Genetic Factors Determine the Blood Pressure Response to Insulin Resistance and Hyperinsulinemia: A Call to Refocus the Insulin Hypothesis of Hypertension (43862C)

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Yesterday upon the stair
I met a man who wasn't there.
I met him there again today.
I wish that man would go away.

The hypothesis that insulin resistance and compensatory hyperinsulinemia contribute to the pathogenesis of essential hypertension and hypertension in obesity has gained enormous interest due in large part to the research of Reaven (1), Landsberg (2), Ferrannini (3), Rocchini (4), DeFronzo (5), Modan (6), Sowers (7), and Tuck (8).

Stimulated by the hypothesis, in 1989 we began studies in humans and rats on the sympathetic and vascular actions of insulin in an effort to elucidate further mechanisms linking insulin resistance and hyperinsulinemia with hypertension. Based on the previous research, we began our work with enthusiasm for the hypothesis. However, based on the evidence that emanated from our laboratory and others, we quickly emerged (9, 10) (along with Brands [11], Hall [12–14], and Julius [15]) in publications, presentations, and debates as skeptics of the hypothesis that insulin resistance and hyperinsulinemia promote hypertension.

Several months ago, for reasons that escape us, Dr. Landsberg asked us to contribute an article arguing the affirmative in a Point/Counterpoint on this hypothesis. Advocates of the insulin hypothesis may rightly argue that asking us to argue the affirmative on this hypothesis is like asking a fox to guard the chicken coop. We can only reply that we were invited to do so by an advocate of the hypothesis. We accepted the charge primarily because we continue to encounter studies that support this hypothesis (i.e., we continue to "meet a man" whom we thought "wasn't there") at the same time that we confront evidence from our laboratory and others that seems to contradict the hypothesis. We believed that reviewing the evidence in an effort to argue the affirmative might provide us with new insight and help focus our future research and perhaps that of others on this topic. We believe—and hope the reader agrees—that our impulsive decision has been vindicated, because in attempting to reconcile the supportive and contradictory evidence, we have concluded that future progress in evaluating the insulin hypothesis will require inclusion of the concept that there is "sensitivity or resistance" to the blood pressure effects of insulin resistance and that genetic factors may play a decisive influence in this effect.

We want to acknowledge here that the evidence we cite supporting this concept has derived primarily from experiments by others. Our goal in this perspective is to emphasize the conceptual significance of this evidence in an effort to surmount the impasse between those who believe that insulin resistance and hyperinsulinemia generally promote hypertension and those who believe they do not. We suggest that an analogy to this concept was the introduction of the concept that salt sensitivity or resistance may be determined by genetic factors. Until this concept was introduced, the arguments between those who believed that high-salt diet either did or did not promote hypertension seemed at an impasse. The introduction of the concept of ge-

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netic determination of salt sensitivity and resistance helped surmount this impasse and guided future research.

It is our goal in this article to review the evidence for the insulin hypothesis from a variety of different sources (from epidemiology to pharmacology). We hope that our review will lead to a refocusing of the insulin hypothesis on genetic factors in determining the blood pressure response to insulin resistance and hyperinsulinemia.

Epidemiological Studies

A number of investigators have demonstrated an association between insulin resistance, obesity, and hypertension (6, 16). In addition, subsequent studies have shown that even lean individuals with essential hypertension have a higher frequency of insulin resistance and hyperinsulinemia (3, 17). However, hyperinsulinemia is not found in secondary renovascular hypertension, and it often persists during antihypertensive therapy in patients with essential hypertension (18). These observations indicate that the hyperinsulinemia is not secondary to elevated arterial pressure *per se*; this lends support to the view that insulin resistance and hyperinsulinemia contribute to and are not caused by elevated arterial pressure in obese and lean essential hypertensives. This concept derives additional support from two other observations. First, normotensive offspring of hypertensive parents are insulin resistant and hyperinsulinemic compared with the offspring of normotensive parents (19–22). Second, individuals with insulin resistance have an increased risk of subsequent development of hypertension (23). These observations suggest that insulin resistance precedes and could contribute to the later development of hypertension.

In contrast to this supporting evidence, there are also studies that at first glance seem inconsistent with the view that insulin resistance and hyperinsulinemia contribute to the development of essential hypertension. For example, a number of epidemiological studies have failed to confirm the relationship between plasma insulin concentration and hypertension (24, 25). In addition, many subjects (either obese or lean) have insulin resistance and hyperinsulinemia without hypertension (26, 27). Finally, it is recognized that there are several populations, such as Pima Indians and Mexican Americans in the United States, who have a high frequency of insulin resistance without an increased frequency of hypertension (28, 29).

Does this contradictory epidemiological evidence negate the concept that insulin resistance and hyperinsulinemia may contribute to the pathogenesis of essential hypertension? Not at all. Then what are we to make of this contradictory evidence? First, the epidemiological evidence demonstrates that insulin resistance and hyperinsulinemia alone are not sufficient to cause hypertension. This should not be surprising since there are few factors which alone invariably cause hypertension. Thus, the finding that insulin resistance and hyperinsulinemia are found independent of hypertension (and are therefore presumably not sufficient to cause hypertension) does not negate the concept that insulin resistance and hyperinsulinemia may, under some circumstances, contribute to hypertension.

There is ample precedent for this thinking in the role of salt in the pathogenesis of hypertension. A high-salt diet clearly does not cause hypertension in the majority of individuals (so called salt resistance), but in some individuals a high-salt diet promotes hypertension (so called salt sensitivity).

A Call to Refocus the Insulin Hypothesis

We suggest that the time is past to ask whether insulin resistance and hyperinsulinemia *per se* cause hypertension in humans. The epidemiological evidence alone, not to mention the experimental evidence, suggests that in many individuals insulin resistance and hyperinsulinemia do not cause hypertension (we would refer to this as "blood pressure resistance to insulin resistance"). Instead, we suggest that attention now turn to determining if there are factors—genetic and/or acquired—that promote a hypertensive response to insulin resistance and hyperinsulinemia ("blood pressure sensitivity to insulin resistance").

Genetic Factors. There is convincing evidence that genetic factors can play a decisive influence in salt sensitivity or resistance. Is there evidence that genetic factors might also influence sensitivity or resistance to the hypertensive effects of insulin resistance and hyperinsulinemia? Studies in rats suggest that the answer is yes. For example, Tomiyama *et al.* (30) found that insulin infusion increased blood pressure in Dahl salt-sensitive rats but not in Dahl salt-resistant rats (Fig. 1). This study indicates that genetic factors are important in determining the blood pressure response to hyperinsulinemia. This study does not provide evidence that these genetic factors are distinct from those promoting hypertension in response to other stresses such as high-salt diet.

In contrast, a recent study by Reed *et al.* (31) suggests that genes responsible for "blood pressure sensitivity to insulin resistance" may be distinct from those responsible for salt sensitivity. These investigators studied the blood pressure response to fructose-induced insulin resistance and hyperinsulinemia in three strains of rats: Sprague-Dawley, Fischer 344, and Wistar rats. All three strains developed a significant increase in plasma insulin, but only the Sprague-Dawley rats showed an increase in blood pressure in response to the diet-induced insulin resistance and hy-

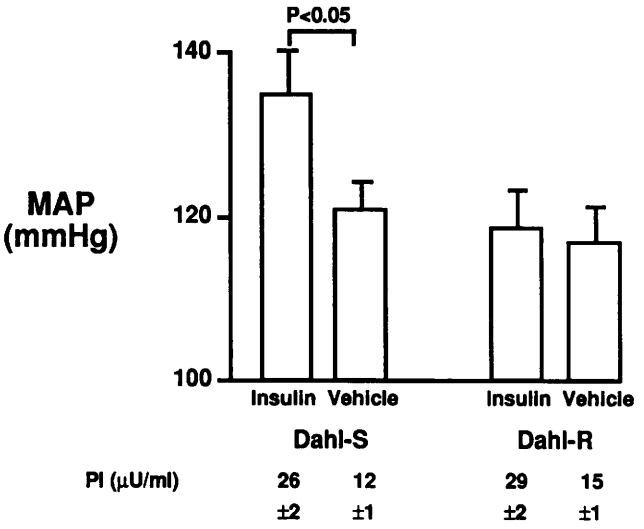

Figure 1. Insulin infusion increased arterial pressure in Dahl salt-sensitive (S) rats but not in Dahl salt-resistant (R) rats, despite comparable increases in plasma insulin in the two strains. Additional studies indicated that the insulin induced increase in arterial pressure in S rats was prevented by α-adrenergic blockade, which suggests that it was sympathetically mediated. (Adapted from Tomiyama *et al.* Hypertension **20**:596–600, 1992.)

perinsulinemia (Fig. 2). Interestingly, in this study a high-salt diet increased blood pressure in the Fischer 344 rats, but not in the Sprague-Dawley or Wistar rats.

These studies prompt the concept that (i) genetic factors may critically determine the blood pressure response to insulin resistance and hyperinsulinemia; and (ii) these factors may be distinct from the genetic factors that influence the blood pressure response to a high-salt diet. The knowledge that insulin resistance and hyperinsulinemia are associated with a higher frequency of hypertension in some populations, but not in Pima Indians and Mexican Americans, is consistent with this hypothesis. We believe support for a modified version of the insulin hypothesis may be found if future research is directed at a search for genetic factors determining sensitivity or resistance to the hypertensive effects of insulin resistance.

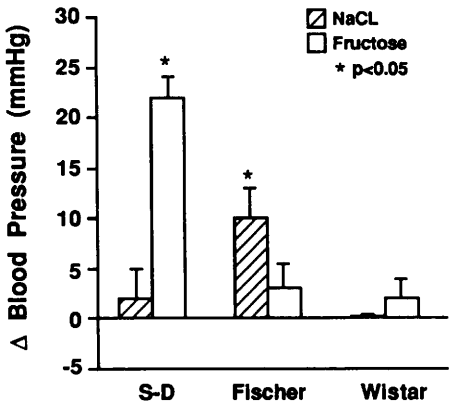

Figure 2. Blood pressure in rats consuming either diets enriched in NaCl (striped bars) or fructose (open bars). Only the Sprague-Dawley (S-D) group had a significant increase in blood pressure in response to fructose feeding. In contrast, NaCl increased blood pressure only in the Fischer 344 rats. Values are mean ± SEM. *P* values indicate significant difference from normal chow (data not shown), which did not alter arterial pressure. (Adapted from Reed *et al.* Blood Pressure **3**:197–201, 1994.)

Acquired Factors. Is there evidence that acquired factors could promote a hypertensive response to hyperinsulinemia? An answer to this question requires brief discussion of the mechanisms by which insulin could influence blood pressure.

Insulin has a number of actions that could promote hypertension. In addition to its effects on glucose uptake, insulin normally promotes sodium reabsorption, increases sympathetic nerve activity to skeletal muscle, and produces vasodilation in skeletal muscle (2, 9). The antinatriuresis reflects direct renal actions (11, 12, 33); the sympathetic activation probably results from central neural actions (2, 33, 34), and there is recent evidence that the vasodilation is caused by release of nitric oxide (35).

The evidence suggests that in normal humans and dogs, the pressor (renal and sympathetic) and depressor (vasodilator) actions of insulin are balanced so that blood pressure does not increase (9, 32, 36). Several years ago, we proposed that adaptive responses to hypertension and/or insulin resistance might tip the balance between the pressor and depressor actions in favor of the hypertensive actions (37). We are not aware of factors that exaggerate the antinatriuretic actions of insulin, but there is evidence that diet-induced insulin resistance promotes a renal sympathetic nerve response to insulin in rats (38, 39). In addition, humans with insulin resistance, obesity, and hypertension have either an attenuation or reversal of the normal skeletal muscle vasodilator response to insulin (40, 41). This should not be surprising given awareness that endothelial function is impaired in essential hypertension. These observations lend credence to the concept that acquired, perhaps adaptive, responses to hypertension and/or insulin resistance could tip the balance between the pressors and depressors actions of insulin in favor of the pressor actions (42). It has not been shown that this imbalance produces an increase in arterial pressure. Nevertheless, it is still tempting to speculate that the adaptive responses to hypertension and insulin resistance could promote a hypertensive response to insulin.

Species Differences in Blood Pressure Responses to Insulin. To our knowledge, there have been no studies demonstrating a pressor response to physiological increases in plasma insulin in dogs or humans. The studies in humans have evaluated primarily the responses to acute infusions of insulin (10, 36, 43), but studies in dogs have failed to demonstrate an increase in blood pressure even with chronic infusions (11–13). In contrast to humans and dogs, there are now several reports of a pressor response to acute

and chronic infusions of insulin in rats (44–46). Moreover, there are several reports that diet-induced insulin resistance and hyperinsulinemia increase arterial pressure in rats (31, 47) and that this can be blocked by somatostatin (48).

It is tempting to dismiss the significance of the findings in rats by suggesting that they do not appear to apply to humans. However, it may be more constructive to ask why there are species differences in the blood pressure responses to insulin and then to determine if this information might provide insight into conditions under which insulin might increase blood pressure in humans. In preliminary studies, Morgan *et al.* in our laboratories failed to observe a vasodilator response to insulin in rats (unpublished observations), and we have been informed that other investigators have obtained similar results (Hall *et al.*, personal communication). The pressor response to insulin may be explained by the lack of a vasodilator response to offset the pressor effects of sodium reabsorption and sympathetic stimulation. This contrasts with normal humans and dogs, in which the pressor effects of insulin are offset by depressor influence of vasodilation (10, 32, 36, 43). This implies that if hypertension or obesity eliminates the vasodilator response to insulin in humans, the substrate exists for the pressor actions of insulin to prevail.

Vascular and Sympathetic Mechanisms as a Cause of Insulin Resistance

Baron (40) and Julius (15) have advanced variations on the hypothesis that abnormalities in skeletal muscle vascular and sympathetic regulation may underlie insulin resistance in essential hypertension and obesity. Baron and his colleagues have performed an elegant series of studies demonstrating that hyperinsulinemia produces vasodilation in skeletal muscle, which appears to be mediated by nitric oxide (35). These investigators have proposed that the increase in skeletal muscle blood flow is important in glucose delivery and uptake during insulin and have further suggested that an impairment in this increase in muscle blood flow contributes importantly to insulin resistance in obesity and presumably essential hypertension (41). Julius and colleagues have proposed that enhanced sympathetic drive may contribute importantly to the insulin resistance in essential hypertension including hyperkinetic borderline hypertensives (15). These investigators have proposed three mechanisms (Fig. 3) by which sympathetic stimulation could promote insulin resistance: (i) stimulation of β-adrenergic receptors; (ii) conversion of slow twitch to fast twitch muscle fibers; (iii) vasoconstriction with a decrease in nutritional or capillary blood flow in skeletal muscle. These mechanisms could ultimately lead to vascular changes (Fig. 3, upper left).

If Baron and Julius are correct in suggesting that abnormal vascular and/or sympathetic regulation may cause insulin resistance in essential hypertension and obesity, this would not disprove the concept that insulin resistance and hyperinsulinemia contribute to increases in arterial pressure. Nevertheless, their hypotheses would offer potentially serious challenges to the concept that insulin resistance and hyperinsulinemia promote hypertension. Why? If one can offer a credible mechanism(s) by which essential hyperten-

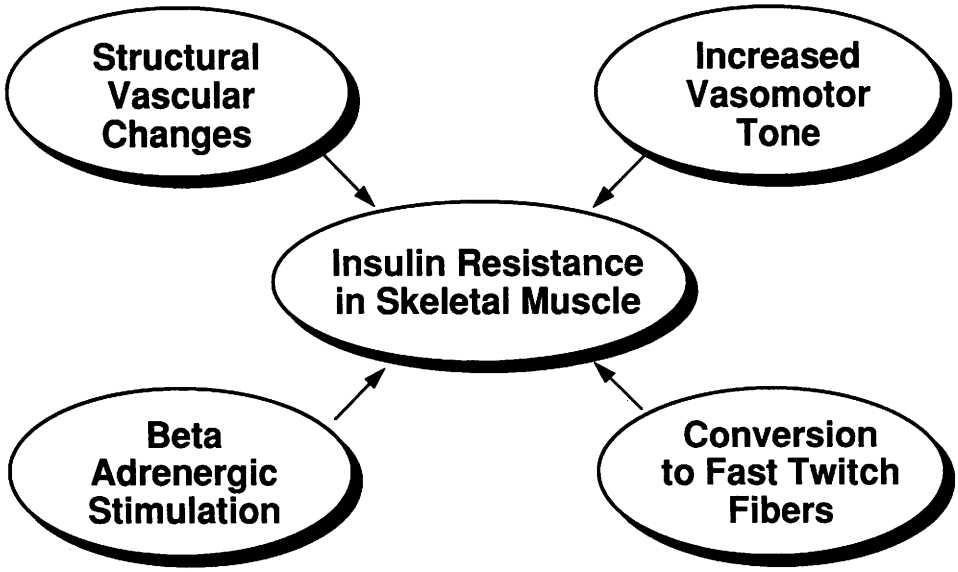

Figure 3. Schematic representation adapted from Julius *et al.* J Hypertension **9**:983–986, 1991. This schematic suggests that increased vasomotor tone, conversion of slow-twitch to fast-twitch fibers, β-adrenergic stimulation. Structural vascular changes could promote and explain the finding of insulin resistance in essential hypertension.

sion and obesity could cause insulin resistance, then one could explain the early link between insulin resistance, hyperinsulinemia, and essential hypertension without suggesting that insulin resistance promotes hypertension. In contrast, if one cannot identify a credible mechanism by which essential hypertension and/or obesity causes insulin resistance, then the association of insulin resistance and hypertension will continue to suggest that insulin resistance may contribute to increases in arterial pressure.

Therefore, we believe these ideas of Baron and Julius merit a critical analysis. First, the proposed mechanisms do not explain the finding that insulin resistance occurs in essential hypertension but not in secondary renovascular hypertension, which is also characterized by vasoconstriction and by intense angiotensin-induced sympathetic stimulation to skeletal muscle. Second, impairment in vasodilation or an increase in vascular resistance do not necessarily indicate a decrease in total or nutritional blood flow. For example, essential hypertension is not accompanied by decreased blood flow to skeletal muscle (despite increased vascular resistance) because the increase in arterial pressure maintains tissue perfusion in face of the increased vascular resistance. Indeed, patients with hyperkinetic borderline hypertension may have increased skeletal muscle blood flow. Third, while reflex sympathetic stimulation caused acute insulin resistance in the forearm, this response was transient (49). Although borderline hypertensives have been shown to have increased sympathetic nerve activity to skeletal muscle (50), it is not yet known whether the normotensive offspring of hypertensive parents (who are insulin resistant) also have increased sympathetic nerve activity.

For the above reasons, we believe it is unlikely that either sympathetic or vascular mechanisms cause insulin resistance and hyperinsulinemia in essential hypertension. If our conclusion is correct, the early and frequent association of insulin resistance, hyperinsulinemia, and the evolving syndrome of essential hypertension suggests that insulin resistance may contribute to the increases in arterial pressure.

Responses to Pharmacologic Agents That Increase Insulin Sensitivity

Antihyperglycemic agents that act by increasing insulin sensitivity and lowering plasma insulin should constitute pharmacologic tools with which to test the hypothesis that insulin resistance and hyperinsulinemia promote hypertension. The thiazolidenediones and the biguanides represent two classes of agents that act in large part by increasing insulin sensitivity. This contrasts with the sulfonylureas that act largely by increasing insulin secretion. As would be expected the sulfonylureas are not antihypertensive, but as would be expected from the insulin hypothesis, the thiazolidinediones have been found in numerous studies to lower arterial pressure in Dahl salt-sensitive rats (50), obese Zucker rats (51), Sprague-Dawley rats (52) with hypertension produced by high fructose diet, and renal hypertensive rats, but not in normotensive rats (52). In addition, metformin (a biguanide) has been found to improve insulin sensitivity and lower arterial pressure in spontaneously hypertensive rats, but not in normotensive Wistar-Kyoto or Sprague-Dawley rats (53).

The effects of these agents in human hypertension is not clear. Although a preliminary uncontrolled study suggested that metformin might lower arterial pressure in lean, insulin-resistant essential hypertensives (54), subsequent controlled studies have failed to confirm an improvement in insulin sensitivity or a lowering of arterial pressure in human hypertensives (55). To our knowledge, there have been no controlled studies of the effects of thiazolidinediones in human hypertension.

At first glance, the studies in rat would appear to provide strong support for the concept that insulin resistance and hyperinsulinemia contribute significantly to hypertension. However, there is evidence that the thiazolidinediones might lower arterial pressure through mechanism(s) independent of improved insulin sensitivity. First, Dubey *et al.* demonstrated that pioglitazone inhibits growth of cultured preglomerular renal arteriolar smooth muscle cells (56). Pershadsingh and Kurtz demonstrated that ciglitazone dramatically attenuates the capacity of platelet-derived growth factor to induce sustained increases in intracellular calcium in rat aortic smooth muscle cells (51). In addition, Zhang *et al.* recently reported that pioglitazone inhibits inward calcium current through L-type channels in vascular smooth muscle (57). Second, Zhang *et al.* in Kotchen's laboratory found that pioglitazone lowered arterial pressure in renal hypertensive rats; this model of hypertension is not insulin resistant, and the drug lowered arterial pressure without altering insulin sensitivity (58). The above observations suggest that the thiazolidinediones may lower arterial pressure through actions independent of improved insulin sensitivity. Nevertheless, it is still tempting to speculate that the antihypertensive effect of the thiazolidinediones results at least in part from improved insulin sensitivity and lowered plasma insulin, particularly in hypertensive models with insulin resistance.

Summary

We have briefly reviewed the controversy regarding the role of insulin resistance and hyperinsulinemia in the pathogenesis of hypertension in an attempt to emphasize the evidence in support of this concept. In

so doing, we have highlighted the concept that genetic factors may determine sensitivity or resistance to the hypertensive effects of insulin resistance and hyperinsulinemia. We hope that this idea will help to reconcile seemingly conflicting evidence on this hypothesis and will focus future research.

1. Reaven GM. Role of insulin resistance in human disease. Diabetes **37**:1595–1607, 1988.
2. Landsberg L. Diet, obesity and hypertension: An hypothesis involving insulin, the sympathetic nervous system, and adaptive thermogenesis. Q J Med **236**:1081–1090, 1986.
3. Ferrannini E, Buzzigoli G, Bonadonna R, Giorico MA, Oleggini M, Graziadei L, Pedrinelli R, Brandi L, Bevilacqua S. Insulin resistance in essential hypertension. N Engl J Med **15**:350–357, 1987.
4. Rocchini AP. Insulin resistance and blood pressure regulation in obese and nonobese subjects. Hypertension **17**:837–842, 1991.
5. DeFronzo RA, Cooke RA, Andres R, Faloona GR, Davis PJ. The effect of insulin on renal handling of sodium, potassium, calcium and phosphate in man. J Clin Invest **55**:845–855, 1975.
6. Modan M, Halkin H, Almog S, Lusky A, Eshkil A, Shefi M, Shitrit A, Fuchs Z. Hyperinsulinemia: A link between hypertension, obesity and glucose intolerance. J Clin Invest **75**:809–817, 1985.
7. Sowers JR, Standley PR, Ram JL, Jacober S, Simpson L, Rose K. Hyperinsulinemia, insulin resistance, and hyperglycemia: Contributing factors in the pathogenesis of hypertension and atherosclerosis. Am J Hypertens **67**:260S–270S, 1993.
8. Tuck ML. Metabolic considerations in hypertension. (review) Am J Hypertens **3**(12 Pt 2):355S–365S, 1990.
9. Anderson EA, Hoffman RP, Balon TW, Sinkey CA, Mark AL. Hyperinsulinemia produces both sympathetic neural activation and vasodilation in normal humans. J Clin Invest **87**:2246–2252, 1991.
10. Anderson EA, Balon TW, Hoffman RP, Sinkey CA, Mark AL. Insulin increases sympathetic activity but not blood pressure in borderline hypertensive humans. Hypertension **19**:621–627, 1992.
11. Brands MW, Mizelle HL, Gaillard CA, Hildebrandt DA, Hall JE. The hemodynamic response to chronic hyperinsulinemia in conscious dogs. Am J Hypertens **4**:164–168, 1991.
12. Hall JE, Coleman TG, Mizelle HL. Does chronic hyperinsulinemia cause hypertension? Am J Hypertens **2**:171–173, 1989.
13. Hall JE, Brands MW, Dixon WN, Mizelle HL, Hildebrandt DA. Blood pressure regulation during chronic hyperinsulinemia in obese, insulin resistant dogs. (abstract) J Hypertension **10**:S224, 1992.
14. Hall JE, Summers RL, Brands MW, Keen H, Alonso-Galicia M. Resistance to metabolic actions of insulin and its role in hypertension. Am J Hypertens **7**:772–788, 1994.
15. Julius S, Gudbrandsson T, Jamerson K, Shahab ST, Andersson O. The hemodynamic link between insulin resistance and hypertension. J Hypertension **9**:983–986, 1991.
16. Lucas CP, Estigarribia JA, Darga LL, Reaven GM. Insulin and blood pressure in obesity. Hypertension **7**:702–706, 1985.
17. Bonora E, Zavaroni I, Alpi O, Pezarossa A, Bruschi F, Dall'-Aglio E, Guerra L, Coscelli C, Butturini U. Relationship between blood pressure and plasma in insulin in non-obese and obese non-diabetic subjects. Diabetologia **30**:719–723, 1987.
18. Shen DC, Shieh SM, Fuh MT, Wu DA, Chen YDI, Reaven GM. Resistance to insulin-stimulated-glucose uptake in patients with hypertension. J Clin Endocrinol Metab **66**:580–583, 1988.
19. Facchini F, Ida Chen Y-D, Clinkingbeard C, Jeppesen J, Reaven GM. Insulin resistance, hyperinsulinemia, and dyslipidemia in nonobese individuals with a family history of hypertension. Am J Hypertens **5**:694–699, 1992.
20. Weidmann P, de Courten M, Böhlen L. Insulin resistance, hyperinsulinemia and hypertension. J Hypertension **11**(Suppl 5): S27–S38, 1993.
21. Beatty OL, Harper R, Sheridan B, Atkinson AB, Bell PM. Insulin resistance in offspring of hypertensive parents. Brit Med J **307**:92–96, 1993.
22. Ferrari P, Weidmann P, Shaw SG, Giachino D, Riesen W, Allemann Y, Heynen G. Am J Med **91**:589–596, 1991.
23. Haffner SM, Ferrannini E, Hazuda HP, Stern MP. Clustering of cardiovascular risk factors in confirmed prehypertensive individuals. Hypertension **20**:38–45, 1992.
24. Asch S, Wingard DL, Barrett-Connor EL. Are insulin and hypertension independently related? Ann Epidemiol **1**:231–244, 1991.
25. Muller DC, Elahi D, Pratley RE, Tobin JD, Andres R. An epidemiological test of the hyperinsulinemia-hypertension hypothesis. J Clin Endocrinol Metab **76**:544–548, 1993.
26. Manolio TA, Savage PJ, Burke GL, et al. Association of fasting insulin with blood pressure and lipids in young adults: The CARDIA study. Arteriosclerosis **10**:430–436, 1990.
27. Cambien F, Warnet J-M, Eschwege E, Jacqueson A, Richard JL, Rosselin G. Body mass, blood pressure glucose and lipids: Does plasma insulin explain their relationships? Arteriosclerosis **7**:197–202, 1987.
28. Saad MF, Knowler WC, Pettitt DJ, Nelson RG, Mott DM, Bennett PH. Insulin and hypertension: Relationship to obesity and glucose intolerance in Pima Indians. Diabetes **39**:1430–1435, 1990.
29. Saad MF, Lillioja S, Nyomba BL, Castillo C, Ferraro R, De Gregorio M, Ravussin E, et al. Racial differences in the relation between blood pressure and insulin resistance. N Engl J Med **324**:733–739, 1991.
30. Tomiyama H, Kushiro T, Abeta H, Kurumatani H, Taguchi H, Kuga N, Saito F, Kobayashi F, Otsuka Y, Kanmatsuse K, et al. Blood pressure response to hyperinsulinemia in salt-sensitive and salt-resistant rats. Hypertension **20**:596–600, 1992.
31. Reed MJ, Ho H, Donnelly R, Reaven GM. Salt-sensitive and carbohydrate-sensitive rodent hypertension: Evidence of strain differences. Blood Pressure **3**:197–201, 1994.
32. Hall JE, Brands MW, Kivlighn SD, Mizelle HL, Hildebrandt A, Gaillard CA. Chronic hyperinsulinemia and blood pressure. Hypertension **15**:519–527, 1990.
33. Muntzel MS, Morgan DA, Mark AL, Johnson AK. Intracerebroventricular administration of insulin produces nonuniform regional increases in sympathetic nerve activity. Am J Physiol (in press).
34. Muntzel M, Beltz T, Mark AL, Johnson AK. Anteventral third ventricle lesions abolish lumbar sympathetic responses to insulin. Hypertension **23**(Pt 2):1059–1062, 1994.
35. Steinberg HO, Brechtel G, Johnson A, Fineberg N, Baron AD. Insulin-mediated skeletal muscle vasodilation is nitric oxide dependent: A novel action of insulin to increase nitric oxide release. J Clin Invest **94**:1172–1179, 1994.
36. Frandsen HA, Snitker S, Christensen NJ, Masbad S, Lielsen SL. Effects of insulin on muscle sympathetic nerve activity during euglycemia and hypoglycemia. (abstract) Circulation **84**(Suppl 2):267, 1991.
37. Anderson EAA, Mark AL. The vasodilator action of insulin: Implications for the insulin hypothesis of hypertension. Hypertension **21**:136–141, 1993.
38. Morgan DA, Balon TW, Mark AL. High fructose diet promotes exaggerated sympathetic and pressor responses to hyperinsulinemia in rats (abstract) FASEB J **5**:A1497, 1991.
39. Morgan DA, Mark AL, Ray CA. High fat diet evokes increases

in sympathetic nerve responses to insulin in rats. (abstract) FASEB J **6**:A946, 1992.
40. Baron AD, Brechtel-Hook G, Johnson A, Hardin D. Skeletal muscle blood flow: A possible link between insulin resistance and blood pressure. Hypertension **21**:129–135, 1993.
41. Laakso M, Edelman SV, Brechtel G, Baron AD. Decreased effect of insulin to stimulate skeletal muscle blood flow in obese man: A novel mechanism for insulin resistance. J Clin Invest **85**:1844–1853, 1990.
42. Anderson EA, Gudbjörnsdottir S, Elam M, Sellgren J, Mark AL. Insulin causes vasoconstriction and increases in arterial pressure in obese, insulin resistant hypertensive humans. (abstract) Hypertension **20**:409, 1992.
43. Berne C, Fagius J, Pollare T, Hjemdahl P. The sympathetic response to euglycaemic hyperinsulinaemia. Diabetologia **35**:873–879, 1992.
44. Brands MW, Hildebrandt DA, Mizelle HL, Hall JE. Hypertension during chronic hyperinsulinemia in rats is not salt-sensitive. Hypertension **19**(Suppl 1):83–89, 1992.
45. Brands MW, Garrity CA, Holman MG, Hall JE. Exaggerated pressor and chronotropic response to chronic hyperinsulinemia in SHR versus WKY rats. Am J Hypertens **7**:75–81, 1994.
46. Brands MW, Hildebrandt DA, Mizelle HL, Hall JE. Sustained hyperinsulinemia increases arterial pressure in conscious rats. Am J Physiol **260**:R764–R768, 1991.
47. Hwang I-S, Ho H, Hoffman BB, Reaven GM. Fructose-induced insulin resistance and hypertension in rats. Hypertension **10**:512–516, 1987.
48. Reaven GM, Ho H, Hoffman BB. Somatostatin inhibition of fructose-induced hypertension. Hypertension **14**:117–120, 1989.
49. Jamerson KA, Julius S, Gudbrandsson T, Andersson O, Brant DO. Reflex sympathetic activation induces acute insulin resistance in the human forearm. Hypertension **21**:618–623, 1993.
50. Dubey RK, Zhang YH, Reddy SR, Boegehold MA, Kotchen TA. Am J Physiol **265**(Regulatory Integrative Comp Physiol 34):R726–R732, 1993.
51. Pershadsingh HA, Szollosi J, Benson S, Hyun WG, Feuerstein BG, Kurtz TW. Effect of ciglitazone on blood pressure and intracellular calcium metabolism. Hypertension **21**:1020–1023, 1993.
52. Johnson MD, Zhang HY, Kotchen TA. Sucrose does not raise blood pressure in rats maintained on a low salt intake. Hypertension **21**:779–785, 1993.
53. Morgan DA, Ray CA, Balon TW, Mark AL. Metformin increases insulin sensitivity and lowers arterial pressure in spontaneously hypertensive rats. (abstract) Hypertension **20**:421, 1992.
54. Landin K, Tengborn L, Smith U. Treating insulin resistance in hypertension with metformin reduces both blood pressure and metabolic risk factors. J Intern Med **229**:181–187, 1991.
55. Gudbjörnsdottir S, Fribert P, Elam M, Attvall S, Lonnroth P, Wallin BG. The effect of metformin and insulin on sympathetic nerve activity, norepinephrine spillover and blood pressure in obese, insulin resistant, normoglycemic, hypertensive men. SUP Blood Pressure (in press).
56. Dubey RK, Zhang HY, Reddy SR, Boegehold MA, Kotchen TA. Pioglitazone attenuates hypertension and inhibits growth of renal arteriolar smooth muscle in rats. Am J Physiol **265**(Regulatory Integrative Comp Physiol 34):R726–R732, 1993.
57. Zhang F, Sowers JR, Ram JL, Stanley PR, Peuler JD. Effects of pioglitazone on calcium channels in vascular smooth muscle. Hypertension **24**:170–175, 1994.
58. Zhang HY, Reddy SR, Kotchen TA. Antihypertensive effect of pioglitazone is not invariably associated with increased insulin sensitivity. Hypertension **24**:106–110, 1994.