the fundamental nature of the association between obesity and hypertension has been obscure. Recent epidemiological and physiological studies, however, suggest that insulin and the sympathetic nervous system may be involved, and that the hypertension of obesity may be the unfortunate by-product of mechanisms that establish energy balance and limit weight gain.

BODY FAT DISTRIBUTION, HYPERTENSION AND HYPERINSULINEMIA

Not all obese are hypertensive. Recent anthropometric studies [5, 6] have confirmed earlier impressions [7] that cardiovascular disease in general, and hypertension in particular, is associated with fat accumulation in the abdomen and chest rather than in the gluteal and femoral regions. These studies have demonstrated convincingly that hypertension is associated with the upper body or 'android' (male) pattern of obesity rather than the lower body or 'gynoid' (female) pattern. The distribution of body fat, moreover, is a far more important risk factor for the development of hypertensive cardiovascular disease than the degree of obesity *per se*.

Of further interest is the relationship between body fat distribution and hyperinsulinemia. Insulin levels, both basal and in response to glucose challenge, are higher in obese subjects with upper body, as compared with lower body fat distribution [8, 9]. The hyperinsulinemia of obesity, although well recognized, is incompletely understood. Elevated circulating levels of insulin in obese subjects are generally ascribed to diminished sensitivity to the actions of insulin that promote glucose uptake and utilization by skeletal muscle and adipose tissue [10], although dietary intake, particularly of carbohydrate, may play a role as well [11]. Many factors appear to contribute to the 'insulin resistance' of obesity including: (i) increased adipose cell size, since large hypertrophic adipocytes from obese subjects are less sensitive to insulin [12–14]; (ii) decreased numbers of insulin receptors, perhaps as a consequence of diet-induced hyperin-

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sulinemia since 'down regulation' or decrease in insulin receptors has been shown to follow increases in circulating insulin [15]; (iii) post-receptor defects involving the glucose transport system [16]; and (iv) effects related to increased circulating free fatty acid levels which diminish glucose uptake in skeletal muscle [17] and decrease hepatic insulin clearance [18]. As a consequence of diminished insulin sensitivity higher levels of insulin are required to maintain normal glucose uptake and metabolism. When insulin reserve is adequate, normal or near normal glucose tolerance is maintained despite insulin resistance; when pancreatic insulin reserve is insufficient, type II diabetes mellitus develops. The fact that type II diabetes is much more common in obese patients with upper body obesity [19, 20] is consistent with insulin resistance in this group. The association of hyperinsulinemia with upper body obesity may relate to the observation that adipocytes from this region are particularly sensitive to the metabolic effects of hormones. Adipocytes from abdominal, as compared with femoral regions, are more sensitive to the anti-lipolytic effects of insulin [18] suggesting that they become hypertrophic when exposed to insulin. The fact that these cells are also more sensitive to the lipolytic effects of catecholamines [8, 21] may contribute to the increased free fatty acid levels which antagonize insulin action [17] and hepatic insulin clearance [18] in the obese.

Thus, both hyperinsulinemia and hypertension segregate together in the group of obese subjects characterized anthropometrically by an upper body fat distribution. Other recent studies show a close correlation between hyperinsulinemia and hypertension in the same obese subjects [22–24]. In both animals and humans, moreover, evidence from physiological studies suggests that insulin predisposes to hypertension (i) by stimulating renal sodium reabsorption and (ii) by stimulating the sympathetic nervous system. A considerable body of evidence, derived from studies in experimental animals and man, demonstrates that insulin diminishes sodium excretion by an effect exerted on renal tubular epithelium [25, 26]. By altering the capacity of the kidney to excrete sodium, insulin would be expected to change the 'pressure–natriuresis' relationship so that higher renal (and hence arterial) perfusion pressures are necessary to excrete the same amount of salt [27, 28]. The hyperinsulinemia of obesity may, therefore, be one important factor contributing to the 'natriuretic handicap' displayed by hypertensive patients; the inhibitory effect of insulin on sodium excretion means that sodium balance can be maintained only by an increase in blood pressure once the recruitment of other natriuretic mechanisms is exhausted.

Insulin has also been demonstrated to increase sympathetic nervous system activity [29, 30]. When infused into normal human subjects, along with sufficient glucose to prevent the plasma glucose level from falling, insulin increases plasma noradrenaline level, pulse rate, blood pressure and cross-product (systolic blood pressure×pulse rate) in dose-dependent fashion [30]; the higher the insulin level achieved the greater the sympathetic stimulation. The available evidence, furthermore, indicates that resistance to the effects of insulin on the sympathetic nervous system may not develop in the obese [31]. Despite a substantial decrease in muscle glucose uptake in response to insulin, obese men demonstrate similar sympathetic nervous system responses to further elevations in insulin levels as do lean insulin-sensitive subjects with normal glucose uptake. The hyperinsulinemia of obesity, therefore, may stimulate excessively the sympathetic nervous system. Noradrenaline released from sympathetic nerve endings in the kidney, heart, and blood vessels raises blood pressure by enhancing sodium reabsorption, increasing cardiac output, and increasing peripheral resistance [32]. The antinatriuretic effects of both catecholamines and insulin prevent the kidney from compensating for the increase in blood pressure consequent to sympathetic stimulation of the heart and vasculature. The actions of insulin on the kidney and the sympathetic nervous system, therefore, provide a potential physiological explanation for the development of hypertension in the obese that could account for the epidemiological association of hypertension and hyperinsulinemia in obese subjects.

HYPERINSULINEMIA, SYMPATHETIC NERVOUS SYSTEM ACTIVITY AND DIETARY THERMOGENESIS

Hypertension may thus be viewed as a patho-physiologic consequence of the hyperinsulinemia that complicates insulin resistance in the obese. Other considerations, moreover, suggest a potential physiological role for the hyperinsulinemia in regulating energy expenditure in the obese state. The relationship between insulin and energy expenditure can be best understood in terms of dietary effects on sympathetic activity. Dietary intake is known to exert a profound influence on the sympathetic nervous system [33], as may be briefly summarized: (i) fasting suppresses sympathetic activity [34, 35]; (ii) overfeeding a mixed diet increases sympathetic activity [36]; (iii) a variety of carbohydrates and fats increase sympathetic activity even when total caloric intake is not increased [37–39]; and (iv) diets low in protein increase sympathetic activity [40] since the relative proportion of carbohydrate and/or fat is increased in these diets and since protein *per se* does not stimulate sympathetic activity [41]. Insulin is a major signal that relates dietary intake to sympathetic activity. Insulin-mediated glucose metabolism within critical neurons related to the ventromedial portion of the hypothalamus appears to be one important mechanism that couples dietary intake and sympathetic nervous system activity [29] Thus, increments in circulating insulin, in association with normal or elevated levels of glucose such as occur in some obese subjects, result in sympathetic stimulation.

The sympathetic nervous system is known to play an important role in the regulation of mammalian thermogenesis [42, 43], and diet-induced changes in sympathetic activity have been shown to contribute to the changes in energy expenditure that accompany changes in diet [44, 45]. The generation of metabolic heat in response to cold exposure ('non-shivering thermogenesis') and in response to dietary intake ('diet-induced thermogenesis') is under the direct control of the sympathetic nervous system. In laboratory rodents both these forms of adaptive thermogenesis involve brown adipose tissue which functions as a heat-producing organ regulated by sympathetic nerves [46, 47]. Although a functional role for brown adipose tissue in adult humans remains unproved, it is quite clear that catecholamines increase metabolic rate in human subjects [48] and that insulin induces a sympathetically mediated increase in metabolic rate in normal humans [49, 50]. If brown adipose tissue is not involved, the site of heat production in response to catecholamines in adult humans remains to be elucidated.

Insulin, thus, serves to couple dietary intake with sympathetically mediated thermogenesis. The potential implications of the relationship between energy output and dietary intake are great. During fasting suppression of sympathetic activity results in a decrease in metabolic rate that conserves energy while caloric intake is limited. The stimulatory effect of overfeeding, on the other hand, provides the capability of dissipating calories consumed in excess of need. This capability is of particular advantage to an organism faced with a subsistence diet low in protein; by consuming larger amounts of a low-protein diet an organism would be able to satisify basic nitrogen requirements for growth and development while dissipating the excess calories and avoiding the liability of increased fuel storage as fat. Since thyroid hormones potentiate the thermogenic effects of catecholamines, diet-induced changes in the peripheral deiodination of thyroxin to triiodothyronine (decrease with fasting, increase with overfeeding) [51, 52] would amplify the changes in metabolic rate induced by dietary alterations in sympathetic activity. The capacity to dissipate excess calories as heat, generally referred to as dietary thermogenesis, provides, therefore, a potential natural defense against obesity.

THERMOGENESIS, OBESITY AND THERAPEUTIC WEIGHT LOSS

It is obvious that the development of obesity results from a prolonged disequilibrium between energy intake and energy output. Until recently the disequilibrium was attributed entirely to

excessive dietary intake; it is now increasingly recognized, however, that energy output may contribute to the disequilibrium and that thermogenesis, as well as exercise, contributes importantly to energy output [53, 54]. The range of caloric intakes over which different individuals can maintain energy balance is known to be highly variable, suggesting large individual variation in the capacity for dietary thermogenesis; while some individuals gain incrementally when caloric intake is increased, others resist weight gain by increasing metabolic rate [55–57]. It is a reasonable hypothesis, therefore, supported by a developing body of evidence, that in some obese a diminished capacity for dietary thermogenesis plays a role in the pathogenesis of the obese state [53].

The importance of a defect in thermogenesis in the causation of obesity has been controversial since, in the obese, metabolic rate in both the basal and postprandial state is higher than in lean controls. The obese, however, are much larger; when expressed per unit of weight, metabolic rate in the obese is lower than in lean controls since the metabolic rate of adipose tissue is lower than that of lean body mass. When expressed per unit of fat-free mass, metabolic rate in obese and lean are frequently similar [58]. The question of the appropriate denominator for expressing the rate of oxygen consumption confounds the comparison of metabolic rate between lean and obese, a problem that admits of no easy solution. Furthermore, if obesity is associated with a compensatory mechanism recruited to increase thermogenesis, it follows that comparisons of thermogenesis between lean and obese are not meaningful when carried out in the obese (or compensated) state. In fact, after weight loss, metabolic rate (both basal and postprandial) is reduced in some obese to levels below those of control subjects [53, 59]. It seems likely that human obesity represents a continuum that stretches from pure dietary excess ('gluttony') on the one hand, to a genetically determined [60] 'thrifty' metabolic trait characterized by impaired thermogenic mechanisms, on the other. Those with a 'thrifty' metabolic trait have a high efficiency metabolism that would fare well during intermittent periods of famine; when faced with an abundant supply of calories, however, such individuals become obese. Diminished thermogenic capacity, therefore, limits the possibility of expending excess calories and reduces the level of caloric intake over which energy balance can be achieved.

As shown in Fig. 1 both excessive dietary intake and diminished thermogenesis may lead ultimately to obesity with associated insulin resistance, hyperinsulinemia, and sympathetic nervous system stimulation. Since infusions of noradrenaline increase oxygen consumption in the obese [48] the increase in sympathetic activity associated with hyperinsulinemia [31, 49, 50] would be expected to increase thermogenesis. The increase in thermogenesis would antagonize further weight gain, and stabilize body mass thus tending to compensate for the increase in dietary intake or thermogenic defect (or both). Although the hypothetical scheme shown in Fig. 1 requires further experimental validation (as discussed below) available evidence is consistent with the formulation as depicted.

Thus, the hypothesis developed here may be summarized as follows: increased sympathetic activity, related to hyperinsulinism and recruited in the interest of increasing thermogenesis, contributes, along with the antinatriuretic effect of insulin itself, to the hypertension of obesity. This formulation depends upon continuing sensitivity of peripheral effector tissues to the thermogenic and pressor actions of noradrenaline despite sustained sympathetic stimulation. This is an important issue to address since many alpha and beta receptor-mediated responses to catecholamines have been shown to undergo desensitization [61]. With regard to thermogenesis, however, it is clear that sustained increases in sympathetic activity such as occur in chronically cold exposed animals and man, are associated with enhanced thermogenic response to catecholamines [42, 62, 63]; the augmented thermogenic response to noradrenaline, in fact, defines the cold acclimated state. Chronic overfeeding in animals similarly increases the thermogenic response to noradrenaline [47] despite a sustained increase in sympathetic activity

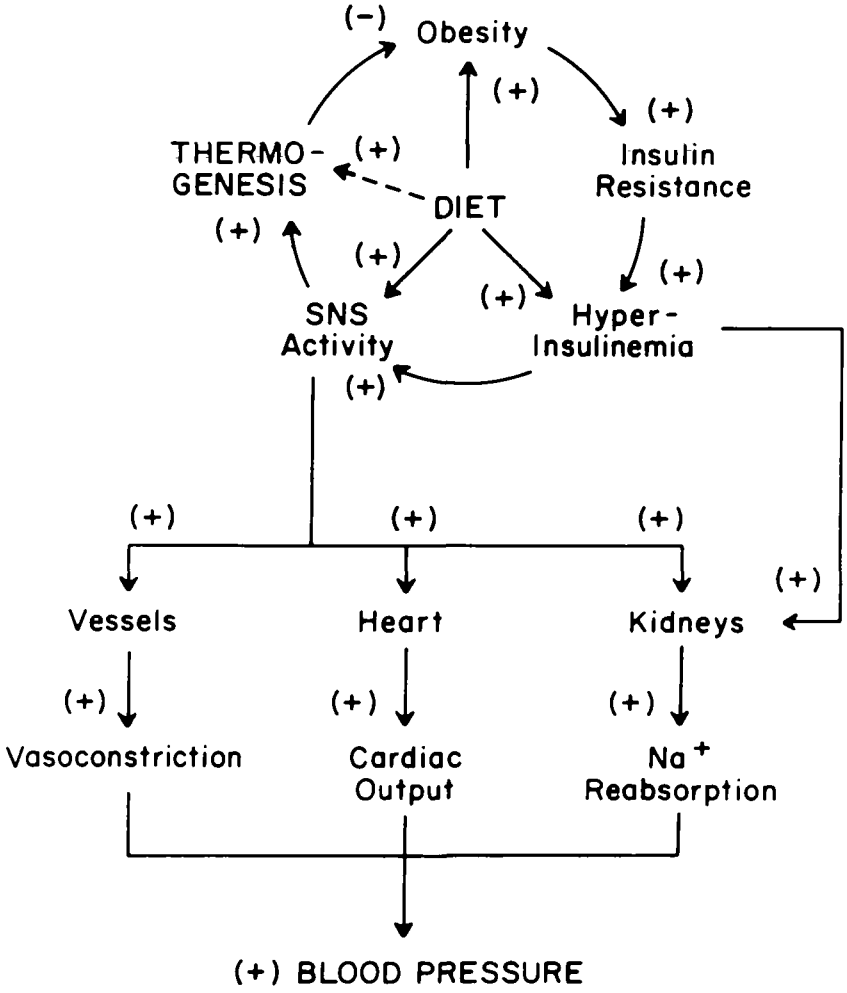

FIG. 1. Relationship between diet, thermogenesis, and blood pressure. (+) Indicates stimulation or elevation; (−) indicates antagonism. The rationale behind the model proposed is provided in detail in the text. Obesity is seen to be the consequence of excessive dietary intake and a defect in dietary thermogenesis; in individual cases one or the other may predominate. Stimulation of insulin by diet favors the development of large hypertrophic adipocytes distributed in the upper body regions and abdomen since these fat cells are most sensitive to the anti-lipolytic effects of insulin. Insulin resistance develops as obesity progresses augmenting the development of hyperinsulinemia which in turn (down regulation) may increase insulin resistance. Hyperinsulinemia stimulates the sympathetic nervous system (SNS) since the obese are not resistant to this action of insulin; hyperinsulinemia also restores glucose uptake and utilization which is impaired by insulin resistance at the level of skeletal muscle. Diet may also stimulate sympathetic activity by mechanisms unrelated to hyperinsulinemia. The increased sympathetic activity stimulates thermogenesis which antagonizes further weight gain and, in some cases, limits weight gain despite dietary excess. In addition to stimulating thermogenesis, however, the hyperinsulinemia and heightened sympathetic nervous system activity increase blood pressure by enhancing sodium reabsorption and by stimulating the heart and blood vessels. The dotted line between diet and thermogenesis represents the obligatory heat produced by the processes of digestion, absorption, and assimilation (non-adaptive) in distinction to the adaptive or regulatory stimulation of thermogenesis that results from hyperinsulinemia and activation of the sympathetic nervous system. With a decrease in dietary intake fat stores diminish and the stimulatory effects on thermogenesis and blood pressure are reversed leading to a decrease in metabolic rate and a fall in blood pressure. This model is not intended to describe the totality of the relationship between hypertension and obesity; undoubtedly other blood pressure regulating systems are involved as well. The effects of dietary intake (and hyperinsulinemia) on those other systems, however, are not well established.

[36]. In man the thermogenic response to noradrenaline is preserved (although apparently not augmented) in both obese and lean during weight maintenance and chronic overfeeding [48]. Tachyphylaxis, therefore, does not develop to the thermogenic effects of noradrenaline. The effect of chronic sympathetic stimulation on the cardiovascular effects of catecholamines is, however, problematic since cold acclimation diminishes blood pressure responses to both cold exposure [64] and noradrenaline infusion [63]. The blood pressure responses, however, although diminished still persist in cold acclimated subjects, and the hormonal milieu, which influences responses to catecholamines is not the same in cold exposure and obesity. The obese, in fact, are not known to differ from lean subjects in the cardiovascular responses to noradrenaline [31, 48].

Additional evidence of a sympathetic contribution to the hypertension of obesity is provided by the response to caloric restriction. When obese hypertensive subjects diet successfully blood pressure falls rapidly, preceding substantial loss of body fat and long before the attainment of ideal body weight [65–67]. The fall in blood pressure, moreover, is unrelated to a decrease in sodium intake [65] but is temporally associated with diminished insulin secretion [68, 69] and reduction in circulating levels of noradrenaline [66, 67]. Thus, the decrease in caloric intake with associated reductions in insulin and sympathetic activity may contribute to the hypotensive effect of dieting long before substantial weight is lost.

Two other implications of the relationship portrayed in Fig. 1 are worth specific mention. In the first place, it should be obvious that the relationship between dietary intake, insulin, and sympathetic activity may explain some of the relationship between dietary intake and hypertension in non-obese subjects. In individuals with a high capacity for thermogenesis, dietary effects on sympathetic activity may result in sufficient activation of thermogenic mechanisms to avoid the development of obesity; the increase in sympathetic activity might, none the less be sufficient to increase blood pressure in predisposed individuals. The association between hyperinsulinemia and hypertension even in non-obese subjects [22, 24] and the correlation between fasting insulin levels and urinary noradrenaline excretion in hypertensives [70] supports such an hypothesis.

Secondly, the suppression of sympathetic activity with caloric restriction results in a reduction in sympathetically mediated thermogenesis [71]. This conservative mechanism, appropriate in response to famine, antagonises weight loss when evoked during therapeutic dieting in obese subjects. Physiological or pharmacological interventions that increase metabolic rate may play a useful role as an adjunct to low energy diets in the treatment of obesity. The treatment of obesity by caloric restriction alone may be likened to the treatment of hypertension by salt restriction; it is effective, provided restriction is severe enough, but is not practical as a sole therapeutic modality in the long run.

AREAS REQUIRING FURTHER STUDY

Before the hypothesis outlined here can be regarded as established, several of the relationships depicted in Fig. 1 need to be substantiated. Fortunately, many of the suggested relationships are amenable to direct experimental validation. The major deficits in the available evidence reflect the heterogeneity of the obese population. The hypothesis advanced here relates to a particular subgroup of obese. Surprisingly few studies on the pathophysiology of hypertension in the obese have compared hypertensive obese with normotensive obese. Since epidemiological studies have identified the obese group (upper body) at risk for hypertension and cardiovascular disease only recently, physiological studies comparing subsets of obese characterized with regard to body fat distribution have just begun to appear. As noted above, the association of hyperinsulinemia with upper body obesity and the relationship between hyperinsulinemia

and blood pressure contributed importantly to the genesis of the hypothesis presented here. Validation of the hypothesis will depend upon careful studies that compare hypertensive hyperinsulinemic obese with both normal controls and normotensive non-hyperinsulinemic obese as well as with normal weight non-hyperinsulinemic hypertensives.

The linchpin of the hypothesis (Fig. 1) is the increase in sympathetic activity predicted in hyperinsulinemic hypertensive obese. Despite the difficulty in assessing sympathetic activity in human subjects [61] judicious use of plasma and urinary catecholamine determinations, in conjunction with tracer methods to correct for changes in norepinephrine clearance, should adequately address the level of sympathetic activity in obese hyperinsulinemic hypertensive subjects compared with normotensive obese and normal weight subjects. Available data on this point are consistent with the hypothesis. Plasma norepinephrine levels, frequently low in obese subjects with normal blood pressure [48] have been reported to be elevated in obese hypertensive patients [72]. Further studies of appropriate subgroups should be decisive.

Of greater difficulty is establishing a causal relationship between sympathetic activity and thermogenesis on the one hand and sympathetic activity and hypertension on the other. The fact that insulin, plasma norepinephrine, and blood pressure fall during caloric restriction in obese hypertensive subjects at a roughly similar rate, as noted above, is consistent with the hypothesis outlined in Fig. 1. A relationship between sympathetic activity and thermogenesis in the obese is suggested by the observation that beta adrenergic blockade decreases resting metabolic rate in obese subjects on a high energy diet but is without effect during low energy intake [73]. The hypothesis predicts that metabolic rate in hyperinsulinemic hypertensive obese would be more sensitive to adrenergic blocking agents than similarly obese normotensive non-hyperinsulinemic subjects. The blood pressure response of obese hyperinsulinemic hypertensives to adrenergic blockade should, by the same token, exceed the response obtained in normal weight non-hyperinsulinemic hypertensives. Sensitivity of obese hyperinsulinemic subjects to infused norepinephrine also needs to be established.

The relationship between hyperinsulinemia and sympathetic activation also requires substantiation. Preliminary evidence, reviewed above [31], suggests that the obese stimulate sympathetic activity during euglycemic insulin infusions; further studies in hypertensive hyperinsulinemic obese are required to demonstrate an increase in plasma norepinephrine (sympathetic activity) as well as an increase in blood pressure and oxygen consumption. The relative effects of somatostatin on indices of sympathetic activity in hyperinsulinemic and non-hyperinsulinemic obese subjects might be another way of establishing a relationship beween insulin and sympathetic activation.

Additional work will either confirm or disprove the hypothesis set forth here that relates hyperinsulinemia to increased sympathetic activity and increased thermogenesis and blood pressure. New work in this area may also clarify the role of other blood pressure regulating systems in the pathogenesis of hypertension in the obese. Pending further studies, the hypothesis set forth here, based on currently available evidence, provides a useful context for understanding the association of high blood pressure and obesity.

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