Obesity, Metabolism, and Hypertension

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The relationship between obesity and hypertension is complex and poorly understood. A developing body of information suggests that metabolic factors related to the obese state are importantly involved. The pertinent observations include: *(1)* Diet influences sympathetic nervous system activity. Fasting suppresses, while carbohydrate and fat feeding stimulate, sympathetic activity. *(2)* Dietary-induced changes in sympathetic activity contribute to the changes in metabolic rate that accompany changes in dietary intake. *(3)* Insulin-mediated glucose metabolism in the hypothalamus provides a link between dietary intake and sympathetic nervous system activity. And *(4)* hyperinsulinemia, a consequence of insulin resistance in the obese, is associated with hypertension.

These observations have suggested the following hypothesis. Hyperinsulinemia results in sympathetic stimulation which drives thermogenic mechanisms, thereby increasing metabolic rate. The net result is a restoration of energy balance at the expense of hyperinsulinemia and increased sympathetic activity. Hypertension is thus the unfortunate consequence of hyperinsulinemia, which increases renal sodium reabsorption, and sympathetic stimulation of the heart, kidney, and vasculature. The data on which this hypothesis is constructed are reviewed and the implications discussed.

Obesity and hypertension are curiously intertwined. The fact that obesity is associated with increased blood pressure, and predicts the subsequent development of hypertension in normotensives, is widely appreciated [1]; less well recognized is the observation that lean hypertensive subjects are at increased risk of becoming obese [1]. The extent of the clinical problem is vast [2]: the incidence of hypertension among the obese approaches 50 percent in some age groups [1], and obesity accounts for a substantial portion of overall hypertensive disease [1]. Despite the importance of the problem, the nature of the association between blood pressure and obesity has remained obscure.

Recent experimental observations have suggested that the linkage between obesity and hypertension is rooted in the relationship between diet and the sympathetic nervous system (SNS) [3,4,5]. Coupled with clinical and epidemiologic studies that demonstrate an association between insulin levels and hypertension [6,7,8,9], these observations have led to the development of an hypothesis that involves insulin-mediated sympathetic stimulation in the pathogenesis of obesity-related hypertension. According to this hypothesis, the insulin resistance of obesity, and consequent hyperinsulinemia, stimulates the SNS; sympathetic activity, in turn, increases thermogenesis, thereby restoring energy balance and limiting further weight gain. The

hyperinsulinemia and sympathetic stimulation, however, via effects imposed on the kidney, the heart, and the blood vessels, result in hypertension [10]. The evidence upon which this hypothesis is based is summarized herein.

DIET AND SYMPATHETIC NERVOUS SYSTEM ACTIVITY

The application of kinetic techniques to assess norepinephrine (NE) turnover rate in sympathetically innervated tissues of laboratory rodents has permitted a detailed evaluation of the influence of dietary intake on SNS activity in these species [11]. The following observations about diet and sympathetic activity have been made: *(i)* Fasting suppresses sympathetic activity [12]. *(ii)* Overfeeding stimulates the SNS [13]. *(iii)* Dietary carbohydrate and dietary fat stimulate sympathetic activity even when total caloric intake is not increased [14,15,16]. *(iv)* Low-protein diets stimulate the SNS [17], while protein is without effect [18]. *(v)* Dietary changes in sympathetic activity depend upon absorption of the specific nutrient. Fat malabsorption induced by cholestyramine antagonizes the stimulatory effect of fat but not of sucrose [15]; the stimulatory effect of sucrose, on the other hand, is antagonized by the disaccharidase inhibitor, acarbose [16].

Although originally described in rodents, the application of less sensitive techniques in human subjects demonstrates that dietary changes in sympathetic activity occur in humans as well [19,20].

DIETARY THERMOGENESIS

Dietary thermogenesis refers to alterations in metabolic rate that accompany changes in dietary intake. Two components have been identified: an increase in oxygen consumption in the postprandial state over and above that accounted for by the metabolic disposition of the nutrients [21,22] and an effect of antecedent diet on the resting metabolic rate [23,24]. It is generally acknowledged that dietary changes in thermogenesis are mediated, at least in part, by dietary changes in sympathetic activity. The linkage between dietary thermogenesis and the sympathetic nervous system depends, in part, on observations demonstrating that diet influences sympathetic outflow to brown adipose tissue in the rodent [13]. Brown adipose tissue (BAT) is the thermogenic effector organ in the rat [25]; the SNS is the major physiologic regulator of heat production in this organ [26]. Sympathetic stimulation of this organ enhances the synthesis of uncoupling protein, a unique BAT polypeptide that permits protons to enter the inner mitochondrial matrix without the concomitant synthesis of ATP, thereby driving the respiratory chain and uncoupling oxidative phosphorylation [27]. The observation that diet exerts an important influence on sympathetic outflow to BAT [13] as well as heart provides a link between dietary intake and oxygen consumption or thermogenesis. The fact that diet is without effect on sympathetic outflow to skeletal muscle, conversely, is evidence against muscle as an important site of dietary thermogenesis in the rodent [28]. Although a decisive role for BAT in adult humans is still controversial [29,30], studies utilizing beta adrenergic antagonists are consistent with a role for the SNS in the regulation of dietary thermogenesis in man [21,22,24].

Suppression of sympathetic activity with fasting would serve the useful role of diminishing energy expenditure in the face of diminished caloric intake, thereby prolonging survival during famine. The capacity to enhance thermogenesis in the face of a subsistence diet low in protein would, on the other hand, permit an organism to maintain adequate supplies of nitrogen for growth and development by overeating a
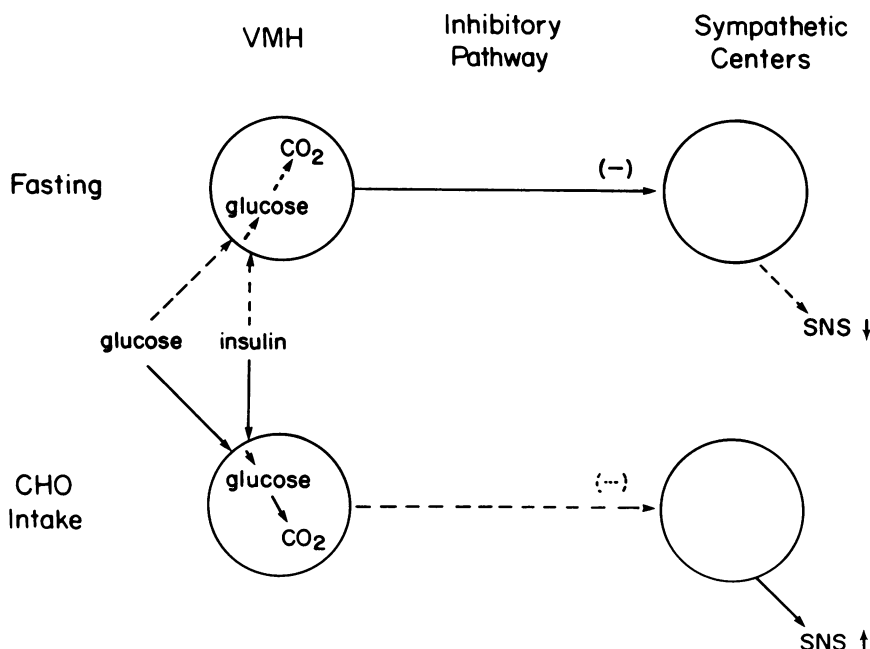
FIG. 1. Insulin-mediated glucose metabolism in the regulation of sympathetic outflow. According to this model, insulin-mediated glucose metabolism within insulin-glucose sensitive neurons related anatomically to the ventromedial hypothalamus (VMH) regulates discharge in sympathetic brainstem centers via an inhibitory pathway. The data on which this model is based are summarized in the text. Diminished circulating levels of insulin and glucose, such as occur during fasting or caloric restriction, diminish insulin-mediated glucose uptake and metabolism in hypothalamic regulatory neurons sensitive to glucose and insulin. This decrease in intracellular glucose metabolism enhances an inhibitory pathway to the brainstem, thereby diminishing sympathetic outflow. Conversely, during carbohydrate intake, or in the presence of insulin resistance, elevated levels of glucose and insulin stimulate glucose uptake and metabolism in these same neurons. Increased intracellular glucose metabolism inhibits the inhibitory pathway to the brainstem, resulting in disinhibition of tonically active lower neurons and an increase in central sympathetic outflow (from [32] with permission).

diet low in protein while avoiding obesity by dissipating the excess calories. Whatever the evolutionary origins of dietary thermogenesis, however, it is clear that this mechanism would allow an organism to maintain energy balance over a variable range of dietary intakes. A mismatch of intake over expenditure of a few percent would, over time, result in the accumulation of significant amounts of fat [31]. Dietary thermogenesis, therefore, to the extent that it is expressed in a given individual, provides a buffer against the development of obesity.

ROLE OF INSULIN

The mediation of dietary changes in sympathetic activity is a subject of considerable interest. Since sympathetic outflow depends upon integrated changes within the central nervous system, mechanisms must exist that couple sympathetic outflow with changes in dietary intake. Evidence accumulated over the last decade indicates that insulin-mediated glucose metabolism within critical central neurons sensitive to insulin and glucose is critically involved in this linkage of diet and SNS [32] (Fig. 1). The following observations bear importantly on this relationship: *(i)* Hypoglycemia sup-

presses sympathetic activity despite concomitant adrenal medullary stimulation [33,34]. *(ii)* 2-Deoxyglucose administration suppresses sympathetic activity (despite adrenal medullary stimulation) in the face of increased circulating glucose levels [35]. *(iii)* Insulin administration, to rats and humans, along with provision of sufficient glucose to prevent the development of hypoglycemia, stimulates the SNS [36,37]. *(iv)* The induction of experimental diabetes in rats with streptozotocin, conversely, diminishes sympathetic activity despite the elevated glucose levels [38]. *(v)* Gold-thioglucose treatment in mice, which destroys insulin-glucose sensitive neurons related to the ventromedial portion of the hypothalamus, blocks dietary changes in sympathetic activity. Animals treated with gold-thioglucose fail to suppress sympathetic activity with fasting [39], implying that fasting is normally associated with stimulation of an inhibitory pathway from the hypothalamus to tonically active regulatory sympathetic centers in the brainstem (Fig. 1).

The fact that fasting and 2-deoxyglucose are not additive in their suppressive effect on sympathetic activity suggests that the fasting effect is induced by diminished glucose metabolism in the central nervous system [35]. Fasting, therefore, appears to suppress sympathetic activity by decreasing insulin-mediated glucose metabolism (within these critical hypothalamic neurons) which in turn stimulates an inhibitory pathway to the brainstem. Enhanced insulin-mediated glucose metabolism in these neurons, conversely, suppresses the inhibitory pathway, resulting in disinhibition of tonically active lower neurons and an increase in sympathetic outflow. The development of insulin resistance in response to fat feeding, associated as it is with elevated levels of insulin and glucose, would be expected to stimulate sympathetic activity in a manner analogous to that shown for carbohydrate intake in Fig. 1.

Insulin, therefore, serves as an important signal that couples dietary intake and sympathetic outflow.

INSULIN AND BLOOD PRESSURE IN THE OBESE

Clues to the involvement of insulin in the pathogenesis of obesity-related hypertension came initially from two sources. Epidemiologic studies of large population groups demonstrated that the cardiovascular and metabolic complications of obesity, including hypertension, were associated with a pattern of body fat distribution that favored the upper body segments [40,41,42]. Clinical studies of smaller numbers of obese subjects demonstrated that hyperinsulinemia and insulin resistance were more marked in obese subjects with this same upper body fat distribution [43,44,45]. A direct link between insulin and blood pressure was also demonstrated in epidemiological [8] and clinical studies of obese subjects [6,7]. Both clinical and epidemiologic studies have, moreover, demonstrated that hyperinsulinemia and insulin resistance are noted in non-obese hypertensives as well [8,9].

The relationship between hyperinsulinemia and blood pressure remains obscure. A plausible hypothesis relating insulin to hypertension, however, can be constructed from the direct effects of insulin on renal sodium reabsorption and the effects of insulin on the SNS as summarized in Fig. 2. According to this formulation, the hypertension associated with hyperinsulinemia results from the antinatriuretic effects of insulin [46,47] and the SNS [48,49,50] in conjunction with sympathetic stimulation of the heart and vasculature [51]. Antinatriuretic effects induce hypertension by shifting the pressure-natriuresis relationship so that higher renal perfusion pressures are required to maintain extracellular fluid volume [52,53]. Insulin and sympathetic stimulation in
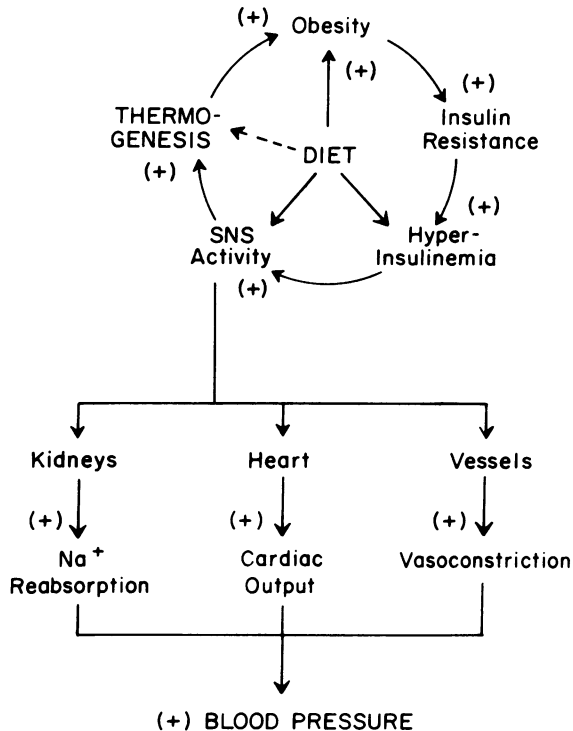
FIG. 2. Relationship between obesity, insulin, sympathetic activity, thermogenesis, and blood pressure. According to this model, obesity, whether the consequence of dietary excess or diminished capability for thermogenesis, or both, results in insulin resistance and hyperinsulinemia. The hyperinsulinemia stimulates sympathetic activity, thereby increasing thermogenesis and restoring energy balance. Hypertension in association with obesity, according to this model, is the consequence of mechanisms recruited (insulin resistance, sympathetic stimulation) to achieve energy balance and stabilize body weight; see text for details (from [4] with permission).

the obese are potential factors, therefore, in the pathogenesis of obesity-related hypertension.

INSULIN-MEDIATED SYMPATHETIC STIMULATION IN THE OBESE

A larger question is the physiological role subserved by the development of insulin resistance in the obese. A potential role for insulin resistance and hyperinsulinemia in the metabolic economy of the obese is suggested in Fig. 2. Insulin resistance may be viewed as a mechanism recruited in the obese to restore energy balance and limit further weight gain. Insulin resistance at the level of the adipocyte would antagonize the deposition of free fatty acids in triglyceride stores in adipose tissue. The hyperinsulinemia that develops as a consequence of insulin resistance might, furthermore, stimulate sympathetically mediated thermogenesis, thereby increasing energy production, restoring energy balance, and limiting further weight gain. According to the hypothesis presented in Fig. 2, thermogenesis is enhanced at the expense of hyperinsulinemia and SNS stimulation in the obese. Such a mechanism would come into play in the setting of either excessive dietary intake or diminished thermogenic capability.

In support of the above hypothesis, it has been demonstrated that insulin infusions increase plasma NE level in lean [36] and obese [54] subjects, along with cardiovascular and thermogenic manifestations of sympathetic stimulation. The obese, therefore, are not resistant to the effect of insulin on the SNS. The linchpin of the hypothesis, nonetheless, is the level of sympathetic activity in obese hypertensives. This level remains the subject of ongoing investigation but preliminary epidemiologic [55] and clinical studies utilizing somatostatin infusions to suppress insulin release [D. Elahi

and L. Landsberg] are consistent with increased sympathetic stimulation in the obese.

INSULIN-MEDIATED SNS STIMULATION IN NON-OBESE HYPERTENSIVES

Hypertension in the obese, therefore, may be the unwelcome consequence of mechanisms recruited primarily to restore energy balance. Since the morbid complications of hypertension are not usually expressed during the reproductive years, genetic pressure against insulin-mediated sympathetic stimulation would be unlikely. Inspection of Fig. 2, moreover, suggests that similar mechanisms may be involved in the pathogenesis of hypertension in the non-obese as well. In the presence of effective thermogenic mechanisms, increased dietary intake with consequent hyperinsulinemia and sympathetic stimulation might compensate effectively for the increase in caloric consumption. The compensatory mechanisms, however, involving insulin and the sympathetic nervous system might contribute to the development of hypertension. Since thermogenic capability is known to diminish with advancing age, the mechanisms shown in Fig. 2 might explain the puzzling observation that hypertension predisposes to the development of obesity [1]. As the capacity for thermogenesis diminishes, the mechanism outlined in Fig. 2 would compensate less effectively for increased dietary intake. Under these circumstances, the consequences of continued excessive dietary intake would be the development of obesity along with hypertension.

THERAPEUTIC IMPLICATIONS

This model has clear therapeutic implications. Non-pharmacologic interventions that increase insulin sensitivity and decrease insulin secretion would be expected to reduce SNS activity and lower blood pressure. Decreased caloric intake, weight loss, exercise, and high-fiber diets have all been proposed as effective forms of treatment for obesity-related hypertension [56,57,58,59]. Each of these modalities increases insulin sensitivity and decreases insulin secretion and, where studied, have been shown to diminish SNS activity.

Caloric restriction exerts a hypotensive effect soon after the initiation of a low-energy diet [56], before appreciable loss of weight. The hypotensive effect appears to reflect alterations in renal sodium excretion (the "natriuresis of fasting") [60] and suppression of the SNS [61,62]. Weight loss has also been demonstrated to lower blood pressure in obese hypertensives [63], although this effect may be difficult to distinguish from caloric restriction. Diminished insulin resistance and decreased SNS activity are likely to be involved in the hypotensive response [64]. Interestingly, relatively small amounts of weight loss may be efficacious in lowering blood pressure [65]. Exercise lowers blood pressure with a greater effect in hypertensives than in normotensives, even in the absence of weight loss [57,59]. Training is known to decrease sympathetic activity and increase insulin sensitivity as well, consistent with involvement in the hypotensive response to exercise.

The beneficial effects of each of these interventions is consistent with the model depicted in Fig. 2 and suggests that other treatment strategies directed at insulin resistance and the SNS may be effective as well.

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