Insulin Resistance, Hyperinsulinemia, and Obesity-Associated Hypertension

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ABSTRACT

Recent work to elucidate the cause of obesity-associated hypertension has focused on insulin resistance and hyperinsulinemia. A significant amount of epidemiologic and correlational evidence suggests a link between these factors and obesity-associated hypertension, and acute insulin infusion studies have revealed renal, neural, and cardiovascular effects of this hormone that, if maintained chronically, could cause hypertension. However, correlations and acute effects may not reliably predict a chronic cause-and-effect relationship, and the fundamental question of whether chronic increases in plasma insulin concentration per se can produce a sustained increase in arterial pressure has not been completely resolved. Recent studies designed to address this question directly have found no evidence of a hypertensive effect of insulin in normal dogs, or in dogs with a 70% reduction in kidney mass and given a high sodium intake. Chronic hyperinsulinemia also did not potentiate the pressor effects of angiotensin II or norepinephrine. In fact, hyperinsulinemia caused significant reductions in total peripheral vascular resistance in dogs and a decrease in arterial pressure. Furthermore, induction of insulin resistance in dogs made obese by being fed a high-fat diet eliminated the decrease in peripheral vascular resistance during chronic insulin infusion but did not uncover a pressor effect of hyperinsulinemia. In contrast, insulin infusion for up to 7 days produced a sustained increase in arterial pressure in rats. Although the mechanism for this pressor response is unknown, these data indicate either that there are major species differences in the chronic blood pressure response to insulin or that specific, presently unknown, conditions must exist in order for insulin to raise blood pressure. Also, it is not clear whether humans respond more like rats or dogs with respect to blood pressure changes during chronic hyperinsulinemia. However, it is apparent that obesity hypertension is probably much too complex to be ascribed to insulin resistance and hyperinsulinemia alone.

Key Words: kidney, insulin, blood pressure, sodium excretion, sympathetic nervous system

Hypertension has become recognized as a potential clinical complication associated with obesity. Several studies have reported a correlation between body weight and blood pressure (1–4), and weight loss lowers blood pressure in obese hyperten-

sives (5–10), even when sodium intake is maintained at a high level (6). Furthermore, excessive weight gain in experimental animals produces a significant rise in blood pressure that is reversed by weight loss (11, 12). However, the mechanisms responsible for weight-related changes in blood pressure are unclear.

One factor that has been advanced as a potential link between obesity and hypertension is insulin (13–20). Insulin resistance and compensatory hyperinsulinemia are common features of obesity (14, 17, 21, 22), and in addition to its blood pressure-lowering effect, weight loss decreases plasma insulin levels (5, 12). Hyperinsulinemia and insulin resistance also have been reported to be associated with hypertension independent of obesity (14, 15, 21–24), further suggesting that these abnormalities can contribute to high blood pressure. Moreover, acute studies have reported multiple effects of insulin on the kidney, the sympathetic nervous system, and the cardiovascular system that, if maintained chronically, could lead to hypertension. Thus, epidemiologic and correlational evidence linking insulin to obesity and hypertension, and evidence from acute studies for potential pressor effects of insulin, have been interpreted as suggesting that hyperinsulinemia is important in the development of hypertension associated with obesity. However, most of these studies have not addressed directly the question of whether a chronic rise in plasma insulin concentration per se
is capable of producing a sustained increase in arterial pressure, and there have been several recent reports that have questioned whether hyperinsulinemia and insulin resistance are key to hypertension associated with obesity.

EPIDEMIOLOGIC AND CORRELATIONAL EVIDENCE LINKING INSULIN RESISTANCE, HYPERINSULINEMIA, AND HYPERTENSION

A positive correlation between insulin and blood pressure has been reported in obese patients (14,17,21,22) and also may occur independent of obesity (14,21–24). Christlieb et al. (14), in a study of 195 patients with impaired glucose tolerance, reported that serum insulin was significantly elevated in hypertensive patients, and this relationship persisted after correction for body weight. In a random population sample of approximately 2,500, Modan et al. (21) reported a strong association between hypertension, glucose intolerance, and obesity and also noted that fasting and postglucose-load insulin levels in 1,241 hypertensives were significantly elevated independent of obesity. Ferrannini et al. (24) reported that hyperinsulinemia was consistently associated with hypertension independent of obesity in a survey of nearly 3,000 subjects in the San Antonio Heart Study. However, the slope of the relationship between blood pressure and postglucose-load plasma insulin concentration in 2,241 normotensive, non-diabetic subjects predicted that a 200 μU/mL increase in plasma insulin concentration could account for only a 1 mm Hg rise in blood pressure (24), thus suggesting minimal sensitivity of blood pressure to insulin levels per se.

A positive relationship between insulin resistance, insulin, and blood pressure also has been observed in animal models of hypertension. Hyperinsulinemia and insulin resistance have been measured in several genetic models of hypertension, including the spontaneously hypertensive rat (25,26) and the Milan hypertensive rat (27). Furthermore, maintaining Sprague-Dawley rats on a high intake of simple sugars has been reported to cause insulin resistance, raise plasma insulin levels, and increase tail-cuff systolic pressure (15,28,29) and blunting the rise in insulin by administering somatostatin appears to decrease systolic pressure (28). Hyperinsulinemia and insulin resistance also have been measured in obese hypertensive dogs (11,12,30,31). Thus, a large body of correlational data exists to suggest that insulin resistance, hyperinsulinemia, and hypertension may be related.

Insulin resistance has been postulated to be fundamental in this relationship by inducing a compensatory rise in plasma insulin concentration, which then acts through various mechanisms to increase blood pressure (13–20). However, insulin resistance also has been suggested to act by mechanisms that increase peripheral vascular resistance independent of hyperinsulinemia (19,20,32–34). Regardless of the proposed mechanisms linking insulin resistance, hyperinsulinemia, and hypertension, it is important to note that not all hypertensives are insulin resistant and that many patients with hyperinsulinemia and insulin resistance are not hypertensive (35–37). Similarly, obese Zucker rats have been reported to be normotensive despite significant hyperinsulinemia (38) and some forms of hypertension, such as renovascular hypertension, are not associated with hyperinsulinemia or insulin resistance (39,40). In addition, it is important to remember that a cause-and-effect relationship cannot be inferred or refuted from correlational evidence. In experimental and human hypertension, many variables are highly correlated with blood pressure, even though their importance in causing hypertension may be questionable. For example, increased total peripheral resistance is highly correlated with hypertension, with almost all forms of hypertension being characterized by elevated total peripheral resistance. However, this association often leads to erroneous conclusions regarding the importance of increased vascular resistance in causing the rise in blood pressure, because the rise in peripheral vascular resistance often occurs secondary to various autoregulatory adjustments after the onset of hypertension (41). Therefore, one must exercise caution before embracing the concept that insulin resistance and hyperinsulinemia can cause hypertension solely on the basis of correlational evidence.

ACUTE EFFECTS OF INSULIN ON BLOOD PRESSURE CONTROL MECHANISMS

Perhaps the most widely accepted hypothesis linking insulin, insulin resistance, and hypertension is that the onset of insulin resistance necessitates a compensatory rise in plasma insulin concentration in order to maintain glucose homeostasis. The rise in plasma insulin is then postulated to cause effects on the kidney and sympathetic nervous system that eventually lead to increased blood pressure. However, support for these effects of insulin is derived mainly from acute studies.

Early studies in humans reported an antinatriuretic response to insulin administration (42,43), and withdrawal of insulin therapy from diabetic patients increased sodium excretion (42). This effect of insulin appears to be direct because acute, intrarenal insulin infusions have been reported to decrease sodium excretion (16), even in isolated kidneys (44). The mechanism for the antinatriuretic action is unclear, but micropuncture data suggest that insulin has a direct effect to stimulate sodium reabsorption at a site beyond the proximal tubule (16,45). This
effect of insulin to decrease renal sodium excretory capability, if maintained chronically, could increase blood pressure through sodium retention and expansion of the extracellular fluid volume. The rise in blood pressure eventually would offset the antinatriuretic effect of insulin, via pressure natriuresis, similar to the effect of aldosterone (41). Thus, in the steady-state, sodium balance would be reattained, but at the expense of an elevated arterial pressure. This putative response to hyperinsulinemia, however, has been proposed based on the results from acute insulin infusions (16) and has not been demonstrated chronically.

Another action of insulin that has been postulated to raise blood pressure is stimulation of the sympathetic nervous system. There is evidence that increased caloric intake produces parallel increases in plasma insulin levels and tissue norepinephrine turnover, although high fat or carbohydrate diets also can stimulate sympathetic activity even if caloric intake is not increased (18,46). Troisi et al. (47) reported that, in 572 men from the Normative Aging Study, total caloric intake was independently correlated with 24-h urinary norepinephrine excretion and that norepinephrine excretion was higher in hyperinsulinemic subjects. In addition, high sucrose, fructose, or glucose intake in rats stimulates sympathetic nervous system activity and increases blood pressure (15,48,49), and also produces insulin resistance and hyperinsulinemia (15,29). Thus, there appears to be a positive correlation between hyperinsulinemia and increased sympathetic activity.

The sympathetic nervous system could chronically raise blood pressure by increasing tubular sodium reabsorption and pregglomerular resistance (41,50,51). A peripheral vasoconstrictor effect of sympathetic stimulation could shorten the time for development of hypertension and may underlie the pressor response to insulin infusion observed during acute experiments. Many studies have demonstrated that insulin-induced hypoglycemia can increase plasma epinephrine concentration (18,52–54), but insulin also may have a direct effect to stimulate sympathetic nervous system activity independent of hypoglycemia (18,52,55,56). Pereda et al. (57) reported an effect of acute, iv infusion of large doses of insulin to increase arterial pressure and cardiac output in dogs. This response occurred in the absence of hypoglycemia, could be duplicated by infusing insulin in the carotid artery, and was inhibited by ganglionic or adrenergic receptor blockade. Liang et al. (52) reported that epinephrine and norepinephrine levels rose if hypoglycemia occurred during acute insulin infusion in dogs but that only norepinephrine increased when euglycemia was maintained. Blood pressure also increased slightly (approximately 5 mm Hg) with the euglycemic insulin infusions at high rates (52). Similar results have been obtained in humans (55). These observations are consistent with the hypothesis that hyperinsulinemia may increase blood pressure by stimulating the sympathetic nervous system.

A potential problem with most of these studies is that large, nonphysiologic doses of insulin were used and only administered acutely. Recently, Anderson et al. (57) reported that acute insulin infusion, at rates that produced plasma insulin levels in the pathophysiologic range, increased sympathetic nerve activity in humans. It is important to note, however, that acute insulin infusion did not increase arterial pressure in that study and also that the demonstration of an acute relationship between two variables (e.g., insulin and sympathetic nervous system activity) does not provide evidence that this effect can be sustained chronically. Furthermore, the correlational evidence is just that: evidence that insulin and the sympathetic nervous system are positively correlated, not evidence for a cause-and-effect relationship. Therefore, a role of the sympathetic nervous system in mediating any putative, chronic hypertensive effect of hyperinsulinemia remains to be established.

Thus, there is a significant amount of evidence relating hyperinsulinemia in insulin-resistant states, such as obesity, to the development of hypertension. Correlational studies are consistent with the involvement of the sympathetic nervous system that could mediate this effect by combined antinatriuretic and vasoconstrictor actions. Acute studies support a stimulatory effect of insulin on the sympathetic nervous system and also provide evidence for a direct antinatriuretic action. However, regardless of the mechanism, a cause-and-effect relationship between insulin and chronic hypertension has not been definitively established.

**CHRONIC EFFECTS OF HYPERINSULINEMIA ON BLOOD PRESSURE**

Although the demonstration that insulin has acute effects on the sympathetic nervous system and on the cardiovascular system is consistent with a role for hyperinsulinemia in hypertension, short-term studies do not address directly the question of whether chronic hyperinsulinemia can increase blood pressure. An example of the potential danger involved when attempting to extrapolate information derived from acute studies to a chronic setting is the acute versus chronic effects of some vasoconstrictors such as vasopressin. Vasopressin is one of the most powerful vasoconstrictors; yet, although the acute pressor effect of vasopressin can be demonstrated readily, chronic infusion of vasopressin causes only small increases in arterial pressure as long as kidney
function is not impaired (58,59). Thus, the acute effect of this hormone does not accurately predict the long-term response. To address the question of whether chronic hyperinsulinemia per se can produce hypertension, we conducted several series of experiments in dogs and rats (60–64).

Chronic Hyperinsulinemia in Dogs

These studies were designed to test whether chronic increases in plasma insulin concentration, comparable to those found in obese hypertensives, would cause sustained elevations in blood pressure. In these experiments, insulin was continuously infused iv at a dose of 1 mU/kg/min; plasma insulin concentration increased approximately fivefold to sixfold, but plasma glucose concentration was maintained within the normal range by a simultaneous iv glucose infusion. The effects of insulin infusion for 7 days in chronically instrumented, conscious dogs maintained on a normal sodium intake are illustrated in Figure 1 (61). The most important finding was that 7 days of hyperinsulinemia did not increase blood pressure but, instead, produced an approximate 10 mm Hg fall in blood pressure. This occurred despite a transient decrease in urinary sodium and water excretion and the cumulative retention of approximately 120 mEq of sodium after 7 days of insulin infusion. The antinatriuretic effect of insulin was due to increased tubular sodium reabsorption rather than decreased filtered sodium load, because GFR and effective RPF increased by 15 to 20%.

One mechanism through which insulin has been postulated to raise blood pressure is by causing renal sodium and volume retention (16). Because the hypertensive actions of other antinatriuretic hormones, such as aldosterone, are exacerbated by either a high-salt intake or reduced kidney mass (41), we also tested the possibility that hyperinsulinemia might exert a hypertensive effect when renal function is impaired or sodium intake is high (60). This possibility also has clinical relevance, because many obese hypertensives are elderly and there is a gradual reduction in the number of functional nephrons with aging (65).

The effects of chronic hyperinsulinemia in dogs with kidney mass surgically reduced to approximately 30% of normal are shown in Figure 2 (68). The dogs were maintained on a high sodium intake (over 300 mEq/day) to further increase their susceptibility to any potential hypertensive effect of insulin, and insulin was infused for 28 days to be certain that sufficient time was allowed for insulin to exert a hypertensive action. Insulin infusion caused marked sodium retention and, similar to the response in normal dogs, GFR increased, indicating that the insulin infusion increased tubular sodium reabsorption. However, despite the sodium retention, these dogs responded to insulin with an approximate 10 mm Hg decrease in blood pressure. Although blood pressure returned towards control levels after 2 to 3 wk of hyperinsulinemia, there was no evidence of hypertension. Chronic hyperinsulinemia also did not increase blood pressure in reduced kidney mass, high-salt dogs that were continuously infused with angiotensin II and mildly hypertensive (60), even though some studies suggest that insulin potentiates the acute pressor and aldosterone-stimulating effects of angiotensin II (66).

Because insulin infusion caused significant sodium retention in normal dogs and dogs with reduced kidney mass and high salt intake, the absence of hypertension and, more specifically, the decrease in blood pressure that was measured, appear at first to be paradoxical. Chronic infusions of some antinatriuretic hormones, such as angiotensin II (ANG II) and aldosterone, cause marked hypertension mainly because of their direct renal actions (41,67). In contrast, insulin infusion caused transient antinatriuresis and a reduction in blood pressure. The fact that the antinatriuresis was transient is not surprising, because even the most powerful antinatriuretic hormones cause only a temporary decrease in sodium excretion. This is because sodium retention initiates various compensatory mechanisms, especially increases in blood pressure and pressure natriuresis, which then help to return sodium excretion to normal and restore

![Figure 1. Effects of insulin infusion (1.0 mU/kg/min iv) on mean arterial pressure and urinary sodium excretion in normal, conscious dogs (N = 6). Adapted with permission from reference 61.](image-url)
Hyperinsulinemia and Hypertension

sodium balance. The observation that the antinatriuresis during hyperinsulinemia was accompanied by a decrease in blood pressure is reminiscent of the sodium retention that often occurs as a compensation for low blood pressure in circumstances such as hemorrhage or administration of a peripheral vasodilator such as nitroprusside. In fact, we reported recently that hyperinsulinemia in dogs significantly decreased total peripheral resistance and increased cardiac output by 30 to 40%, indicative of peripheral vasodilation (Figure 3) (62).

This information suggests that in these studies much of the sodium retention likely was secondary to the fall in renal perfusion pressure (41,67). This is supported by the observation that chronic intrarenal insulin infusion in dogs, at rates that produced renal arterial plasma insulin concentrations comparable to those attained with the iv insulin infusions but that caused no decrease in blood pressure, caused much less sodium and water retention than that measured during iv insulin infusion (Figure 4) (68). Thus, insulin does not appear to have a major direct antinatriuretic effect that can be sustained sufficiently to cause hypertension in dogs (60–62,68).

Because insulin has been observed to acutely activate the sympathetic nervous system and increase plasma norepinephrine concentration, even when plasma glucose concentration is maintained constant (52), we examined the potential for interaction between insulin and catecholamines to increase blood pressure. During chronic insulin infusion in normal dogs, however, we found no effect of hyperinsulinemia.

Figure 2. Effects of insulin infusion (1.0 mU/kg/min iv) on mean arterial pressure and urinary sodium excretion in dogs with reduced kidney mass maintained on a high-sodium intake of approximately 319 mEq/day (N = 7). Adapted with permission from Reference 60.
Hyperinsulinemia on plasma catecholamines (61). In addition, hyperinsulinemia did not potentiate the pressor effects of norepinephrine when norepinephrine was chronically infused in dogs to produce a sustained, 17-fold increase in plasma norepinephrine concentration (61). However, these findings do not rule out the possibility that increased sympathetic activity may accompany insulin infusion in dogs, because we observed consistent increases in heart rate during chronic hyperinsulinemia (61,62). The mechanisms responsible for the rise in heart rate are still unclear and also could be related to a direct chronotropic effect of insulin on the heart or to withdrawal of parasympathetic tone; further study will be needed to resolve this issue.

Thus, several studies in dogs have directly addressed the question of whether chronic increases in plasma insulin concentration per se could raise blood pressure and revealed no evidence of a hypertensive effect. In fact, these studies demonstrated that the direct antinatriuretic action of insulin was mild and that much of the sodium retention occurred during systemic insulin administration may have been due to a peripheral vasodilatory and depressor effect of hyperinsulinemia.

**Chronic Hyperinsulinemia in Rats**

Several genetic models of hypertension in rats are associated with insulin resistance and hyperinsulinemia (25–27). In addition, correlational evidence from Reaven et al. (15,28,29) suggests that hyperinsulinemia may be responsible for the increase in tail-cuff systolic pressure measured in rats maintained on a high intake of simple sugars. Furthermore, lowering plasma insulin concentration during a period of high-fructose diet in rats, by continuously infusing a somatostatin analog, lowered systolic pressure (28). Similar results have been obtained in human studies, where somatostatin has been reported to lower blood pressure and plasma insulin in insulin-resistant, hyperinsulinemic subjects with hypertension (69,70). However, somatostatin has many other effects besides inhibition of insulin secretion that were not controlled for in those studies, thus leaving some question as to whether the depressor response was due solely to lower insulin levels. Furthermore, the use of the tail-cuff technique may have had a confounding effect on the assessment of blood pressure.
in the rat studies (15,28,29). Under conditions of heightened sympathetic nervous system activity, as has been reported during the high intake of simple sugars (15,18,48,49), blood pressure could be more labile, such that any acute measurement of blood pressure—especially in restrained animals with a tail cuff—would be more likely to register a high pressure.

To directly test the chronic effect of insulin on blood pressure in rats, insulin was infused continuously in conscious, chronically instrumented rats while decreases in plasma glucose concentration were prevented (63,64). An important feature of these studies was that potential errors due to the acute measurement of blood pressure commonly used, whether from a catheter or by the tail-cuff technique, were avoided by continuously measuring arterial pressure from an aortic catheter, 19 h/day, from rats undisturbed in their metabolic cages. The results from these studies indicated that sustained hyperinsulinemia produced an increase in arterial pressure that could be maintained for at least 7 days (Figure 5: [70]). The elevated blood pressure could not be attributed to significant sodium retention (63,64) or to increased activity of the renin-angiotensin system (64), but further study is needed to determine the role of other mechanisms, such as the sympathetic nervous system, in mediating the hypertensive effect of chronic insulin infusion in rats.

Another interesting finding in these studies was that the control mean arterial pressures were normal (93 ± 1 mm Hg [63] and 86 ± 2 mm Hg [64]), although the rat chow we used (like most commercially available, pelleted rat chows) was high in sucrose. Consistent with other reports (15, 28, 29) on the effects of high-sugar intakes, the rats also appeared hyperinsulinemic during the control period (63). As to why arterial pressure was normal despite insulin resistance and modest hyperinsulinemia, it is possible that the insulin levels simply were not high enough to activate the mechanisms that produced the pressure rise during the insulin infusion.

**POSSIBLE EFFECTS OF VERY LONG-TERM HYPERINSULINEMIA**

One other potential effect of hyperinsulinemia, of considerably longer duration, may relate to mitogenic effects of insulin on vascular smooth muscle (71,72) and/or to atherosclerotic lesions resulting from the dyslipidemic actions of insulin (20,73). These effects of hyperinsulinemia, particularly those on plasma triglyceride and cholesterol profiles, have been implicated in the development of atherosclerosis and in increased risk for coronary artery disease, but their role in altering structure and function in the vasculature and in the development of hypertension is unclear.

It is important to recall that primary changes in the vasculature, if their sole effect is to raise total peripheral resistance, could not lead to chronic hypertension (41). This is because any increase in arterial pressure not accompanied by a decrease in renal sodium excretory capability will result in a pressure natriuresis that serves to return pressure to normal (41,67). If structural changes were to occur in the renal vasculature, particularly in preglomerular vessels, increases in blood pressure could result. However, it is noteworthy that RBF was increased rather than reduced in obese, hyperinsulinemic dogs, in which hypertension was induced by 5 wk of a high-fat diet (74). Moreover, renal vascular resistance is lower and RBF is higher in obese hypertensive patients (75). Thus, although protracted hyperinsulinemia may be able to promote changes in vascular structure, currently there is little evidence to suggest that this effect can lead to hypertension.

Thus, epidemiologic and correlational studies implicate an effect of hyperinsulinemia to produce a chronic increase in arterial pressure, but only a few studies have directly addressed this possibility experimentally (60–64,68). Most of these studies have been in dogs and have found no evidence of a direct hypertensive effect of insulin (60–62,68). However, studies in rats (63,64) suggest that hyperinsulinemia can increase blood pressure, but the associated conditions that allow the expression of this pressor effect are unknown. Also, it is not clear whether humans respond more like rats or dogs with respect to the chronic blood pressure effects of insulin.

Acute insulin infusions cause vasodilation in humans (57,76), and chronic, physiologic increases in plasma insulin decrease total peripheral resistance in normal dogs (62). In addition, patients with insulinoma and plasma insulin levels approximately sevenfold higher than normal showed no evidence of hypertension (77) and no increase in blood pressure.
was measured with chronic, similar percent increases in insulin concentration in dogs (60–62). Ferrannini et al. (24) also reported in human subjects that blood pressure was relatively insensitive to insulin levels, such that a 200 \( \mu \text{U/mL} \) increase in plasma insulin concentration would account for only a 1 mm Hg rise in blood pressure. However, normal humans and dogs are not insulin resistant, whereas insulin resistance is a feature of obese hypertensives (14,17,21,22) and many essential hypertensives (23,24), and evidence suggests that the high-sucrose-fed rats in our insulin infusion studies (63,64) were insulin resistant. Thus, features of both experimental models of chronic hyperinsulinemia draw some parallels with humans. However, although insulin resistance might appear to be a key element in determining a pressor response to hyperinsulinemia, there is no convincing evidence that this condition per se can directly cause chronic hypertension, as discussed below.

**THE EFFECT OF INSULIN RESISTANCE ON BLOOD PRESSURE**

Initial hypotheses relating insulin resistance to hypertension proposed that renal and cardiovascular effects of the compensatory hyperinsulinemia provided the causative link. However, it was clearly demonstrated that chronic hyperinsulinemia per se did not cause hypertension in dogs (60–62) or humans with insulinoma (77). A concept now emerging is that hyperinsulinemia can raise blood pressure only under conditions of insulin resistance, therefore suggesting that some effect of insulin resistance, independent of hyperinsulinemia, provides an environment that permits the pressor effect of insulin to be expressed.

A fundamental action of insulin is to increase peripheral tissue glucose uptake and utilization. One effect of an increase in peripheral tissue glucose uptake is an increase in metabolic rate (78), which would be expected to cause peripheral vasodilation in order to allow tissue blood flow to rise sufficiently to meet the increased metabolic demands (41). Thus, one effect of insulin infusion under conditions where the tissues have normal sensitivity to the metabolic actions of insulin should be vasodilation and a decrease in total peripheral resistance.

Evidence from chronic insulin infusions in normal dogs suggests that they have normal insulin sensitivity even after prolonged hyperinsulinemia, because when insulin was infused for up to 28 days, the glucose infusion rate required to maintain normal plasma glucose concentrations remained constant (60–62). If insulin resistance had developed during the insulin infusion, a decrease in the glucose infusion rate would have been required to prevent plasma glucose levels from rising. This finding is in agreement with the observation that chronic hyperinsulinemia does not cause insulin resistance in humans (77) and is consistent with the concept that hyperinsulinemia is a compensatory response to insulin resistance, rather than a simple down-regulation of insulin receptors. The fact that normal dogs retain their sensitivity to the metabolic effects of insulin probably explains our finding that systemic insulin infusion produced a marked and progressive fall in total peripheral resistance and a 30 to 40% increase in cardiac output (Figure 3) (62).

In contrast to normal dogs, there is evidence (presented above) that the rats used in our studies (63,64) were insulin resistant. One predicted effect of peripheral tissue insulin resistance is a decrease in the ability of insulin to stimulate glucose uptake, which correspondingly should diminish the requirement for an increase in tissue blood flow during hyperinsulinemia. Recent studies in humans indicate that the effect of insulin to increase local blood flow in normal human subjects (57,76) was blunted in insulin-resistant subjects (76). Therefore, one potential explanation for the pressor effect of insulin infusion in rats could be that the hypertensive actions of insulin were unopposed by the metabolic, depressor actions because of peripheral tissue insulin resistance.

If this concept is correct, one could speculate that if rats were made insulin resistant, such that the peripheral vasodilatory effects of insulin were absent or attenuated, hyperinsulinemia would cause hypertension. Conversely, if insulin sensitivity were improved in rats, insulin infusion should decrease arterial pressure similar to the response in normal, insulin-sensitive dogs. Because the underlying postulate is that systemic vasodilation prevents the hypertensive actions of insulin from raising blood pressure, we conducted a study in which the effects of insulin’s direct renal actions were measured in the absence of peripheral vasodilation (68).

In that study (68), insulin was infused chronically into the artery of the remaining kidney in uninephrectomized dogs. Because the intrarenal infusion of other antinatriuretic hormones has been demonstrated to raise blood pressure independent of systemic mechanisms (79), this protocol allowed us to test whether the direct antinatriuretic effect of insulin was capable of elevating blood pressure in the absence of insulin’s systemic metabolic actions. However, although significant increases in systemic plasma insulin concentration were avoided, no increase in blood pressure was measured. The insulin infusion did cause some sodium retention, but this effect was mild and transient, thus suggesting that the direct, antinatriuretic effect of insulin was incapable of increasing blood pressure even when the vasodilatory response was prevented. However, this
finding does not rule out the possibility that indirect renal and circulatory effects of systemically infused insulin, possibly mediated by the sympathetic nervous system, for example, could cause hypertension if the decrease in peripheral resistance was blocked because of insulin resistance.

To test this possibility, we examined the effects of chronic hyperinsulinemia in obese dogs that were resistant to the metabolic effects of insulin (31). In these experiments, dogs were placed on a high-fat diet for 6 wk, causing obesity, increased blood pressure, and insulin resistance. The subsequent infusion of insulin for 7 days in these obese dogs caused no significant changes in total peripheral resistance or cardiac output. This contrasts sharply with the marked decrease in total peripheral resistance and increase in cardiac output measured in insulin-sensitive, normal dogs (62) and suggests that inducing insulin resistance in dogs indeed prevents the systemic vasodilation, because of insulin’s metabolic effects, from occurring during iv insulin infusion. However, despite insulin resistance, there were no significant increases in blood pressure in obese dogs when insulin was infused for 7 days (31). In fact, there was actually a small decrease in blood pressure, similar to that found in normal dogs. Thus, the presence of insulin resistance does not markedly alter the blood pressure response to chronic hyperinsulinemia in dogs and is therefore unlikely to explain entirely the differences in blood pressure responses to insulin in dogs versus rats.

Potential Effects of Insulin Resistance on Blood Pressure Independent of Hyperinsulinemia

In the above discussion, the hypertensive effect of insulin resistance has been considered mainly to result from various pressor effects of insulin, with insulin resistance playing a permissive role in the development of hypertension. Insulin resistance, by preventing vasodilation during hyperinsulinemia, would allow other effects of insulin to raise blood pressure. However, it also has been suggested that insulin resistance could maintain, or even increase, vascular tone through a more direct interaction with the regulatory mechanisms for vascular smooth muscle contraction (19,20,32–34). This hypothesis not only might explain how vasodilation is prevented from hampering insulin’s putative pressor actions, but also provides the potential for a direct effect of insulin resistance to increase total peripheral resistance.

Insulin has been reported to attenuate the contractile response of vascular smooth muscle to constrictor agonists (80) and may have a direct vasodilatory action (57,76,81). Insulin may stimulate sodium-potassium ATPase (81), which might decrease vascular tone by hyperpolarizing the vascular smooth muscle and increasing sodium-calcium exchange. In addition, insulin may stimulate calcium ATPase activity (19). Presumably, in insulin-resistant states, these actions of insulin to decrease intracellular calcium concentration would be blunted, allowing calcium levels to rise and causing increased vascular smooth muscle tone. Recent studies have reported that intracellular calcium is increased in vascular smooth muscle in insulin-resistant animals such as the Zucker obese rat (19), although these changes in cell membrane ion transport also may be unrelated to insulin or insulin resistance. Theoretically, however, this provides another mechanism, in addition to reduced metabolic effects, whereby vasodilation during hyperinsulinemia may be prevented in insulin-resistant states. Additionally, the premise that insulin has a physiologic effect to lower calcium concentration in vascular smooth muscle cells has provided the basis for suggesting that insulin resistance, independent of hyperinsulinemia, could cause hypertension by causing vasoconstriction.

Several investigators have suggested that vasoconstriction caused by insulin resistance could contribute to the development of hypertension (19,20,32–34). However, although increased total peripheral resistance is a hallmark of most forms of established hypertension, experimental and theoretical studies have shown that increased peripheral vascular resistance per se is unlikely to cause hypertension unless the constriction also occurs in renal vessels and shifts pressure natriuresis to higher blood pressures (41,67,82). This is because, if there is no decrease in renal sodium excretory capability, the rise in arterial pressure resulting from systemic vasoconstriction will increase renal sodium excretion and decrease extracellular fluid volume until blood pressure returns to normal (Figure 6) (41,67,82). The increase in peripheral vascular resistance measured in many forms of hypertension may be the result of autoregulatory adjustments to maintain normal tissue blood flow in the face of increased perfusion pressure (67).

Also arguing against the hypothesis that a primary increase in total peripheral resistance, initiated by insulin resistance, is a cause of obesity-induced hypertension is the finding that cardiac output is elevated, as is blood flow to many tissues (e.g., skeletal muscle), rather than reduced in obese hypertensives (12,83). Experimental forms of hypertension associated with potent vasoconstriction are usually associated with normal or reduced cardiac output and tissue blood flows, rather than increases, as occurs in obesity (41). Thus, it seems unlikely that a mechanism that causes peripheral vasoconstriction could be the explanation for hypertension in obese individuals, unless the vasoconstriction also occurred in
renal vessels and shifted the renal-pressure natriuresis mechanism (41,67,82). Recent studies suggest, however, that obesity and insulin resistance do not cause renal vasoconstriction (30,75). In fact, marked increases in RBF and GFR have been noted in obese, insulin-resistant dogs (30,74).

In summary, insulin resistance has been postulated to play a role in the etiology of hypertension primarily by causing a compensatory hyperinsulinemia. The effects of chronic hyperinsulinemia on blood pressure regulation, however, remain unclear. Initial studies in rats have suggested that insulin can produce a sustained increase in blood pressure, but much study is needed to delineate the mechanism for that effect. In contrast, an extensive series of studies in dogs has provided strong evidence that hyperinsulinemia per se does not cause hypertension. These studies, however, do not rule out the possibility that some other, as yet unknown, factor or factors coexistent with hyperinsulinemia may allow the expression of a hypertensive effect. One candidate for this "insulin cofactor" has been insulin resistance. However, although much correlational evidence suggests an important role for insulin resistance in defining the relationship between insulin and blood pressure regulation, recent experiments designed to address this issue directly found no supportive evidence. Although further investigation is needed to fully understand the effects of insulin and insulin resistance on blood pressure regulation, clearly other mechanisms also should be pursued to understand the cause of obesity-associated hypertension.

RENNAL MECHANISMS OF OBESITY-ASSOCIATED HYPERTENSION

Considerable evidence that an abnormality in renal sodium handling exists in all forms of hypertension has been previously reviewed (41,67,82,84). In hypertension, the relationship between arterial pressure and sodium excretion, the pressure natriuresis mechanism, is shifted to a higher pressure such that sodium balance is maintained at an elevated pressure (41,67,82). If it were not, the high arterial pressure would cause unabated natriuresis, culminating in circulatory collapse. Thus, pressure natriuresis must be shifted in chronic hypertension associated with obesity. The question that remains to be answered is: what is the cause of the decrease in renal sodium excretory capability that leads to the rise in arterial pressure?

The pressure natriuresis relationships for normal

![Figure 6](image1)

**Figure 6.** Probable chronic relation between arterial pressure and urinary sodium excretion under the influence of a powerful peripheral vasoconstrictor that acutely raises blood pressure from A to B but has no effect on renal sodium excretory capability (*i.e.*, does not shift the renal function curve).

![Figure 7](image2)

**Figure 7.** Steady-state relation between arterial pressure and urinary sodium excretion for nonobese adolescents (*N* = 18), obese adolescents (*N* = 60), and obese adolescents after weight loss (*N* = 36). Adapted with permission from reference 7.
Hyperinsulinemia and Hypertension

Individuals, obese adolescents, and obese adolescents after weight loss were recently compared by Rocchini et al. (7) and are presented in Figure 7. In normal subjects, the relationship is very steep, indicating that blood pressure is insensitive to changes in sodium intake over a wide range of intakes. In obese subjects, the pressure natriuresis curve was shifted to higher pressures, indicating that renal sodium excretory capability was reduced and the slope of the curve was decreased (7). In many forms of hypertension characterized by a decrease in the slope of the pressure natriuresis curve, the reduction in renal sodium excretory capability and the elevated blood pressure appear to be initiated by increased tubular reabsorption, such as in mineralocorticoid hypertension. Thus, although the mechanisms responsible for the obesity-induced shift of pressure natriuresis have not been elucidated, it is possible that some factor that tends to increase renal tubular sodium reabsorption is involved.

In support of this possibility, we have observed in preliminary studies that obesity-induced hypertension in dogs is associated with increased renal tubular sodium reabsorption, because marked sodium retention occurred despite large increases in GFR and effective RPF (74). The focus of this discussion has centered on the possibility that insulin, pathologically increased to compensate for insulin resistance, might increase tubular reabsorption. However, numerous studies in dogs suggest that hyperinsulinemia per se cannot produce the changes in renal function required to cause chronic hypertension (31, 60–62, 68).

Recent studies in our laboratory indicate that obesity-induced hypertension is associated with increased PRA. Because ANG II has powerful effects to increase renal tubular sodium reabsorption (85), it is possible that part of the shift of pressure natriuresis observed in obesity hypertension may be mediated by the renin-angiotensin system. However, we also have found that weight-induced changes in blood pressure in dogs can occur independently of changes in ANG II formation (30). Therefore, additional factors besides hyperinsulinemia and increased ANG II must be considered as possible mediators of the reduced sodium excretory capability and shift of pressure natriuresis in obesity-induced hypertension.

Recent, preliminary observations (74) in our laboratory also have revealed potential changes in renal pathology in obese dogs that are suggestive of another mechanism for shifting pressure natriuresis. Measurements of renal interstitial fluid hydrostatic pressure (RHIP) in anesthetized, obese dogs are considerably higher than in anesthetized, normal dogs. Previous studies have demonstrated a natriuretic effect of small increases in RHIP (86–88). However, Burnett and Knox (88) demonstrated that greater increases in RHIP actually decreased sodium excretion, and the measurements of RHIP in obese dogs thus far are comparable with those antinatriuretic levels of RHIP. A mechanism through which high RHIP could decrease urinary sodium excretion could be through compression of renal tubular structures (88), which would increase tubular transit time, thereby increasing tubular sodium reabsorption. Histologic studies suggest that tubular compression in kidneys from obese dogs may be due to proliferation of extracellular matrix material as well as increased numbers of interstitial cells in the medulla. Although further study is needed to confirm these observations and elucidate the mechanism for the increase in RHIP in obese dogs, such changes in renal function are consistent with a mechanism for producing a shift in pressure natriuresis caused by increased tubular sodium reabsorption.

Thus, the shape of the pressure natriuresis curve in obese humans and measurements of renal function in obese humans and dogs suggest similar causes, involving increased tubular sodium reabsorption, in the development of hypertension with obesity in these species. Considerable evidence suggests that insulin resistance and hyperinsulinemia per se cannot cause the changes in renal function necessary to produce chronic hypertension. However, early studies in rats have suggested that under some conditions, hyperinsulinemia can produce a sustained increase in arterial pressure. Therefore, how might sodium excretory capability be reduced in hyperinsulinemic rats and how might this relate to obesity hypertension in humans?

The rise in blood pressure in rats was not sensitive to changes in sodium intake, thus resulting in a parallel shift of the pressure natriuresis curve (64). This response is characteristic of hypertension produced primarily by increased pregglomerular resistance, such as one-kidney, one-clip Goldblatt hypertension (41, 67, 82). Interestingly, norepinephrine, with relatively weak effects on tubular sodium reabsorption (51) and a preferential constrictor effect on the afferent arterioles (89), also produces a shift in pressure natriuresis that is relatively insensitive to changes in sodium intake (51). Taken together with the large body of correlational evidence that the sympathetic nervous system is more active in hyperinsulinemic states (15, 18, 46, 47), increased sympathetic activity could play a role in causing hypertension in rats chronically infused with insulin (64). However, the parallel shift in the pressure natriuresis curve found in insulin-infused rats is not consistent with the decreased slope of the pressure natriuresis curve found in obese hypertensive humans (7), further suggesting that another factor besides, or in addition to, hyperinsulinemia is involved in causing obesity hypertension.
SUMMARY

Analyses of obesity-induced hypertension and its potential causes have proven to be much more complex than the initial hypotheses that were based on correlational studies and acute experiments linking hyperinsulinemia to hypertension. However, the results from chronic animal studies, which have addressed directly the question of whether hyperinsulinemia can produce sustained increases in arterial pressure, have shed new light on the subject and have pointed toward a new direction of research in this area. Fundamental to our understanding of the mechanism for developing hypertension in obesity is the concept that a decrease in renal sodium excretory capability—a shift in pressure natriuresis—must occur and be maintained in order for chronic hypertension to occur. When viewed in this light, it is difficult to envision a mechanism whereby insulin resistance per se, purportedly via effects on peripheral vascular resistance, could lead to chronic increases in blood pressure. However, the original supposition that hyperinsulinemia, occurring as compensation for insulin resistance, is responsible for high blood pressure in obese subjects has not been completely resolved.

What has evolved from chronic insulin infusion studies in normal dogs is the concept that hyperinsulinemia per se does not cause an increase in blood pressure, clearly indicating that other factors also should be considered. The inability of obesity-induced insulin resistance to uncover a hypertensive effect of hyperinsulinemia in dogs strongly suggests insulin resistance is not the answer. The data from chronic studies in rats, on the other hand, lend support to the concept that under certain conditions hyperinsulinemia can increase blood pressure. The question now becomes: what are the conditions that allow hyperinsulinemia to chronically raise blood pressure and which model best represents humans? The parallel shift of the pressure natriuresis curve in insulin-hypertensive rats suggests that mechanisms for constricting the preglomerular vasculature should be investigated, but how this will relate to humans is unclear. It is interesting to note, however, that the pressure natriuresis curve in obese hypertensive humans is shifted with a decrease in slope, suggesting that increased tubular sodium reabsorption may underlie the shift. The specific intrarenal and neurohumoral mechanisms that shift pressure natriuresis in obese hypertensives remain an important area for further investigation.

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REFERENCES

20. DeFronzo RA, Ferrannini E: Insulin resist-


