

## REVIEW ARTICLE

## MECHANISMS OF DISEASE

FRANKLIN H. EPSTEIN, M.D., *Editor***HYPERTENSION AND ASSOCIATED METABOLIC ABNORMALITIES — THE ROLE OF INSULIN RESISTANCE AND THE SYMPATHOADRENAL SYSTEM**GERALD M. REAVEN, M.D., HANS LITHELL, M.D.,  
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**A**BNORMALITIES of glucose, insulin, and lipoprotein metabolism are common in patients with hypertension. These changes can also be discerned in normotensive first-degree relatives of hypertensive patients. They are not present in patients with secondary forms of hypertension, do not necessarily improve when blood pressure is lowered pharmacologically, and may even be made worse by some forms of antihypertensive treatment. These metabolic abnormalities may play a part in both the pathogenesis and the complications of hypertension in many patients. We hypothesize that the metabolic abnormalities are linked to the hypertension by a pathophysiologic process that involves the sympathoadrenal system and exerts both prohypertensive and atherogenic effects. In this review we summarize changes in glucose, insulin, and lipoprotein metabolism in patients with hypertension, examine the role of the sympathoadrenal system in the development of hypertension and the related metabolic changes, and review the metabolic effects of antihypertensive drugs that affect the sympathoadrenal system.

In general, insulin resistance is said to be present when the ability of insulin to stimulate the uptake and disposal of glucose by muscle is impaired. Insulin resistance is common in obesity and non-insulin-dependent diabetes mellitus (NIDDM). In these two conditions, as well as in hypertension, the defect is in the ability of insulin to stimulate the metabolism of glucose by muscle and its storage as glycogen. Insulin resistance need not be global, however; insulin-stimulated glucose disposal in muscle can be decreased, for example, while other effects of insulin are normal.

**GLUCOSE, INSULIN, AND LIPOPROTEINS IN PATIENTS WITH HYPERTENSION**

As a group, patients with hypertension have stronger plasma glucose and insulin responses to an oral glucose

challenge than do matched normotensive subjects.<sup>1,2</sup> Moreover, the pharmacologic reduction of blood pressure does not necessarily restore insulin and glucose concentrations to normal. The abnormalities occur in both obese and nonobese patients.<sup>1,2</sup> The higher plasma concentrations of glucose and insulin in patients with hypertension result from the resistance of peripheral tissue to the action of insulin to stimulate glucose uptake.<sup>1,4</sup> Like hyperinsulinemia, insulin resistance is found in both obese and nonobese patients with hypertension and may still be detected despite effective antihypertensive treatment.<sup>1,2</sup> Furthermore, patients with hypertension tend to have dyslipidemia, with higher plasma triglyceride concentrations and lower concentrations of high-density lipoprotein (HDL) cholesterol than normotensive subjects.<sup>2,5</sup> Rodents with genetic or diet-induced hypertension have similar metabolic changes.<sup>6-9</sup> What do the relations among resistance to insulin-mediated glucose uptake, hyperinsulinemia, and hypertriglyceridemia in patients and rodents with hypertension signify? More specifically, do the metabolic changes play any part in the pathogenesis or the clinical course of patients with hypertension?

**Hypertension and Metabolic Disorders**

Not all patients with hypertension have metabolic abnormalities, and it is not easy to determine how frequently the two are associated. Resistance to insulin-mediated glucose uptake and compensatory hyperinsulinemia are continuous variables, not dichotomous ones, as demonstrated in Figure 1 by the distribution of plasma insulin concentrations two hours after the ingestion of 75 g of glucose in 41 patients with hypertension and 41 normotensive subjects.<sup>10</sup> These hypertensive patients were studied as part of a routine health survey, and the normotensive subjects were participants in the same survey, selected to match the patients with respect to variables such as sex, degree of obesity, ethnic background, type of employment, and level of physical activity. Only 10 percent of the normotensive subjects had two-hour plasma insulin concentrations greater than 80  $\mu$ U per milliliter (480 pmol per liter), as compared with 45 percent of the patients with hypertension. On the basis of these and other findings,<sup>4</sup> at least half of patients with hypertension can be considered to have insulin resistance and hyperinsulinemia. Normotensive first-degree relatives of patients with hypertension also have insulin resistance and dyslipidemia,<sup>11</sup> but patients with secondary forms of hypertension do not.<sup>12</sup> Furthermore, resistance to the effect of insulin on glucose uptake does not necessarily imply resistance to the effects on other insulin-stimulated processes, such as renal tubular reabsorption of sodium.<sup>13</sup>

Because resistance to insulin-mediated glucose disposal and compensatory hyperinsulinemia are common in patients with hypertension, the possibility has been raised that insulin resistance causes the hypertension. Not all hypertensive patients, however, have insulin re-

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sistance and hyperinsulinemia, nor does hypertension occur in all patients with hyperinsulinemia. This is not surprising, since isolated alterations are rarely sufficient to cause hypertension. Patients with insulinomas, for example, do not have a greater prevalence of hypertension than those without insulinomas.<sup>14</sup> In patients with insulinoma, however, hyperinsulinemia is primary, not due to insulin resistance. In such patients, hyperinsulinemia is most evident in the fasting state, plasma insulin concentrations are often only slightly increased, and the increase is relative to a decrease in the plasma glucose concentration. In patients with hypertension, hyperinsulinemia is due to resistance to insulin-mediated glucose disposal, and the increases are both absolute and present throughout the day.

In normal subjects, infusions of insulin that produce plasma insulin concentrations in the physiologic range, along with sufficient glucose to prevent hypoglycemia, cause vasodilation, not increased blood pressure.<sup>15</sup> The relation of these short-term experiments to possible long-term effects of hyperinsulinemia in humans is uncertain, although prolonged insulin infusions in dogs do not increase blood pressure.<sup>16</sup> Racial factors may be important as well. In a recent population study of normotensive subjects, blood pressure and fasting plasma insulin concentrations were significantly correlated in whites, but not in blacks or Pima Indians.<sup>17</sup> On the other hand, blacks with hypertension, as compared with those with normal blood pressure, had insulin resistance and hyperinsulinemia,<sup>18</sup> which suggests a relation between blood pressure and plasma insulin in blacks. Other clinical and experimental evidence also supports such a relation. Insulin infusions in rats increase blood pressure.<sup>19</sup> Furthermore, blood pressure falls when the dose of insulin is decreased in obese, hypertensive patients with NIDDM,<sup>20</sup> and it increases when insulin treatment is begun in patients with NIDDM whose plasma glucose concentrations were poorly controlled with an oral hypoglycemic drug.<sup>21</sup>

It seems reasonable to conclude that abnormalities of glucose, insulin, and lipoprotein metabolism are common in patients with hypertension. Although not all questions have been resolved, and some contradictions remain, the accumulated findings support the possibility that the metabolic changes described play a part in the regulation of blood pressure.

#### METABOLIC ABNORMALITIES AND THE CLINICAL COURSE OF PATIENTS WITH HYPERTENSION

Coronary heart disease and stroke are major causes of morbidity and mortality in patients with hypertension. For reasons that are not entirely clear, the treatment of hypertension has decreased the incidence of stroke more than that of coronary heart disease.<sup>22</sup> One possible explanation for the discrepancy is that the changes in glucose, insulin, and lipoprotein metabolism often associated with hypertension independently increase the risk of coronary heart disease. Because these metabolic factors have not been considered in primary-prevention trials,<sup>22</sup> their presence may have accounted for the poorer results in patients with coronary heart disease as compared with

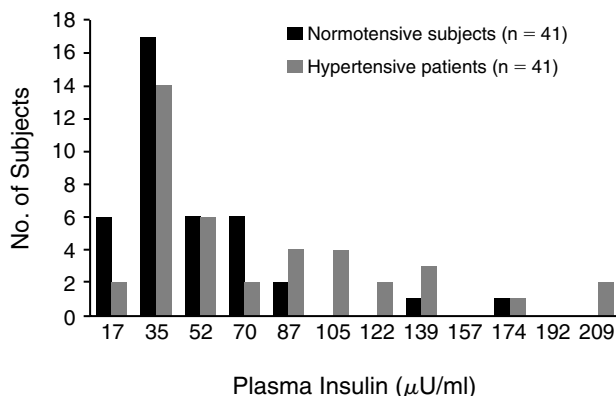


Figure 1. Distribution of Plasma Insulin Concentrations Two Hours after the Oral Administration of Glucose in Hypertensive Patients and Normal Subjects.

To convert plasma insulin values to picomoles per liter, multiply by 6.0. Adapted from Zavaroni et al.<sup>10</sup> with the permission of the publisher.

stroke, because the factors may not have been altered by antihypertensive treatment.

When metabolic risk factors for coronary heart disease are considered, emphasis is usually placed on the part played by a high plasma concentration of low-density lipoprotein (LDL) cholesterol, although coronary heart disease obviously occurs in the absence of hypercholesterolemia.<sup>23</sup> As emphasized previously, patients with hypertension have both resistance to insulin-mediated disposal of glucose and hyperinsulinemia. Although their ability to secrete increased amounts of insulin may prevent them from having overt hyperglycemia, hyperinsulinemia alone is associated with an increased risk of coronary heart disease.<sup>24</sup> Patients with hypertension and electrocardiographic evidence of ischemic heart disease have insulin resistance and hyperinsulinemia, as compared with matched patients with hypertension and normal electrocardiograms.<sup>25</sup> Patients with hypertension tend to have glucose intolerance,<sup>1,2</sup> and among nondiabetic patients with hypertension the risk of coronary heart disease is higher in those with the highest plasma glucose concentrations after the ingestion of glucose.<sup>24,26</sup>

#### Dyslipidemia and Coronary Heart Disease

Dyslipidemia characterized by high plasma concentrations of triglyceride and low concentrations of HDL cholesterol may be an important element in the linkage between hypertension and coronary heart disease.<sup>2,5</sup> The importance of hypertriglyceridemia as a risk factor for coronary heart disease should not be discounted.<sup>27</sup> The combination of high plasma triglyceride and low HDL cholesterol concentrations is a particularly potent risk factor for coronary heart disease<sup>27</sup> and is associated with hyperinsulinemia.<sup>28</sup> In addition, patients with hypertriglyceridemia tend to have both smaller, denser LDL particles than normal subjects,<sup>29</sup> as well as greater postprandial lipemia<sup>30</sup>; both changes increase the risk of coronary heart disease. Finally, there is a direct relation between that disease and plasma concentrations of

triglyceride and plasminogen-activator inhibitor type 1.<sup>31</sup> Thus, there are multiple abnormalities associated with hyperinsulinemia in patients with hypertension that increase the risk of coronary heart disease.

### INSULIN RESISTANCE, SYMPATHOADRENAL ACTIVITY, AND HYPERTENSION

How might the metabolic abnormalities and hypertension be related? Studies of the relation between dietary intake and sympathetic nervous system activity and of the pathogenesis of obesity-related hypertension suggest the involvement of the sympathetic nervous system.

#### Diet and Sympathetic Nervous System Activity

In laboratory animals, food intake increases sympathetic activity and fasting decreases it, according to studies of norepinephrine turnover.<sup>32,33</sup> Similar diet-induced changes in sympathetic activity occur in humans.<sup>34</sup> The increased intake is principally related to the intake of carbohydrate and fat.<sup>35-37</sup>

#### Role of Insulin

Because diet influences sympathetic activity and that activity is begun within the central nervous system, the

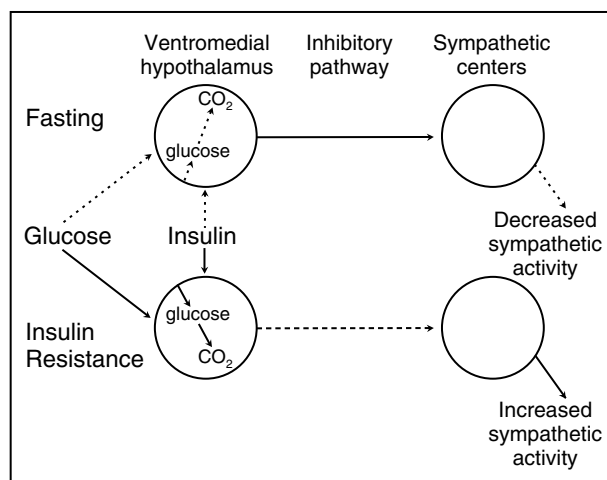


Figure 2. Roles of Insulin and Glucose in Regulating Central Sympathetic Activity.

During fasting, the small decline in the plasma glucose concentration and the larger decrease in the plasma insulin concentration (dotted lines) result in diminished insulin-mediated uptake and metabolism of glucose to carbon dioxide (CO<sub>2</sub>) by insulin-sensitive cells in the ventromedial hypothalamus. The decreased glucose metabolism stimulates the activity of an inhibitory pathway between the hypothalamus and the brain stem, suppressing tonically active sympathetic centers in the brain stem and decreasing central sympathetic activity. Conversely, in the postprandial or insulin-resistant state, the increase in plasma glucose and the greater increase in plasma insulin stimulate insulin-mediated uptake and metabolism of glucose by the hypothalamic cells. The increase in glucose metabolism diminishes the activity of the inhibitory pathway, disinhibiting tonically active brain-stem centers and increasing central sympathetic activity. Solid lines indicate increased activity, and dotted lines indicate suppressed activity. Adapted from Landsberg and Young with the permission of the publisher.<sup>38</sup>

latter must have mechanisms for assessing dietary intake and initiating the appropriate changes in sympathetic outflow. One factor involved in the relation between diet and the sympathetic nervous system is insulin.<sup>38</sup> In the model shown in Figure 2, insulin stimulates the uptake and metabolism of glucose in regulatory cells anatomically related to the ventromedial nucleus of the hypothalamus.<sup>39</sup> Glucose uptake and metabolism in these neurons suppress an inhibitory pathway between the regulatory cells and the brain stem. As a consequence, tonically active sympathetic regulatory centers in the brain stem are disinhibited, and sympathetic activity increases.

#### Dietary Thermogenesis

The sympathetic nervous system is critically involved in regulating adaptive thermogenesis, the homeostatic alteration in the metabolic rate that occurs in response to exposure to cold (nonshivering thermogenesis) or changes in dietary intake (dietary thermogenesis).<sup>40</sup> The physiologic role of diet-induced changes in sympathetic activity relates to the regulation of dietary thermogenesis. Fasting is associated with a decrease in sympathetically mediated thermogenesis, and overfeeding is associated with an increase. This mechanism, which involves insulin and the sympathetic nervous system, establishes a link between dietary intake and energy expenditure, represented by the lower pathway in Figure 2; the increase in sympathetic activity leads to increased energy expenditure. This relation would conserve calories during periods of fasting and would permit the dissipation of calories taken in excess, thereby increasing the range of dietary intake over which energy balance might be achieved. Insulin, therefore, plays a critical part in linking dietary intake with sympathetically mediated energy production.

### OBESITY-RELATED HYPERTENSION

Additional evidence suggestive of a role for the sympathetic nervous system in the relation between insulin and hypertension is drawn from studies of obesity-related hypertension. Insulin resistance and hyperinsulinemia are more severe and more closely associated with hypertension in obese patients than in nonobese patients,<sup>41-46</sup> although there is considerable variation according to race and ethnic group in this linkage.<sup>17</sup> Figure 3 shows a possible scheme linking insulin and hypertension in obese patients.<sup>47</sup> According to this formulation, hyperinsulinemia, a consequence of insulin resistance, stimulates the sympathetic nervous system, increasing sympathetically mediated thermogenesis and reestablishing energy balance. The increase in sympathetic nervous system activity, however, also contributes to hypertension by stimulating the heart, the vasculature, and the kidneys. Obesity-related hypertension may therefore be the unwanted byproduct of mechanisms to restore energy balance and stabilize body weight.

In a population-based cohort followed as part of the Normative Aging Study in Boston, sympathetic nervous system activity, as assessed by measuring 24-hour

urinary excretion of norepinephrine, correlated with the body-mass index and was elevated in subjects with hyperinsulinemia.<sup>48</sup> Obese subjects, moreover, do not have resistance to the effect of insulin on the sympathetic nervous system, as demonstrated by increases in plasma norepinephrine concentrations during studies using euglycemic-hyperinsulinemic clamping<sup>49</sup>; despite a marked decrease in insulin-mediated whole-body uptake of glucose, plasma norepinephrine responses in these subjects were similar to those in lean subjects. The findings were consistent, therefore, with the hypothesis that sympathetic stimulation is mediated by insulin in obese subjects.

### INSULIN AND SYMPATHETIC ACTIVITY IN HYPERTENSION

Both the plasma insulin concentration and urinary norepinephrine excretion were significantly correlated with blood pressure in the Normative Aging Study.<sup>50</sup> Among the subjects below the 50th percentile with respect to both urinary norepinephrine excretion and the plasma insulin concentration two hours after stimulation with glucose, only 15 percent had hypertension, whereas 37 percent of subjects above the 50th percentile for both variables had hypertension.<sup>50</sup> The association of plasma insulin and urinary norepinephrine excretion with blood pressure in that study persisted after adjustment for other variables, such as the body-mass index and the distribution of body fat, and there was a positive interaction between hypertension and both plasma insulin and urinary norepinephrine. These findings suggest that the sympathetic nervous system is the link between insulin and blood pressure.

Alternatively, the association of insulin resistance with hypertension could result from a primary increase in sympathetic nervous system activity.<sup>51</sup> Increases in such activity induced by reflexes antagonize insulin-mediated uptake of glucose in the forearm of humans.<sup>52</sup> Although a primary increase in sympathetic activity might cause both hypertension and insulin resistance, studies in animals indicate that insulin resistance induced by a high-fat diet occurs before the onset of hypertension,<sup>53</sup> an observation consistent with the primacy of insulin-mediated stimulation of the sympathetic nervous system. Further evidence in support of insulin-mediated sympathetic stimulation comes from experiments with somatostatin. This hormone, which inhibits the endogenous secretion of insulin, reduces plasma norepinephrine concentrations<sup>54</sup> and lowers blood pres-

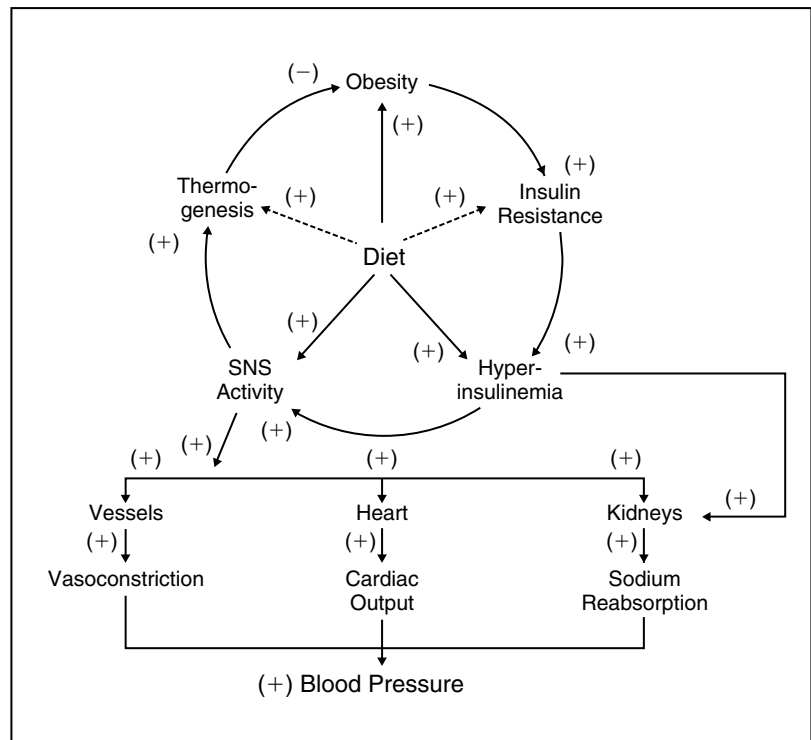


Figure 3. Hypothetical Relation between Insulin and Blood Pressure in Patients with Obesity-Related Hypertension.

Insulin resistance may be viewed as a physiologic mechanism to restore energy balance. Sympathetic stimulation, a consequence of insulin resistance and hyperinsulinemia, drives sympathetically mediated thermogenesis and increases the metabolic rate. The steady-state hyperinsulinemia, acting at the level of the kidney, and the consequent sympathetic stimulation of the vasculature, heart, and kidneys result in hypertension. Plus signs denote positive or stimulatory effects, the minus sign a negative or inhibitory effect, and the dotted line the direct effects of food on insulin resistance and metabolic rate. Adapted from Landsberg<sup>47</sup> with the permission of the publisher.

sure<sup>55</sup> in patients with hyperinsulinemia. Moreover, pharmacologic suppression of sympathetic nervous system activity with guanadrel, an adrenergic-antagonist drug, did not reduce insulin resistance in one study of hypertensive patients.<sup>54</sup>

### Insulin Resistance in Nonobese Patients with Hypertension

In obese subjects, insulin resistance and hyperinsulinemia result from increased fat mass. The cause of insulin resistance in nonobese patients with hypertension is unknown. The fact that insulin resistance is found among normotensive relatives of hypertensive patients implies that the predisposition to insulin resistance is inherited. In the Normative Aging Study, intake of saturated fat was directly related to fasting and plasma insulin concentrations measured after stimulation with glucose,<sup>56</sup> suggesting that dietary factors are also involved in the pathogenesis of insulin resistance. Non-pharmacologic interventions such as caloric restriction,<sup>57</sup> weight loss,<sup>58</sup> and exercise,<sup>59</sup> all of which decrease insulin resistance, reduce sympathetic nervous system activity and blood pressure in parallel.<sup>60</sup> These observations are consistent with, but do not prove, a causal role

for insulin resistance and sympathetic nervous system activity in the pathogenesis of hypertension.

#### Vasodilator Actions of Insulin

As has been noted, insulin has direct vasodilator actions<sup>15</sup> that confound the relation between insulin and hypertension. Insulin infusions in dogs<sup>61</sup> and humans<sup>62</sup> have a vasodepressor action that, at least in humans, is partly offset by sympathetic nervous system stimulation. Because insulin is a direct vasodilator, the imposition of other physiologic mechanisms is clearly required if insulin is to have a causal role in the pathogenesis of hypertension. The sympathetic nervous system, as well as other currently undefined components of the insulin-resistant state, may antagonize the normal vasodilative effects of insulin in obese patients and those with hypertension.

#### Dyslipidemia

Diminished activity of the adrenal medulla, as well as hyperinsulinemia,<sup>28</sup> may play a part in the dyslipidemia associated with the insulin resistance. In the Normative Aging Study, not only plasma insulin concentrations after glucose stimulation but also urinary excretion of epinephrine, a marker of adrenal medullary activity, were related to plasma concentrations of HDL cholesterol and triglyceride.<sup>63</sup> Increasing urinary excretion of epinephrine was associated with decreasing plasma concentrations of triglyceride and increasing plasma concentrations of HDL cholesterol (Fig. 4). These rela-

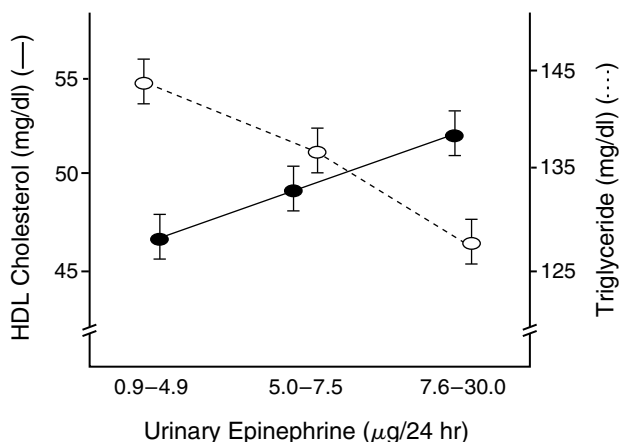


Figure 4. Relation between Urinary Excretion of Epinephrine (a Measure of Adrenal Medullary Activity) and Plasma Concentrations of HDL Cholesterol and Triglyceride in 572 Subjects Followed in the Normative Aging Study.

Mean ( $\pm$ SE) values are shown. Plasma HDL cholesterol concentrations increased, and plasma triglyceride concentrations decreased, with increasing urinary excretion of epinephrine. The subjects with values for urinary epinephrine excretion in the lowest third of the range had the lowest plasma HDL cholesterol concentrations and the highest plasma triglyceride concentrations. To convert values for HDL cholesterol to micromoles per liter, multiply by 0.026; to convert values for triglycerides to micromoles per liter, multiply by 0.011; and to convert values for epinephrine to nanomoles per day, multiply by 5.46. Data were obtained from Ward et al.<sup>63</sup>

tions remained statistically significant after adjustment for total body fat, distribution of body fat, and the plasma insulin concentration.<sup>63</sup> Therefore, adrenal medullary activity, which decreases rather than increases with obesity,<sup>48,64</sup> contributes to dyslipidemia by exerting effects on lipid metabolism that are independent of those exerted by insulin.

#### EFFECTS OF ANTIHYPERTENSIVE DRUGS ON THE SYMPATHETIC NERVOUS SYSTEM

The discovery that treatment with  $\beta$ -adrenergic antagonists, as well as treatment with diuretic agents, is associated with an increased risk of NIDDM<sup>65-68</sup> led to the hypothesis that  $\beta$ -adrenergic antagonists may impair insulin-stimulated uptake of glucose in peripheral tissues. The metabolic effects of antihypertensive drugs have now been evaluated systematically.

#### $\beta$ -Adrenergic Antagonists

Propranolol is a nonselective  $\beta$ -adrenergic antagonist with no intrinsic sympathetic activity. In studies using the hyperinsulinemic-euglycemic clamp technique, glucose uptake in peripheral tissue decreased by 32 percent in propranolol-treated patients.<sup>69</sup> Two nonselective  $\beta$ -adrenergic antagonists with intrinsic sympathetic activity, pindolol and dilevalol, have different effects. With pindolol, glucose uptake diminished by 17 percent,<sup>69</sup> whereas dilevalol, which has more pronounced  $\beta_2$ -agonist action, did not alter insulin sensitivity.<sup>70</sup> Selective  $\beta$ -adrenergic antagonists such as atenolol and metoprolol decrease glucose uptake by about 25 percent.<sup>71,72</sup> The decrease in sensitivity to insulin is associated with increases in plasma concentrations of insulin and glucose after the ingestion of glucose. The increase in plasma insulin concentrations compensates for the worsening of insulin resistance, and the increase in the glucose concentration indicates that the compensation is not fully effective.

#### $\alpha_1$ -Adrenergic Antagonists

Other antihypertensive agents that affect the peripheral sympathetic nervous system include those with  $\alpha_1$ -adrenergic-antagonist actions. Both prazosin and doxazosin increase sensitivity to insulin,<sup>72-75</sup> with a greater effect among the patients with the most insulin resistance.<sup>75</sup> In patients treated with these drugs, insulin resistance improves and the associated hyperinsulinemia and hyperglycemia after glucose stimulation decrease.

#### Blood Flow

Stimulation of the peripheral uptake of glucose by insulin is strongly correlated with increased peripheral blood flow.<sup>76</sup> One explanation for the differing effects of various  $\beta$ -adrenergic antagonists on the action of insulin may be their different effects on blood flow to the large muscle groups in the legs. With blockade of  $\beta_1$ -adrenergic receptors, cardiac output decreases and compensatory vasoconstriction occurs. In a patient receiving a drug with a simultaneous agonistic effect on  $\beta_2$ -adrenergic receptors in the vessel wall, such as pindolol or dilevalol,

vasodilation predominates over the reflex vasoconstriction.

The microvasculature is an important determinant of the capacity for blood flow.<sup>77</sup> Patients with hypertension who have a low capillary density in skeletal muscle may have more pronounced reductions in nutritional blood flow during vasoconstriction. This suggestion is supported by the substantial correlation between capillary density and metabolic response during  $\beta$ -adrenergic blockade; patients with low capillary density had the greatest increases in plasma concentrations of insulin and triglyceride.<sup>78</sup>

#### Other Antihypertensive Drugs

Other classes of antihypertensive drugs do not affect the sympathetic nervous system directly. Although captopril increases insulin sensitivity, angiotensin-converting-enzyme inhibitors as a class do not seem to have this effect. The increases in insulin resistance that occur in patients treated with other antihypertensive drugs may result from activation of the sympathetic nervous system due to vasodilation. For example, patients treated with the short-acting drug nifedipine had increased insulin resistance that correlated with their increased heart rates<sup>79</sup>; the slow release of nifedipine did not affect either insulin resistance or heart rate.<sup>80</sup>

### EFFECTS OF ANTIHYPERTENSIVE DRUGS ON LIPOPROTEIN METABOLISM

#### $\beta$ -Adrenergic Antagonists

The intrinsic sympathetic activity of  $\beta$ -adrenergic antagonists determines the effects of these drugs not only on insulin resistance but also on plasma triglyceride concentrations. Treatment with propranolol (which has no intrinsic sympathetic activity) was associated with a 25 percent increase in plasma triglyceride concentrations.<sup>69</sup> Pindolol (which has intrinsic sympathetic activity) had no effect,<sup>69</sup> whereas dilevalol (which has pronounced intrinsic sympathetic activity) decreased plasma triglyceride concentrations by 22 percent.

Adrenergic-receptor selectivity does not have a major role with respect to plasma lipid concentrations. With atenolol and metoprolol, which are selective  $\beta$ -adrenergic antagonists, plasma triglyceride concentrations increased by about 20 and 30 percent, respectively, effects similar to that of propranolol.<sup>71,72</sup>

During treatment with propranolol, pindolol, atenolol, or metoprolol, plasma concentrations of free fatty acids decrease, indicating inhibition of lipolysis. This decrease would be expected to lower plasma triglyceride concentrations, because fatty acids promote the hepatic synthesis of very-low-density lipoproteins.<sup>81</sup> The

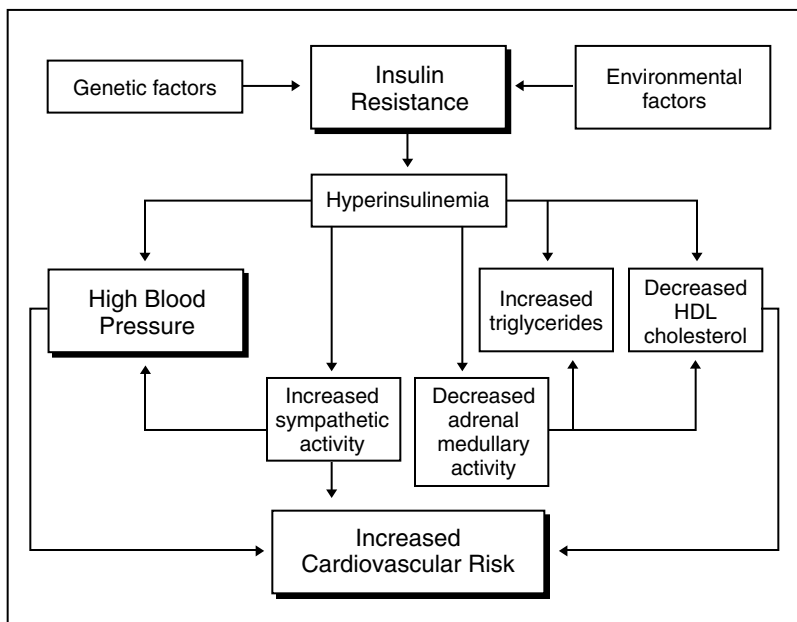


Figure 5. Postulated Relations among Insulin Resistance, High Blood Pressure, and Increased Cardiovascular Risk.

The sympathetic nervous system and adrenal medulla are the effector links between insulin resistance and hypertension and cardiovascular disease.

increased plasma triglyceride concentrations during beta-blockade are thus mediated by changes in lipoprotein lipase.

The action of lipoprotein lipase is exerted in the lumen of the small vessels to which the lipase molecules are attached. The enzyme is synthesized in muscle cells and adipocytes, and its secretion by these cells is regulated hormonally. Epinephrine stimulates the synthesis of lipoprotein lipase in rat heart cells,<sup>82</sup> and there is evidence that epinephrine increases lipoprotein lipase<sup>83</sup> and triglyceride metabolism<sup>63</sup> in humans. The effect of epinephrine on triglyceride metabolism may be mediated in at least two ways: by the direct stimulation of lipoprotein lipase synthesis and by vasodilation in muscle mediated by  $\beta_2$ -adrenergic receptors. Nonselective  $\beta$ -adrenergic antagonists block these triglyceride-lowering actions of epinephrine. It seems likely, therefore, that the increase in plasma triglyceride concentrations that occurs during therapy with propranolol is due to a decrease in the activity of lipoprotein lipase in skeletal muscle.<sup>69</sup> A reduction of cardiac output and blood flow during such therapy would further reduce the availability of lipoprotein lipase for triglyceride hydrolysis.

#### $\alpha_1$ -Adrenergic Antagonists

During therapy with  $\alpha_1$ -adrenergic antagonists, plasma triglyceride concentrations decrease by about 20 percent.<sup>74,75</sup> In addition, the lipoprotein pattern changes. Plasma concentrations of very-low-density lipoproteins decrease, the composition of LDL particles changes so they become less triglyceride-rich, and HDL cholesterol may increase, in a manner consistent with an increased clearance of triglyceride-rich lipoproteins. During dox-

azosin treatment, in fact, when lipoprotein lipase activity is tested after an injection of heparin, an increase is observed, even though there is no increase in the attachment of lipoprotein to endothelium in adipose tissue and skeletal muscle.<sup>84</sup> Therefore, the improvement in both insulin resistance and lipoprotein metabolism that occurs in patients treated with  $\alpha_1$ -adrenergic antagonists probably results from the vasodilation caused by  $\alpha_1$ -adrenergic blockade. The reduction in plasma triglyceride concentrations and the improvement in insulin resistance are correlated,<sup>75</sup> which indicates that they may have a common cause; vasoconstriction may be a basic mechanism for the insulin resistance syndrome, which is improved during treatment with vasodilator agents.

### CONCLUSIONS

The relations postulated to exist among resistance to insulin-mediated glucose disposal, compensatory hyperinsulinemia, and hypertension,<sup>85</sup> all of which lead to an increased cardiovascular risk, are shown in Figure 5. According to this hypothesis, insulin resistance and compensatory hyperinsulinemia are primary events, and enhanced sympathetic activity and diminished adrenal medullary activity are important links between the defect in insulin action and the development of hypertension and the associated metabolic abnormalities. To be sure, hypertension does not develop in all subjects with insulin resistance, and not all hypertensive patients have insulin resistance and hyperinsulinemia; nor do the other changes often associated with insulin resistance and compensatory hyperinsulinemia appear in every subject with these defects in insulin action. Still, these caveats should not detract from the possibility that insulin resistance, and compensatory hyperinsulinemia have major roles in the regulation of blood pressure in susceptible subjects predisposed to hypertension by heredity or environmental factors.

This group of metabolic abnormalities suggests that in the treatment of hypertension, nonpharmacologic interventions that increase sensitivity to insulin, including weight reduction, low-fat diet, and increased physical activity, have a primary role. When pharmacologic treatment is required, a case can be made for drugs that improve insulin sensitivity and the attendant profile of risk factors for coronary heart disease, as well as lower blood pressure.

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