Insulin Resistance and Blood Pressure Regulation in Obese and Nonobese Subjects

Special Lecture

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A review is presented of the potential ways in which insulin resistance and hypertension may be linked. Although controversy exists as to the role insulin resistance and hyperinsulinemia play in the pathogenesis of hypertension, data are presented from both obese and nonobese subjects that strongly suggests that selective insulin resistance and hypertension are directly related. Because insulin resistance may be both tissue and pathway specific, it is possible that the degree to which insulin resistance is tissue specific determines whether hypertension will develop in specific individuals or animals. (Hypertension 1991;17:837-842)

The common association between hypertension, impaired glucose tolerance, and obesity has suggested a common pathogenic mechanism. In numerous epidemiological studies, the majority of patients with essential hypertension have been found to be overweight.1,2 In adolescents and young adults, hypertension is twice as prevalent in subjects who are overweight.3 Modan and coworkers4 have suggested that glucose intolerance, independent of obesity, is significantly associated with hypertension. Analysis of data from the San Antonio Heart Study5 has demonstrated an impressive pattern of overlap among hypertension, diabetes, and obesity. It has been estimated that by the fifth decade of life, 85% of diabetic individuals are hypertensive and obese, 80% of obese subjects have abnormal glucose tolerance and are hypertensive, and 67% of hypertensive subjects are both diabetic and obese.5 Recent data from the CARDIA study have suggested that insulin is an important risk factor for predicting the development of hypertension and serum lipid abnormalities.6 Thus, these studies along with others7-15 have suggested that insulin resistance—that is, the resistance to the effect of insulin on carbohydrate metabolism—is the common feature shared by hypertension, obesity, and diabetes. However, despite the large body of epidemiological data potentially linking insulin to hypertension, a number of major questions still need to be addressed: 1) Which comes first, insulin resistance or hypertension? 2) How does insulin resistance cause hypertension? 3) Does gain in adipose tissue precede both insulin resistance and hypertension? and 4) What causes insulin resistance? The goal of this review is to summarize some of the available data relevant to the first two of these questions.

Insulin Resistance and Hyperinsulinemia: A Potential Cause of Hypertension

Most investigators have suggested that insulin resistance and the resultant hyperinsulinemia are the key metabolic abnormalities that link hypertension, obesity, diabetes, and hyperlipidemia. Welborn and coworkers16 in 1966 provided one of the first reports describing the association between serum insulin and hypertension. Since that report, numerous other investigators have documented the association between hyperinsulinemia and hypertension in both obese and nonobese subjects.4,7,11,13-15 Figure 1 depicts the relation we have observed between diastolic blood pressure and fasting insulin concentration in a group of 58 obese adolescents. Similar relations exist for systolic and mean blood pressures.

Fasting and postglucose insulin values have in the past been used as a rough approximation of insulin sensitivity; however, because these insulin values are the result of secretion, distribution, and degradation and may be differentially affected by various pathophysiological processes, they do not always accurately define insulin sensitivity. A more reliable assessment of insulin sensitivity and resistance can be made using the euglycemic hyperinsulinemic clamp technique.18 Using this technique, numerous investigators have demonstrated a significant inverse relation between

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A significant linear relation exists between insulin and diastolic sure. Fasting insulin concentration is depicted on a log scale. Therefore, in this group of obese adolescents, 41% of variance in diastolic blood pressure can be explained by fasting insulin concentration.

![Graph showing the relation between fasting insulin concentration and diastolic blood pressure.](image)

**Figure 1.** Relation observed in 58 obese adolescents between fasting insulin concentration and diastolic blood pressure. Fasting insulin concentration is depicted on a log scale. A significant linear relation exists between insulin and diastolic blood pressure ($r = 0.64$, $p < 0.001$). Therefore, in this group of obese adolescents, 41% of variance in diastolic blood pressure can be explained by fasting insulin concentration.

whole body glucose uptake and blood pressure in both obese and nonobese subjects.\(^7\)\(^8\)\(^9\)\(^10\)\(^12\)\(^14\)

It also has been shown that factors known to improve insulin resistance are associated with reductions in blood pressure. Weight loss has been documented to be associated with both a decrease in blood pressure and an improvement in insulin sensitivity.\(^13\)\(^15\) The decline in blood pressure associated with exercise training programs seems to be limited to individuals who were initially hyperinsulinemic and had the greatest fall in plasma insulin level as a result of the training program.\(^13\)\(^19\) Finally, Carretta et al\(^20\) have demonstrated in hypertensive obese subjects that a 10-hour infusion of somatostatin, a hormone that can suppress insulin secretion by pancreatic $\beta$-cells, resulted in a reduction both in plasma insulin and in arterial pressure. Because somatostatin has many physiological actions, such as suppressing the secretion of several gastrointestinal hormones in addition to insulin and modifying regional blood flow, the report of Carretta et al does not prove that hyperinsulinemia is the cause of obesity hypertension.

In addition to human data linking insulin and blood pressure, animal data also suggest that insulin is an important regulator of blood pressure. Rocchini et al\(^32\) recently described the development of an animal model of obesity hypertension. These authors demonstrated that the weight gain associated with feeding dogs cooked beef fat was directly associated with an increase in blood pressure and insulin. They also have provided preliminary data in the dog to suggest that in association with a high salt diet, a chronic infusion of insulin results in sodium retention, activation of the sympathetic nervous system, and hypertension.\(^22\)

Reaven and coworkers\(^23\)\(^26\) recently have demonstrated that normal Sprague-Dawley rats fed a fructose-enriched diet develop insulin resistance and hypertension. They also have shown that the hypertension can be eliminated or attenuated by correcting the insulin resistance either with exercise training or the administration of somatostatin. Kurtz et al\(^27\) have shown that the genetically obese, insulin-resistant Zucker rat has an increased blood pressure compared with the genetically lean, non-insulin-resistant Zucker rat or the Lewis rat. Finally, a number of investigators have demonstrated that insulin resistance and hyperinsulinemia also are seen in spontaneously hypertensive rats.\(^28\)\(^30\) In addition, insulin-stimulated glucose uptake has been reported to be lower in adipocytes isolated from these animals.\(^29\)

Thus, based on this data it would appear that insulin resistance and hypertension are directly and possibly even causally related; however, data also suggest that the relation between insulin and hypertension is not so straightforward. Grugni et al\(^31\) have reported that there was no correlation between hyperinsulinemia and hypertension in a group of obese subjects. Data from the San Antonio Heart Study have shown that hyperinsulinemia is more common in Hispanics than in white non-Hispanics, yet the prevalence of hypertension is high in the latter group.\(^5\) Rocchini et al\(^32\) have demonstrated that, although as a group young nonobese hypertensive subjects were insulin resistant when compared with normotensive subjects, more than 40% of the hypertensive subjects had normal insulin-stimulated whole-body glucose uptake (i.e., were not insulin resistant).\(^32\) Hall et al\(^33\) failed to observe an increase in blood pressure when normal dogs were given a chronic infusion of insulin with or without norepinephrine. They speculated that additional factors besides hyperinsulinemia and increased catecholamine levels therefore must play a role in the pathogenesis of obesity hypertension. However, it is important to note that the results of Hall et al differ from those reported by Rocchini et al.\(^22\) The differences between the two studies may relate to the stepwise increase in the insulin infusion rate used by Rocchini et al and the fact that compared with the Rocchini study, Hall et al more rigidly controlled plasma glucose; in fact, the dogs in the Hall study were maintained slightly hyperglycemic. Finally, at least one recent report demonstrates that in the unrestrained conscious state, spontaneously hypertensive rats may be more sensitive to rather than resistant to insulin.\(^34\) The differences between this report by Tsutsu et al and the other reports that document the presence of insulin resistance in the spontaneously hypertensive rat\(^28\)\(^30\) may relate to the strain of animal used or the difference between studying anesthetized versus conscious, unrestrained animals. Further experiments in both conscious and anesthetized animals will be necessary before we will clearly...
understand why some spontaneously hypertensive rats are insulin resistant and others are not.

How Insulin Resistance May Result in the Development of Hypertension

Figure 2 depicts a schematic representation to explain how insulin resistance, obesity, and hypertension may interrelate. We believe that the key variable in this schema is selective insulin resistance. Selective insulin resistance implies that, although an individual or animal may have an impaired ability of insulin to cause whole body glucose uptake, some of the other physiological actions of insulin may be preserved.

With respect to hypertension, one of the potentially important actions of insulin is its ability to induce renal sodium retention. Rocchini et al. recently have demonstrated that obese adolescents have selective insulin resistance, in that they are resistant with respect to glucose uptake yet still are sensitive to the renal sodium-retaining effects of insulin (Figure 3). Finch et al. have confirmed these results in the spontaneously hypertensive rat by documenting impaired whole- rat glucose uptake yet normal insulin sensitivity to induce renal sodium retention. Ferrannini et al. also have demonstrated in nonobese essential hypertensive subjects that insulin resistance involved glucose metabolism but not lipid or potassium metabolism and was limited to the nonoxidative pathways of intracellular glucose disposal. Thus, evidence indicates that in obese and nonobese hypertensive subjects, insulin resistance is selective (predominantly involving glucose metabolism, although amino acid and fatty acid metabolism also can be involved), tissue specific (predominantly affecting skeletal muscle, although liver, adipocytes, and leukocytes also may be affected), and pathway specific (insofar as only glycogen synthesis usually is affected; however, during diabetic ketoacidosis, all anabolic pathways are resistant to the effects of insulin). Therefore, in any individual or animal, the degree to which insulin resistance is tissue or pathway specific may determine whether or not hypertension will develop. For example, if an individual were to have

![Figure 2](image)

**Figure 2.** Schematic representation of a proposed mechanism to explain how insulin resistance may result in development of hypertension. SNS, sympathetic nervous system.

![Figure 3](image)

**Figure 3.** Left panel: Change in urinary sodium excretion (UNaV) that occurred in seven obese and five nonobese subjects during water diuresis and euglycemic hyperinsulinemia. Insulin infusion resulted in a significant decrease in urinary sodium excretion in both obese and nonobese subjects. There was no significant difference in response of urinary sodium excretion to hyperinsulinemia observed between the two groups. Right panel: Change in plasma insulin concentration and glucose uptake (M) during euglycemic hyperinsulinemia in the same subjects. Compared with nonobese individuals, the insulin infusion of 40 milliunits/m²/min resulted in a significant depression in glucose uptake in obese subjects (p<0.001). Plasma insulin response to the insulin infusion was not significantly different between obese and nonobese subjects. (Figure adapted from Reference 14.)
insulin resistance that predominantly affected the skeletal muscle, this resistance to glucose uptake by the muscle would likely result in hyperinsulinemia. Because both the kidneys and sympathetic nervous system may still be sensitive to insulin, the resultant hyperinsulinemia could lead to sodium retention, increased sympathetic activity, and ultimately to the development of hypertension.

As can be seen in Figure 2, some of the physiological and tissue-specific consequences by which insulin resistance could result in hypertension include changes in vascular structure and function, alterations in cation flux, activation of the sympathetic nervous system, and enhanced renal sodium retention.

Insulin and insulinlike growth factors are mitogens capable of stimulating smooth muscle proliferation. Therefore, hyperinsulinemia could result in vascular smooth muscle hypertrophy and ultimately be a cause of insulin resistance.

Hyperinsulinemia could lead to sodium retention, because both the kidneys and sympathetic nervous system, and enhanced renal sodium retention.

Insulin and insulinlike growth factors are mitogens capable of stimulating smooth muscle proliferation. Therefore, hyperinsulinemia could result in vascular smooth muscle hypertrophy and ultimately in the development of hypertension. Alternatively, subjects even could be normally responsive to insulin with respect to glucose control but abnormally sensitive to insulin as a growth factor on their vascular smooth muscle. Finally, Zemel et al have shown that the increased vascular reactivity present in the obese Zucker rat may result from an inability of insulin to stimulate cellular calcium efflux (i.e., resistance of insulin to stimulate calcium efflux normally) and thereby attenuate vasoactive responses.

Insulin has been shown to affect sodium and calcium transport, although controversy still exists regarding the molecular mechanism of this effect. A direct effect of insulin on Na⁺-H⁺ exchange has been demonstrated in vitro. Insulin has been reported to both increase and decrease Na⁺,K⁺-ATPase activity and also has been linked to both Na⁺-Li⁺ countertransport and Na⁺-K⁺ cotransport. Finally, Draznin et al have shown that insulin can elevate cytosolic free calcium levels in adipocytes of normal subjects, although this observation has not been confirmed by others.

Landsberg and Young and their associates have long emphasized that hyperinsulinemia can cause sympathetic nervous system stimulation. They, as well as others, have clearly documented that euglycemic hyperinsulinemia in both normal and obese humans and animals causes activation of the sympathetic nervous system as documented by increases in heart rate, blood pressure, and plasma norepinephrine. In addition, overfeeding with both carbohydrates and fat is associated with stimulation of the sympathetic nervous system. Because increased α- and β-adrenergic tone have been reported to be associated with the development of peripheral insulin resistance, it is possible that chronic activation of the sympathetic nervous system also could be a cause of insulin resistance.

Finally, human and animal data suggest that insulin resistance and hyperinsulinemia can result in chronic sodium retention. Insulin can enhance renal sodium retention directly, through its effects on renal tubules, and indirectly, through stimulation of the sympathetic nervous system and augmentation of angiotensin II-mediated aldosterone secretion. Data also suggest that insulin resistance is directly related to sodium sensitivity in both obese and nonobese subjects.

Rocchini et al have shown that hyperinsulinemia may be responsible for sodium sensitivity in many obese subjects. In particular, they demonstrated that the blood pressure of obese adolescents was more dependent on dietary sodium intake than the blood pressure of nonobese adolescents and that hyperinsulinemia and increased sympathetic nervous system activity appeared to be responsible for the observed sodium sensitivity and hypertension. Rocchini et al have demonstrated that the hypertension associated with weight gain in the dog occurs only if adequate salt is present in the diet. Finally, Rocchini and coworkers have preliminary data suggesting that, in nonobese subjects with essential hypertension, there is a direct relation between sodium sensitivity and insulin resistance. Thus, it appears that insulin resistance can be associated with a sodium-sensitive form of hypertension.

In summary, although it is possible that insulin resistance simply may be a marker for hypertension, ample data from both obese and nonobese subjects strongly suggest that selective insulin resistance and hypertension are directly related. Because insulin resistance may be both tissue and pathway specific, it is possible that in specific individuals or animals, the degree to which insulin resistance is tissue specific may determine whether or not hypertension will develop. Future studies will be necessary not only to clarify the origin, cellular mechanisms, and molecular basis for defects in insulin action that are responsible for the development of insulin resistance, but also to more precisely define the true role that insulin resistance plays in blood pressure homeostasis.

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