Obesity and the Insulin Resistance Syndrome

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Obesity is one component of a risk factor constellation that consists of insulin resistance (and/or hyperinsulinemia), hypertension, and a dyslipidemia characterized by a low HDL cholesterol level and high triglyceride levels. This risk factor constellation, which conveys enhanced risk for cardiovascular disease, is sometimes referred to as the “insulin resistance syndrome”, “syndrome x”, or the “metabolic” syndrome. Although the hyperinsulinemia and insulin resistance associated with the syndrome appear to play a central role, the relationship between insulin and the other manifestations of the syndrome have remained obscure. (Hypertens Res 1996; 19 Suppl. 1: S51-S55)

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Insulin and Hypertension

The association of hyperinsulinemia with hypertension in the obese has been recognized for over a decade (1, 2). This relationship, moreover, extends even to the nonobese (1, 3). Since insulin is a direct vasodilator (4), the nature of the association between insulin and hypertension has not been clear. Experimental evidence, initially in animals and subsequently in human subjects, has demonstrated that insulin stimulates the sympathetic nervous system (SNS) (5-7), suggesting a possible mechanism for the relationship between insulin and hypertension.

Insulin and the SNS

The role of insulin in regulating SNS activity was discovered in follow up to studies that demonstrated an effect of dietary intake on sympathetic activity. Diet and Sympathetic Activity

It has been well established that diet influences SNS activity: fasting suppresses (8) while overfeeding stimulates (9, 10) the SNS. Since alterations in SNS activity originate within the central nervous system a mechanism that links dietary intake with SNS activity is essential; insulin provides such a link. Although described originally in studies involving laboratory rodents, it is clear that the same dietary changes in SNS activity occur in humans (11, 12).

Insulin and SNS Activity

A substantial amount of evidence in laboratory rodents demonstrated that insulin plays an important role in the regulation of SNS activity (6). Experiments in rats with hypoglycemia (13, 14) and 2-deoxyglucose (15) indicated that glucose metabolism was involved. Both of these maneuvers suppressed SNS activity. A role for insulin was established by inducing insulin deficiency with streptozotocin (16) and by insulin administration (17, 18). Insulin deficiency suppressed, and insulin administration increased SNS activity. Experiments with mice demonstrated that gold thioglucose, an agent that destroys glucose and insulin sensitive neurons in the ventromedial hypothalamus, blocked the suppressive effects of fasting on SNS activity (19), indicating that these neurons exerted a tonic inhibitory effect during fasting. These observations were integrated into the model shown in Fig. 1; insulin mediated glucose metabolism, in insulin-glucose sensitive neurons related anatomically to the ventromedial nucleus are important in mediating this relationship.

During fasting, decreased glucose and insulin levels suppress the inhibitory pathway resulting in an increase in sympathetic activity (Fig. 1). It has, moreover, been decisively demonstrated that insulin stimulates the sympathetic nervous system in humans (18), as demonstrated by plasma NE levels, NE, tracer kinetics, and muscle sympathetic nerve activity from implanted microelectrodes (7).

The SNS and Dietary Thermogenesis

The physiology of insulin-mediated sympathetic stimulation involves the regulation of dietary thermogenesis (21). Nutritional status and metabolic rate are linked via insulin and the sympathetic nervous system. Fasting or low energy diets suppress meta-
Insulin-Mediated Sympathetic Stimulation and the Pathogenesis of Obesity-Related Hypertension

Based on the role of insulin in the stimulation of SNS activity, and the association of hyperinsulinemia with hypertension in the insulin-resistance syndrome, an hypothesis was formulated to explain the association of hypertension and obesity (22, 23). According to this formulation, as shown in Fig. 2, insulin-resistance and hyperinsulinemia is a mechanism recruited in the obese to stabilize body weight. The hyperinsulinemia, according to this hypothesis, stimulates the sympathetic nervous system, drives sympathetically mediated thermogenesis, thereby increasing metabolic rate and limiting further weight gain. Like any compensatory mechanism, however, there is a price to pay; in this case, the hyperinsulinemia and sympathetic stimulation, via actions on the kidney, the heart, and the vasculature exert a pro-hypertensive effect and, in susceptible individuals, raise the blood pressure.

Obesity and SNS Activity

The hypothesis outlined in Fig. 2 was investigated in studies of a community dwelling population-based cohort (The Normative Aging Study, Boston MA) (24). Studies using euglycemic hyperinsulinemic clamps demonstrated that the obese were not resistant to the effect of insulin on the sympathetic nervous system despite marked impairment of insulin-mediated glucose uptake (25). The level of SNS activity in the obese, furthermore, as assessed by 24 h urinary NE excretion (Fig. 3), the rate of appearance of tritiated NE in the circulation (23, 26, 27), and implanted microelectrodes (28) was increased in the obese. There was, moreover, a relationship between insulin and glucose levels and SNS activity (26); those individuals in the upper decile for fasting plasma glucose and/or insulin level excreted more NE over a 24 hour period than those in the lower deciles for these variables.
SNS and Insulin in Hypertension
Both insulin and SNS activity were linked to hypertension; in those individuals in the upper tertile for post-glucose insulin levels and 24 h urinary NE excretion the incidence of hypertension was 35% as compared with 10% in those individuals in the lowest tertile for both these variables (29). Maneuvers that decrease insulin levels and/or increase insulin sensitivity such as somatostatin (30, 31), low energy diets (32), weight loss (32) and treatment with thiazolidinediones (33), have all been shown to decrease blood pressure and in all but the last instant, decrease SNS activity. These studies, therefore, provide evidence of a link between insulin, the sympathetic nervous system, and hypertension.

Epinephrine and the Dyslipidemia
A dyslipidemia characterized by low HDL cholesterol and high triglyceride levels is an important component of the insulin resistance syndrome (34, 35). Many studies have demonstrated that insulin plays an important role in the dyslipidemia. This was also true in the normative aging study. As shown in Fig. 4, those individuals in the upper tertile for post-glucose stimulated insulin levels had higher triglycerides and lower HDL-cholesterol levels than those in the lower deciles.

Adrenomedullary Epinephrine and Dyslipidemia
Another factor of potential importance emerged from the normative aging study (36). In distinction to NE, epinephrine decreased with increasing body weight and increasing upper body fat distribution (26, 27). As shown in Fig. 5, those individuals in the upper tertile for body mass index and waist to hip ratio had significantly lower 24 h urinary epinephrine excretions as compared with those in the lowest tertile. The relationship between 24 h urinary epinephrine excretion (an index of adrenal medullary activity) and lipids is shown in Fig. 6. Those individuals in the lowest tertile for epinephrine excretion had the highest triglycerides and the lowest HDL-cholesterol levels; conversely those in the upper tertile had the lowest triglycerides and the highest HDL-cholesterol levels (Fig. 6). This relationship was maintained with
adjustment of the data for body weight, body fat distribution, and insulin level (36). These data demonstrate that lowered levels of epinephrine contribute as an additional factor to the characteristic dyslipidemia.

Obesity and Sympathoadrenal Activity in the Insulin Resistance Syndrome

The data summarized here are consistent with a role for the sympathoadrenal system in mediating some of the actions of insulin in the insulin resistance syndrome. Some of these relationships are summarized in Fig. 7. Obesity, usually a combination of genetic (diminished capability for dietary thermogenesis) and environmental factors (increased caloric intake and high fat diet) results in insulin resistance and hyperinsulinemia (Fig. 7). Evidence reviewed herein demonstrates that both the sympathetic nervous system and the adrenal medulla contribute to this syndrome (38). The sympathetic nervous system is important in the pathogenesis of hypertension while the adrenal medulla contributes to the associated dyslipidemia.

References


Fig. 6. Relationship between epinephrine excretion and HDL-Cholesterol and triglycerides. Note that decreasing epinephrine levels are associated with high triglycerides and low HDL cholesterol. From (23) with permission.

Fig. 7. Schematic representation of the pathogenesis of the insulin resistance syndrome. See text for detail. From (38) with permission.


