The Vasodilator Action of Insulin
Implications for the Insulin Hypothesis of Hypertension

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The last several years have witnessed tremendous interest in the hypothesis that insulin resistance and hyperinsulinemia contribute to the pathogenesis of hypertension. This hypothesis was stimulated by epidemiological studies that demonstrated an association between obesity, insulin resistance, and hypertension. Subsequent studies suggested that even lean individuals with essential hypertension have insulin resistance and hyperinsulinemia. Because hyperinsulinemia persists during antihypertensive therapy and is not found in secondary renovascular hypertension, the hyperinsulinemia does not appear to be secondary to elevated arterial pressure.

In addition to effects on glucose metabolism, insulin has sympathetic and renal actions. In obesity and hypertension, there is resistance to the actions of insulin on glucose uptake but no resistance to the renal and sympathetic actions of insulin. These "secondary" actions of insulin form the basis of the insulin hypothesis of hypertension.

The insulin hypothesis proposes that the compensatory hyperinsulinemia that occurs with insulin resistance increases sodium reabsorption and sympathetic activity, which combine to cause elevated arterial pressure. An implicit and important assumption of this hypothesis is that, because insulin increases sympathetic noradrenergic activity, it increases vascular resistance and arterial pressure.

This editorial will discuss the vasodilator (depressor) action of insulin and the role that this action plays in offsetting the sympathetic and antinatriuretic (pressor) actions of insulin in regulating arterial pressure. The vasodilator actions of insulin have important implications for the insulin hypothesis of hypertension.

The Vasodilator Action of Insulin

In this issue of Hypertension, Baron et al report on a vasodilator action of insulin and its relation to the link between insulin resistance and hypertension. Baron and colleagues have previously contributed several findings and concepts. First, insulin-mediated glucose uptake occurs principally in skeletal muscle. Second, insulin produces vasodilation and capillary recruitment in skeletal muscle. Third, insulin-induced increases in blood flow and glucose and insulin delivery to skeletal muscle contribute substantially to insulin-induced glucose uptake.

Although recognized for years, the vasodilator action of insulin has been relatively neglected in the recent literature, which has focused on the sympathetic and antinatriuretic actions of insulin. The importance of the vasodilation in the influence of insulin on arterial pressure is indicated by studies from John Hall's laboratory. This group has repeatedly demonstrated that physiological increases in plasma insulin levels fail to increase arterial pressure in dogs. This occurs because increases in cardiac output are offset by substantial decreases in vascular resistance.

In humans, three groups have recently demonstrated that, although acute physiological increases in plasma insulin levels produce striking increases in muscle sympathetic nerve activity and plasma norepinephrine levels, insulin fails to increase arterial pressure because the sympathetic vasoconstrictor activation is opposed by vasodilation. For example, Anderson et al reported that modest increases in plasma insulin with euglycemia produced marked increases in muscle sympathetic nerve activity and plasma norepinephrine levels in normotensive humans. Despite this sympathetic excitation, forearm vascular resistance fell and mean arterial pressure did not rise. Berne et al also reported that insulin increased muscle sympathetic nerve activity and plasma norepinephrine without significant changes in arterial pressure.

In summary, it is increasingly clear that the vasodilator action of insulin plays an important role in the hemodynamic responses to hyperinsulinemia. Although insulin increases sympathetic noradrenergic activity to skeletal muscle, this effect is overridden by a vasodilator action of insulin so that insulin increases rather than decreases skeletal muscle blood flow. This insight has important implications for the hypothesis that hyperinsulinemia elevates arterial pressure.

Mechanisms of Vasodilation

Although insulin causes vasodilation in skeletal muscle, the mechanisms mediating the vasodilation remain
obscure. There is evidence for and against both systemic and local dilator mechanisms.

**Systemic mechanisms.** Several systemic mechanisms could mediate the vasodilation. One is sympathetic neural vasodilation. This occurs in skin during insulin-induced hypoglycemia. However, insulin produces hypotension in patients with autonomic failure. If this insulin-induced hypotension is mediated by vasodilation, this would argue against a sympathetic neural mechanism as the mediator of the vasodilator response to hyperinsulinemia.

A second systemic mechanism is release of a humoral vasodilator substance. Although epinephrine would seem a likely candidate, several studies have demonstrated vasodilator responses to insulin in the absence of increased circulating epinephrine levels.

**Local mechanisms.** Potential local vasodilator mechanisms include 1) β-adrenergic mechanisms, 2) endothelium-dependent relaxation, 3) stimulation of the sodium/potassium pump with hyperpolarization of vascular muscle, 4) increased Ca-ATPase activity, and 5) metabolic vasodilation secondary to increased skeletal muscle oxygen consumption.

Several reports implicate β-adrenergic dilator mechanisms. In dogs, Liang et al. reported that propranolol inhibits the skeletal muscle vasodilator response to systemic insulin infusion. In humans, Creager et al. blocked the forearm vasodilation produced by brachial artery infusion of insulin with an intra-arterial administration of propranolol. This vasodilation was observed without increases in circulating epinephrine. The mechanism by which insulin could produce local β-adrenergic receptor stimulation independent of increased circulating epinephrine is obscure.

Endothelium-dependent relaxant effects of insulin have been reported in isolated canine and human arteries. However, it is not known if physiological insulin concentrations produce endothelium-dependent vasodilation in vivo in dogs and humans. Interestingly, Andreas Mügge failed to observe endothelium-dependent relaxation of isolated vessels from rats and guinea pigs even at very high insulin concentrations (unpublished observations). These and other observations addressed below raise the question of species differences in the vascular actions of insulin.

Insulin stimulates sodium/potassium ATPase and the sodium/potassium pump in many tissues. Stimulation of the sodium/potassium pump in vascular muscle causes hyperpolarization and relaxation. Prakash et al. have reported that insulin stimulates sodium/potassium ATPase in vascular smooth muscle. Thus, insulin might produce vasodilation by stimulating the sodium/potassium pump in vascular muscle.

Zemel and coworkers have proposed that insulin may promote vascular relaxation and inhibit vasoconstrictor responses by stimulating increased Ca-ATPase in the plasma membrane, thereby increasing calcium efflux from vascular muscle.

Insulin increases skeletal muscle oxygen consumption, which could produce metabolic vasodilation. Although this mechanism seems compelling, there is contradictory evidence. Specifically, Natali et al. measured forearm vasodilator responses to local insulin infusion in humans in doses that produced local plasma concentrations of 125 microunits/ml. This concentration failed to cause forearm vasodilation despite local metabolic effects including increased glucose uptake and lactate release. Because substantial forearm vasodilation has been observed with comparable plasma concentrations of insulin during systemic insulin infusions, the study by Natali et al suggests that forearm vasodilator responses to physiological insulin concentrations in humans are not mediated by a local action.

In summary, evidence for both systemic and local vasodilator mechanisms of insulin is conflicting. The mechanisms remain mysterious and require further investigation.

**Sympathetic Actions of Insulin**

There is no question that insulin produces marked sympathetic activation. Hyperinsulinemia increases both plasma norepinephrine and muscle sympathetic nerve activity in humans in the absence of hypoglycemia. In addition, hyperinsulinemia increases norepinephrine turnover in rats. Interestingly, there is a striking regional nonuniformity in the sympathetic nerve activity responses to insulin. Morgan and colleagues have reported that hyperinsulinemia increases lumbar sympathetic nerve activity but not renal or adrenal sympathetic nerve activity in normotensive Sprague-Dawley (unpublished observations) or Wistar-Kyoto rats. In humans, Berne et al. have reported that hyperinsulinemic clamp increases sympathetic nerve activity to muscle but not to skin.

The sympathetic actions of insulin have been attributed to central neural actions of insulin. Specifically, the medial hypothalamus has been implicated as a site of the sympathoexcitatory action of insulin. In addition, Muntzel, Morgan, Mark, and Johnson at Iowa have recently demonstrated that infusion of insulin into the third cerebral ventricle increases lumbar sympathetic nerve activity in rats (unpublished observations).

Insulin-mediated vasodilation may cause slight decreases in arterial pressure. This has raised the possibility that increases in sympathetic nerve activity during hyperinsulinemia may simply represent a baroreceptor reflex response and not a central neural action. In a preliminary report, Morgan et al. observed that sinoaortic baroreceptor denervation eliminated the lumbar sympathetic nerve activity response to insulin. In contrast, after sinoaortic denervation, insulin produced substantial increases in adrenomedullary sympathetic nerve activity that were not observed in rats with intact baroreceptors.

In summary, hyperinsulinemia increases sympathetic nerve activity in the absence of hypoglycemia. There is striking regional nonuniformity in the sympathetic nerve responses to insulin. Central neural mechanisms probably contribute to the sympathetic action of insulin, but baroreceptor mechanisms may be involved.

**Arterial Pressure Responses to Insulin**

The 1981 report by Rowe et al. is frequently cited as evidence that hyperinsulinemia increases arterial pressure in humans. However, recent reports indicate that acute physiological increases in plasma insulin levels do not increase arterial pressure in normotensive humans despite evidence for sympathetic activation. In addition, Gans et al. have recently reported that acute hyperinsulinemia does not increase arterial pressure in
normotensive humans despite a decline in fractional sodium excretion.

At first glance, these recent observations appear to contradict the report of Rowe et al.6 In fact, however, Rowe et al found that physiological increases in plasma insulin (44-154 microunits/ml) did not increase arterial pressure despite increased plasma norepinephrine levels. Arterial pressure increased only with supraphysiological insulin levels, i.e., 600 microunits/ml. Furthermore, even at these extremely high insulin levels, mean arterial pressure increased only slightly (approximately 6 mm Hg).6 Thus, the Rowe study does not support the concept that physiological levels of insulin elevate arterial pressure in humans. In addition, the studies by Brands et al15-17 showed that physiological increases in plasma insulin levels persisting for 7-28 days do not increase arterial pressure in normotensive dogs.

Thus, available evidence indicates that acute, physiological increases in plasma insulin do not elevate arterial pressure in normotensive humans or dogs. Interestingly, in rats, physiological increases in insulin may elevate arterial pressure. Edwards and Tipton8 reported that acute insulin administration increases arterial pressure in Sprague-Dawley rats. Elimination of the pressor response by both ganglionic blockade and sympathectomy suggests a role of sympathetic neural mechanisms in insulin-induced increases in arterial pressure in rats. Brands et al9 also reported that physiological increases in plasma insulin for several days significantly increased arterial pressure in rats. Why would physiological increases in plasma insulin raise arterial pressure in rats but not in normotensive humans or dogs? Two possibilities merit mention. First, there may be species differences in cardiovascular, renal, and sympathetic effects of insulin. Specifically, we speculate that the vasodilator effects of insulin may be less pronounced in rats than in dogs and humans. Second, as Brands et al9 noted, rats that develop hypertension during insulin infusion may be insulin resistant compared with normotensive dogs and humans.

Despite evidence for a pressor action of insulin in the rat, the reports that acute physiological increases in plasma insulin levels do not raise pressure in normal dogs or humans present a serious challenge to the hypothesis that hyperinsulinemia contributes to increases in arterial pressure in humans. Given this challenge, attention has recently turned to the concept that abnormalities in skeletal muscle vascular regulation in obesity and hypertension may underlie insulin resistance. Baron and colleagues11-13 have demonstrated attenuation of the vasodilator actions of insulin in skeletal muscle in obesity and non-insulin-dependent diabetes mellitus. Specifically, they noted reduced capillary recruitment during insulin infusion.

In an article in this issue of Hypertension, Baron and colleagues10 have hypothesized that sympathetic stimulation itself can promote insulin resistance by reducing skeletal muscle blood flow. Based on their own research, Baron and colleagues10,11 have proposed that abnormalities in vascular regulation in skeletal muscle contribute to the insulin resistance observed in both obesity and hypertension. Baron et al10 suggest that this may explain the epidemiological link between insulin resistance and hypertension.

Thus, two lines of evidence seem to support the argument that insulin resistance and hyperinsulinemia are markers of the hypertensive process in skeletal muscle. The first is the concept that abnormal skeletal muscle vascular and sympathetic regulation may underlie insulin resistance. The second is the evidence that acute hyperinsulinemia does not increase arterial pressure in normotensive humans.

However, two possibilities should be considered before it can be concluded that hyperinsulinemia does not contribute to hypertension in humans. First, chronic hyperinsulinemia might elevate arterial pressure, because insulin is reported to produce trophic actions on vascular muscle that could, over time, increase vascular resistance and arterial pressure.41 However, Tsutsu et al42 have reported that chronically elevated plasma insulin levels in patients with insulinoma did not result in increased arterial pressure. Furthermore, arterial pressure did not fall in these patients after tumor resection.42 This suggests that even chronic hyperinsulinemia is not sufficient to raise arterial pressure in humans, although extrapolating observations on insulinoma patients (who may be resistant to multiple insulin actions) to patients with selective insulin resistance (i.e., peripheral insulin-mediated glucose uptake only) characteristic of "syndrome X" may be unwise. Second, the pressor action of hyperinsulinemia could depend critically on the presence of insulin resistance, a predisposition to hypertension, or both. This important concept is discussed below.

Interaction of Hyperinsulinemia, Insulin Resistance, and a Genetic Predisposition to Hypertension

Insulin resistance and a genetic predisposition to hypertension may exaggerate the sympathetic and attenuate the vasodilator actions of insulin. Baron and colleagues10,11 have shown that insulin-resistant humans have impaired vasodilator responses to insulin. In addition, rats made insulin resistant by a high fructose diet have exaggerated sympathetic and pressor responses to insulin.44 Finally, spontaneously hypertensive rats have augmented adrenal sympathetic nerve responses to insulin compared with normotensive strains.44

By augmenting the sympathetic or attenuating the vasodilator actions of insulin, a predisposition to hypertension and insulin resistance could tip the balance between the pressor and depressor actions of insulin in favor of the hypertensive actions.

The hypothesis that hyperinsulinemia increases arterial pressure in the presence of insulin resistance and hypertension has been tested by the study of 1) arterial pressure responses to hyperinsulinemic/euglycemic clamp in insulin resistance and hypertension, and 2) the effects of somatostatin or metformin on arterial pres-
sure in the presence of insulin resistance and hypertension.

O'Hare et al.\(^{49}\) reported that increasing plasma insulin levels to 750 microunits/ml did not increase arterial pressure in obese, insulin-resistant humans who tended to be hypertensive. Baron and Brechtel\(^{46}\) have also not observed a pressor response to insulin in obese, insulin-resistant, normotensive humans. Elahi et al.\(^{47}\) and Rochini\(^{48}\) have stated that insulin infusion fails to increase arterial pressure in obese, insulin-resistant, hypertensive humans. Studies of mildly hypertensive humans in our laboratory also did not reveal a pressor response to acute physiological elevation in plasma insulin.\(^{49}\) Finally, Hall and colleagues\(^{50}\) reported that insulin infusion does not increase arterial pressure in obese, insulin-resistant, hypertensive dogs.

To summarize, numerous studies have failed to reveal a pressor response to acute, physiological increases in plasma insulin levels even in insulin-resistant, hypertensive humans. These findings seriously challenge the concept that hyperinsulinemia contributes to increases in arterial pressure in the presence of insulin resistance and hypertension.

A second method of testing the concept that insulin resistance and hyperinsulinemia increase arterial pressure has been to lower plasma insulin with somatostatin and to increase insulin sensitivity with antihyperglycemic agents. Somatostatin inhibits insulin secretion and lowers plasma insulin, but it does not eliminate insulin resistance. It has been used to test the contribution of hyperinsulinemia to elevated arterial pressure.\(^{51-52}\) Normotensive rats made insulin resistant and hyperinsulinemic by high fructose or sucrose diet developed hypertension. Somatostatin prevents both the hyperinsulinemia and the hypertension in this experimental model.\(^{53}\) Somatostatin infused over 8 hours has also been reported to decrease arterial pressure (by approximately 14 mm Hg) in obese, hyperinsulinemic hypertensive humans but not in normoinsulinemic hypertensive humans.\(^{51}\)

These findings are intriguing but do not necessarily support the hypothesis that hyperinsulinemia causes hypertension in the presence of insulin resistance. Somatostatin has multiple endocrine actions that could conceivably influence arterial pressure. To conclude that somatostatin lowers blood pressure by lowering plasma insulin levels and not by other actions, it would be essential to show that restoring insulin levels during somatostatin administration elevates arterial pressure. We recently reported that somatostatin lowers forearm vascular resistance and arterial pressure in obese, insulin-resistant, hypertensive humans.\(^{53}\) Infusing insulin while continuing somatostatin administration increased forearm vascular resistance and arterial pressure.\(^{53}\) However, the increases in arterial pressure were small (3-4 mm Hg) and did not exceed those observed during time/vehicle control experiments. Thus, the depressor response to somatostatin cannot be convincingly attributed to lowering of plasma insulin levels.

Several antihyperglycemic agents that increase peripheral insulin sensitivity and lower plasma insulin have also been used to test the concept that insulin resistance contributes to hypertension. Landin et al.\(^{54}\) reported that 6 weeks of oral administration of metformin, a biguanide, to insulin-resistant, hypertensive men increased insulin sensitivity and significantly decreased arterial pressure (e.g., diastolic pressure fell by \(-24 \pm 5\) mm Hg). The authors emphasized that this was a pilot, uncontrolled study.

In addition to this pilot study in humans, four recent reports show that antihyperglycemic agents that increase insulin sensitivity lower arterial pressure in rats. Dubey et al.\(^{55}\) reported that pioglitazone decreased arterial pressure in Dahl salt-sensitive and renal hypertensive rats but not in normotensive control rats. Pershadsingh and Kurtz\(^{56}\) demonstrated that ciglitazone improved insulin sensitivity and lowered arterial pressure in obese, insulin-resistant Zucker rats. Fujiwara et al.\(^{57}\) found that CS-045, another agent that increases insulin sensitivity, promotes renal sodium excretion and decreases systolic arterial pressure in obese Zucker rats. Finally, Morgan et al.\(^{58}\) recently found that metformin increased insulin sensitivity and decreased arterial pressure in spontaneously hypertensive rats but not in normotensive control rats. The decrease in arterial pressure appears to correlate with a decrease in plasma insulin levels and improved insulin sensitivity.\(^{54-56}\)

The studies with the antihyperglycemic agents provide the strongest experimental support to date for the concept that insulin resistance and hyperinsulinemia contribute significantly to hypertension. However, even these studies do not prove that insulin resistance and hyperinsulinemia contribute to elevated arterial pressure. There are two important caveats. First, it is not yet known whether the antihypertensive influence of these agents results from improved insulin sensitivity or from other actions. For example, Dubey et al.\(^{55}\) demonstrated that pioglitazone inhibited the mitogenic effect of several growth factors on cultured arteriolar smooth muscle cells. Pershadsingh and Kurtz\(^{56}\) found that ciglitazone dramatically attenuated the capacity of platelet-derived growth factor to induce sustained increases in intracellular calcium in rat aortic smooth muscle cells. These findings raise the possibility that these agents may produce cellular actions that lower arterial pressure independent of their ability to increase insulin sensitivity. Parenthetically, although these other actions may confound the use of these agents to test the insulin hypothesis, they do not detract from (and indeed may enhance) the potential of these agents as antihypertensive drugs.

Second, even if it is shown that insulin resistance contributes to hypertension, it remains to be demonstrated that the pressor influence of insulin resistance results from hyperinsulinemia. This is particularly cogent because insulin infusion fails to increase arterial pressure in humans.

**Conclusion**

The sympathetic, antinatriuretic, and trophic actions of insulin are the basis for the concept that insulin resistance and hyperinsulinemia increase arterial pressure. However, insulin also produces vasodilation, an action that has been relatively neglected until recently. In humans, the vasodilator (depressor) and sympathetic (pressor) actions of insulin appear to be offsetting. This challenges the concept that hyperinsulinemia and insulin resistance contribute to increased arterial pressure. As a corollary to this challenge, it has been proposed that abnormalities in skeletal muscle vascular and sym-
pathetic mechanisms in hypertension cause insulin resistance. In other words, hyperinsulinemia and insulin resistance may be markers of the hypertensive process in skeletal muscle and not contributors to elevated arterial pressure. It is, therefore, surprising that preliminary results suggest that oral antihyperglycemic agents that act primarily by increasing insulin sensitivity appear to lower arterial pressure in hypertensive and insulin-resistant rats and in hypertensive humans with insulin resistance. However, these agents also have antihypertensive effects independent of increasing insulin sensitivity. Consequently, it is not yet known if these agents lower arterial pressure by improving insulin sensitivity.

Despite the recent surge of interest, it is not yet clear whether insulin resistance and hyperinsulinemia promote hypertension or whether these are secondary to abnormal skeletal muscle sympathetic and vascular mechanisms in obesity and hypertension. Whatever the outcome of this controversy, there can be little doubt that the concepts advanced by the advocates of the insulin hypothesis have stimulated research that has greatly enhanced our understanding of the relation between metabolic and cardiovascular regulation. This research has recently led to the realization that antihyperglycemic agents that increase insulin sensitivity may exert antihypertensive actions, attenuate trophic effects on vascular muscle, and improve dyslipidemia. Ironically, the antihypertensive and antitrophic effects may not result from increased insulin sensitivity. Nevertheless, the credit for study of these agents in hypertensive cardiovascular disease must ultimately go to the investigators who initially proposed that insulin resistance and hyperinsulinemia promote hypertension in addition to dyslipidemia.

References


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