Insulin Resistance

A Multifaceted Syndrome Responsible for NIDDM, Obesity, Hypertension, Dyslipidemia, and Atherosclerotic Cardiovascular Disease

Ralph A. DeFronzo, MD
Eleuterio Ferrannini, MD

Diabetes mellitus is commonly associated with systolic/diastolic hypertension, and a wealth of epidemiological data suggest that this association is independent of age and obesity. Much evidence indicates that the link between diabetes and essential hypertension is hyperinsulinemia. Thus, when hypertensive patients, whether obese or of normal body weight, are compared with age- and weight-matched normotensive control subjects, a heightened plasma insulin response to a glucose challenge is consistently found. A state of cellular resistance to insulin action subtends the observed hyperinsulinism. With the insulin/glucose-clamp technique, in combination with tracer glucose infusion and indirect calorimetry, it has been demonstrated that the insulin resistance of essential hypertension is located in peripheral tissues (muscle), is limited to nonoxidative pathways of glucose disposal (glycogen synthesis), and correlates directly with the severity of hypertension. The reasons for the association of insulin resistance and essential hypertension can be sought in at least four general types of mechanisms: Na^+ retention, sympathetic nervous system overactivity, disturbed membrane ion transport, and proliferation of vascular smooth muscle cells. Physiological maneuvers, such as calorie restriction (in the overweight patient) and regular physical exercise, can improve tissue sensitivity to insulin; evidence indicates that these maneuvers can also lower blood pressure in both normotensive and hypertensive individuals. Insulin resistance and hyperinsulinemia are also associated with an atherogenic plasma lipid profile. Elevated plasma insulin concentrations enhance very-low-density lipoprotein (VLDL) synthesis, leading to hypertriglyceridemia. Progressive elimination of lipid and apolipoproteins from the VLDL particle leads to an increased formation of intermediate-density and low-density lipoproteins, both of which are atherogenic. Last, insulin, independent of its effects on blood pressure and plasma lipids, is known to be atherogenic. The hormone enhances cholesterol transport into arteriolar smooth muscle cells and increases endogenous lipid synthesis by these cells. Insulin also stimulates the proliferation of arteriolar smooth muscle cells, augments collagen synthesis in the vascular wall, increases the formation of and decreases the regression of lipid plaques, and stimulates the production of various growth factors. In summary, insulin resistance appears to be a syndrome that is associated with a clustering of metabolic disorders, including non-insulin-dependent diabetes mellitus, obesity, hypertension, lipid abnormalities, and atherosclerotic cardiovascular disease. ***Diabetes Care*** **14:173–94, 1991**

Obesity, non-insulin-dependent diabetes mellitus (NIDDM), hypertension, and atherosclerotic cardiovascular disease (ASCVD) are common metabolic disorders that afflict the majority of individuals who live in westernized societies. Moreover, all of these common medical disorders occur with increasing incidence as the population ages (1–3). In young individuals, obesity, NIDDM, hypertension, and ASCVD are uncommon. However, by 70 yr of age, the incidence of these metabolic disorders reaches epidemic proportions (Table 1). Over half of such elderly individuals have evidence of ASCVD (2), and 45–50% are obese and hypertensive (1). The incidence of NIDDM is somewhat lower (~10–12%; 3), although in some

From the Diabetes Division, Department of Medicine, University of Texas Health Science Center, San Antonio, Texas; and the Metabolism Unit, Center National Research Institute of Clinical Physiology, 2nd Medical Clinic, University of Pisa, Pisa, Italy.

Address correspondence and reprint requests to Ralph A. DeFronzo, MD, Chief, Diabetes Division, Department of Medicine, University of Texas Health Science Center, 7703 Floyd Curl Drive, San Antonio, TX 78284-7886.

TABLE 1
Age-related prevalence of non-insulin-dependent diabetes mellitus, obesity, essential hypertension, and atherosclerotic cardiovascular disease in general population

	Overall prevalence (%)	Age-related prevalence (%)	
		20 yr	70 yr
Non-insulin-dependent diabetes mellitus	~7	<1	~10
Obesity	~30	~5	~50
Essential hypertension	~20	~5	~50
Atherosclerotic cardiovascular disease*	~25	<1	~50

*Refs. 1–3.

populations it is much higher (4,5). Because obesity, NIDDM, hypertension, and ASCVD occur frequently in the population at large, it is not surprising that any given individual, especially if he or she is >60–70 yr of age, might manifest two or more of these common medical problems. In the subsequent discussion, we provide evidence that the common occurrence of the pentad—obesity, NIDDM, hypertension, ASCVD, and dyslipidemia—in the same individual is more than a chance occurrence and is related in part to a gene or set of genes for insulin resistance (Table 2). Moreover, it is now recognized that this pentad is commonly associated with hyperinsulinemia (6) and a specific abnormal lipid profile, i.e., elevated plasma triglycerides (7), low high-density lipoprotein cholesterol (HDL-chol) (8), and increased low-density lipoprotein cholesterol (LDL-chol; 9), all of which can predispose to the development of atherosclerosis (Table 2). In the following sections, we review a considerable amount of published data that suggest that insulin resistance, with its compensatory hyperinsulinemia and associated lipid abnormalities, is etiologically related to the high prevalence of NIDDM, obesity, hypertension, and ASCVD in the general population.

OBESITY AND NIDDM: WHAT DO THEY SHARE IN COMMON?

When a nondiabetic person consumes excessive calories and gains weight, the body becomes markedly resistant to the action of insulin (10). With the euglycemic insulin-clamp technique (11), many investigators have shown that tissue sensitivity to insulin declines by ~30–40% when an individual becomes >35–40% over ideal body weight (12–16). The insulin resistance primarily affects muscle (14,17,18) and involves both the oxidative and nonoxidative pathways of glucose disposal (13,14,16,18). Despite the severe impairment in insulin action, however, glucose tolerance remains normal because the pancreatic β-cells are able to augment their insulin secretory capacity to offset the insulin resistance (14,18,19; Fig. 1). The net result is a well-compensated metabolic state in which the insulin resistance is closely counterbalanced by an increase in insulin secretion such that glucose tolerance remains normal or only slightly impaired. The trade-off is hyperinsulinemia. With advancing duration of obesity or with further weight gain, the excessive rates of insulin secretion cannot be maintained. Because of the presence of severe insulin resistance, even the slightest decline in insulin secretion will lead to the development of frank diabetes mellitus (Fig. 1). Nonetheless, both the fasting and meal-stimulated plasma insulin levels remain 1.5- to 2-fold elevated compared with age-matched and weight-matched control subjects (14,18–24). Only much later in the natural history of obesity and diabetes do we see a significant decline in insulin secretion. At this stage, plasma insulin levels return to or below normal, and severe glucose intolerance ensues. The sequence of events for obese/diabetic individuals has been confirmed by a prospective follow-up of the same subjects who were subsequently restudied 10 yr later (25; Fig. 1). Similar results have been published by Saad et al. (20) in a prospective study carried out in Pima Indians. It is important to underscore, however, that, during most of his/her lifetime, the obese person—whether he/she maintains normal glucose tolerance, becomes glucose intolerant, or develops frank diabetes—will be exposed to a persistent state of hyperinsulinemia.

Normal-weight NIDDM individuals are also characterized by insulin resistance (14,18,21,26–30). However, as opposed to obesity, where the defect in insulin action is acquired (10), the insulin resistance is genetically transmitted in NIDDM. In identical twins and in the offspring of two diabetic parents, the incidence of diabetes ranges from 70 to 90% (31–33), whereas in first-degree relatives, the incidence of diabetes is 30–40% (34,35).

The severity of the insulin resistance in NIDDM is of similar magnitude to that observed in nondiabetic obese subjects and involves both the oxidative and nonoxidative (glycogen synthesis) pathways of glucose disposal (14–16,18,19,29,30; Fig. 2). Thus, from the standpoint of insulin action, it is difficult to distinguish between the nondiabetic obese individual and the normal-weight NIDDM person. What distinguishes the two groups is the plasma insulin concentration. In normal-weight NIDDM patients, the plasma insulin response, although elevated compared with the normal-weight control sub-

TABLE 2
Syndrome of insulin resistance

Obesity
Non-insulin-dependent diabetes mellitus
Hypertension
Atherosclerotic cardiovascular disease
Dyslipidemia
Hyperinsulinemia

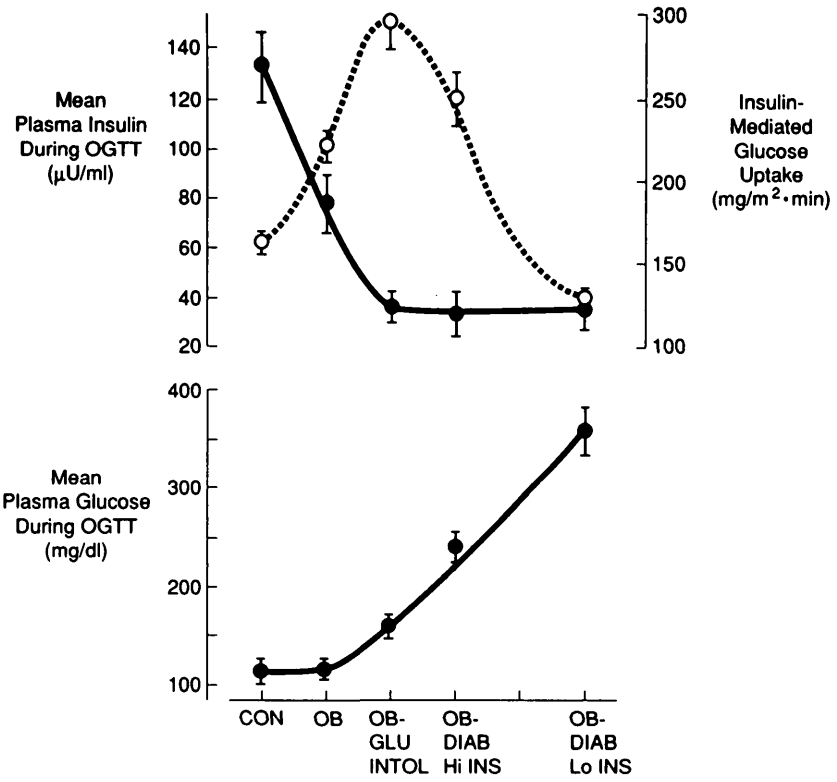

FIG. 1. Summary of plasma glucose (●) and insulin (○) responses during 100-g oral glucose tolerance test (OGTT) and tissue sensitivity to insulin (*top*) in control (CON), obese (OB) nondiabetic, OB glucose-intolerant (OB-GLUINTOL), OB hyperinsulinemic (Hi INS) diabetic (DIAB), and OB hypoinsulinemic (Lo INS) DIAB subjects. From DeFronzo (18). © 1988 by the American Diabetes Association.

jects, is significantly decreased compared with the nondiabetic obese subjects, despite a similar degree of insulin resistance. Early in the evolution of NIDDM, all subjects are hyperinsulinemic, both in the fasting state and in response to insulin (14,18–24,36; Fig. 3). In a group of 77 normal-weight NIDDM patients, both the fasting and glucose-stimulated plasma insulin concentrations rose progressively as fasting plasma glucose increased from 4.4 to 6.6 mM (18,36). Thereafter, the augmented rate of insulin secretion could not be maintained, and there was a progressive decline in both the fasting and glucose-stimulated plasma insulin concentrations. Nonetheless, up to fasting glucose levels of 8.8–10 mM (i.e., moderately severe diabetes), diabetic patients remained hyperinsulinemic compared with normal-weight control subjects even though they were less hyperinsulinemic than nondiabetic obese subjects (Figs. 1 and 3).

From the above discussion, the scenario outlined in Fig. 4 can be constructed. Insulin resistance is a characteristic feature of both obesity and NIDDM. In the former, it is acquired due to excessive calorie intake, whereas in the latter, the diabetic patient inherits a gene or set of genes that confer insulin resistance. The normal β-cell is able to recognize the presence of insulin resistance and to augment its secretion of insulin. In the obese nondiabetic person, the compensatory response is nearly perfect, and no alteration in glucose tolerance ensues. In the diabetic individual, the β-cell response is less than perfect, and glucose intolerance ensues. In both groups, however, day-long hyperinsulinemia is present. Only in the severely diabetic patient (fasting plasma glucose concentration >10–11 mM) does insulinopenia develop. There is now mounting evidence that persistently elevated plasma insulin levels can contribute to the development of hypertension, plasma lipid abnormalities, and atherosclerosis. These associations will be discussed at length subsequently.

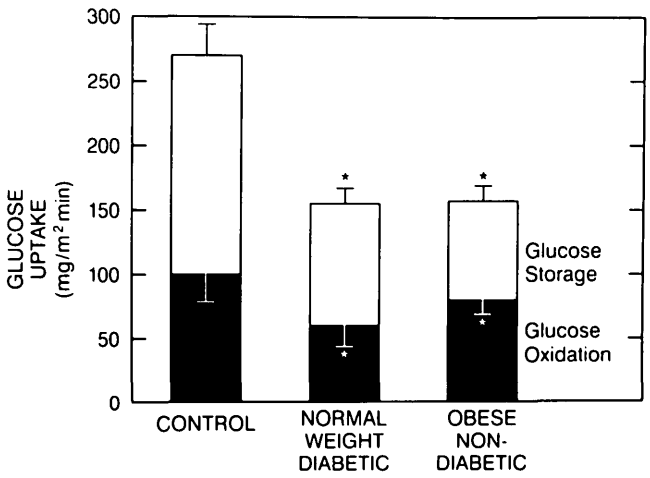

FIG. 2. Insulin-mediated rates (euglycemic insulin-clamp technique) of whole-body glucose uptake (total height of bar), glucose oxidation, and nonoxidative glucose disposal (glycogen synthesis) in control, normal-weight diabetic, and obese nondiabetic subjects. *$P < 0.01$ vs. control. From DeFronzo (18). © 1988 by the American Diabetes Association.

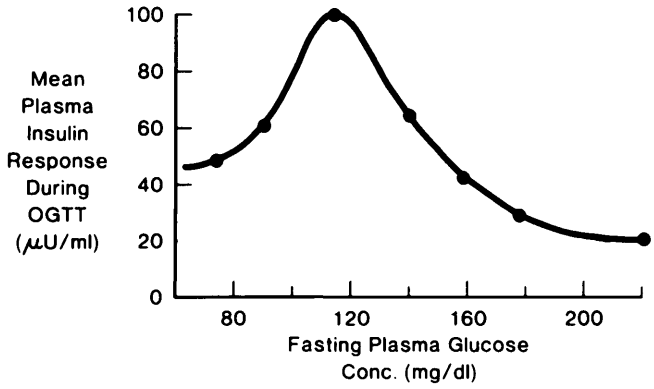

FIG. 3. Starling's curve of pancreas–plasma insulin response during oral glucose tolerance test (OGTT). In normal-weight patients with impaired glucose tolerance and mild diabetes, plasma insulin response to ingested glucose increases progressively until fasting glucose concentration reaches 120 mg/dl. Thereafter, further increases in fasting glucose level are associated with progressive decline in insulin secretion. However, even diabetic patients with moderate fasting hyperglycemia (120–160 mg/dl) maintain hyperinsulinemic response to glucose challenge. Insulinopenic response is not observed until fasting plasma glucose concentration exceeds 180–200 mg/dl. Same curve depicts relationship between fasting plasma insulin and glucose concentrations. From DeFronzo (18). © 1988 by the American Diabetes Association.

In summary, the results reviewed in this section clearly demonstrate that insulin resistance is a characteristic feature of both obesity and NIDDM, involves the pathways of glucose oxidation and nonoxidative glucose disposal, and is compensated for, at least in part, by augmented insulin secretion by the pancreas.

HYPERTENSION, OBESITY, AND DIABETES: COMMON METABOLIC DEFECT?

For many years, it has been recognized that hypertension is very common in obese (1,37,38) and diabetic (1,39–41) individuals. It is also known that weight loss (42–46) and physical training (47–50), interventions that improve the body's sensitivity to insulin (12,51–56), are effective in lowering the blood pressure in obese and diabetic patients. Moreover, the improvement in insulin sensitivity and resultant lowering of the elevated plasma insulin concentration are closely related to the decline in systolic/diastolic blood pressure in nondiabetic obese subjects (12,52). Similar observations have been made by Krotkiewski et al. (48), who demonstrated that after a chronic physical training program, both systolic and diastolic blood pressure fell, even though body weight remained unchanged. Significant decreases in blood pressure were observed only in obese subjects with elevated fasting plasma insulin concentrations and correlated closely with the decline in fasting plasma insulin levels (48). Several prospective epidemiological studies have also shown that the fasting plasma insulin concentration is closely related to the elevation in blood pressure in obese and diabetic subjects (57–63).

Based on the above observations, Manicardi et al. (64) examined the relationship between blood pressure and oral glucose tolerance in age-matched obese hypertensive (174/104 mmHg) and obese normotensive (124/80 mmHg) individuals. Compared with the normotensive group, the obese hypertensive subjects were glucose intolerant, despite a plasma insulin response that was approximately threefold greater (Fig. 5). These results strongly suggest the presence of insulin resistance in the obese hypertensive group. Most important, the plasma insulin response during the oral glucose tolerance test was strongly correlated ($r = 0.75$, $P < 0.001$) to the elevated systolic/diastolic blood pressure in the obese hypertensive group; no correlation between blood pressure and insulin was observed in the normotensive group. As discussed earlier, the plasma insulin response provides an indirect measure of the severity of insulin resistance (Fig. 1). Thus, the results of Manicardi et al. (64) suggest that insulin resistance per se, or acting through hyperinsulinemia, is linked to the increase in systolic/diastolic blood pressure.

Because obesity can lead to insulin resistance (12–16,18,19), Ferrannini et al. (65) studied a group of normal-weight young essential hypertensive individuals with the quantitatively more precise euglycemic insulin-clamp technique. Insulin-mediated total-body glucose uptake was reduced by ~30–40% in the essential hypertensive group (Fig. 6), and the severity of insulin resistance was closely related ($r = 0.76$, $P < 0.001$) to the increase in blood pressure (Fig. 7). The impairment in insulin-mediated glucose disposal was entirely accounted for by a defect in nonoxidative glucose uptake (i.e., glycogen synthesis); stimulation of glucose oxi-

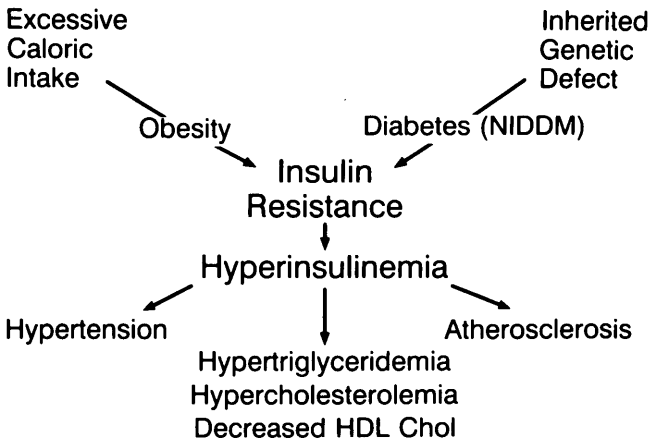

FIG. 4. Syndrome of insulin resistance. Metabolic cascade leading from acquired (obesity) or inherited (non-insulin-dependent diabetes mellitus; NIDDM) insulin resistance to hyperinsulinemia and eventually to hypertension, abnormal plasma lipid profile, and atherosclerosis is depicted. HDL Chol, high-density lipoprotein cholesterol.

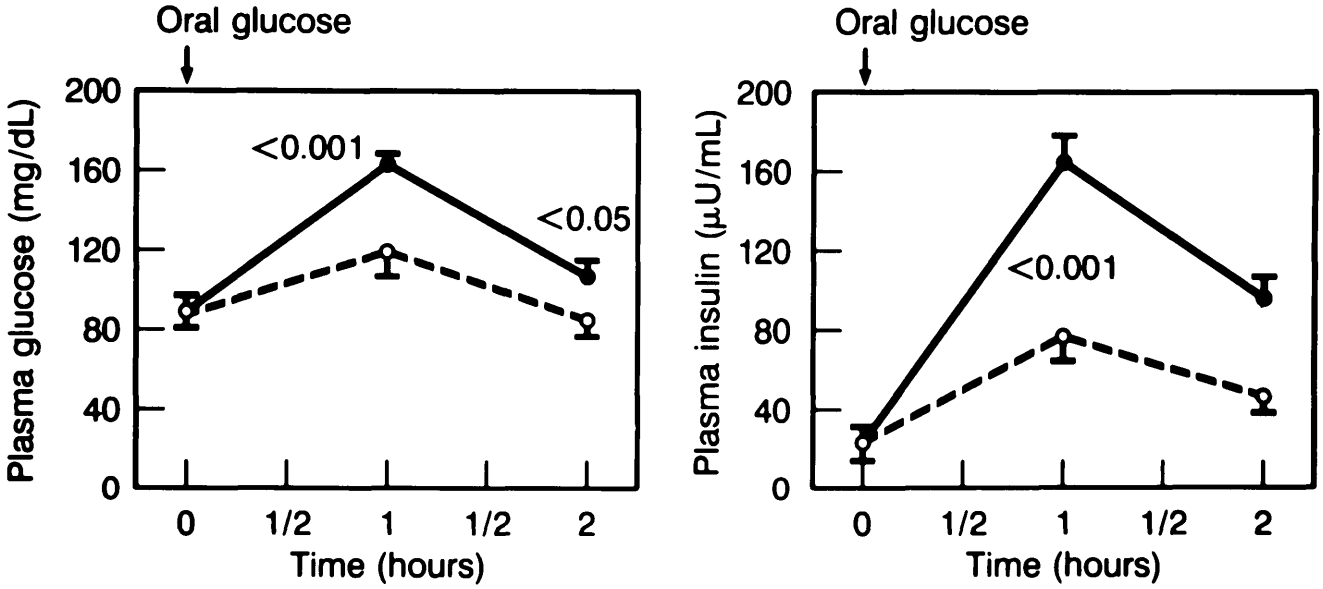

FIG. 5. Plasma glucose and insulin concentrations during standard oral glucose tolerance test performed in obese hypertensive (●) and obese normotensive (○) individuals. From Manicardi et al. (64).

dation by insulin was not diminished (65). With the forearm-catheterization technique, Ferrannini has documented that muscle is the primary site of the insulin resistance in patients with essential hypertension (unpublished observations).

In summary, essential hypertension, like obesity and NIDDM, is an insulin-resistant state. Note, however, that not all essential hypertensive subjects are insulin resistant, and it would be unreasonable to think that insulin resistance and/or its compensatory hyperinsulinemia can explain the development of essential hypertension in all individuals. Nonetheless, in most subjects with essential hypertension, insulin resistance (65,66) and hyperinsulinemia (57–66) are present, and in this group, it is plausible to suggest that these metabolic abnormalities may contribute in a causal fashion to the pathogenesis of hypertension.

INSULIN AND HYPERTENSION

From the preceding discussion, it is obvious that hypertension, obesity, and NIDDM are insulin-resistant states, and their frequent occurrence in the same individual is probably more than a chance association. It is reasonable to ask what then is the link between insulin resistance and hypertension? One potential explanation is that cellular insulin resistance per se is responsible for the development of hypertension by some unidentified mechanism. For instance, it is possible that insulin resistance alters the substrate supply or energy needs of

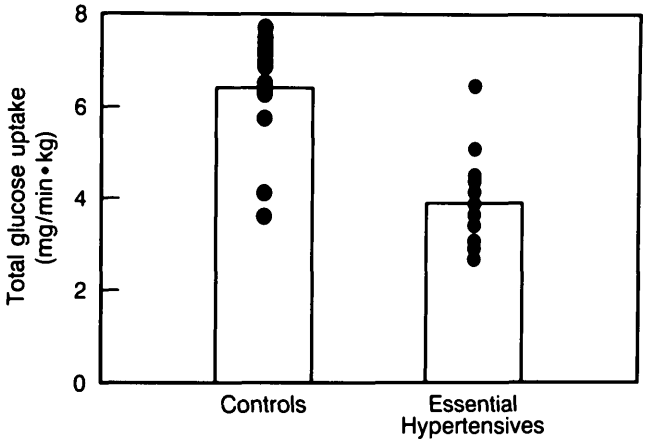

FIG. 6. Insulin-mediated rates (euglycemic insulin-clamp technique) of whole-body glucose uptake in lean subjects with essential hypertension and age- and weight-matched normotensive control subjects. From Ferrannini et al. (65).

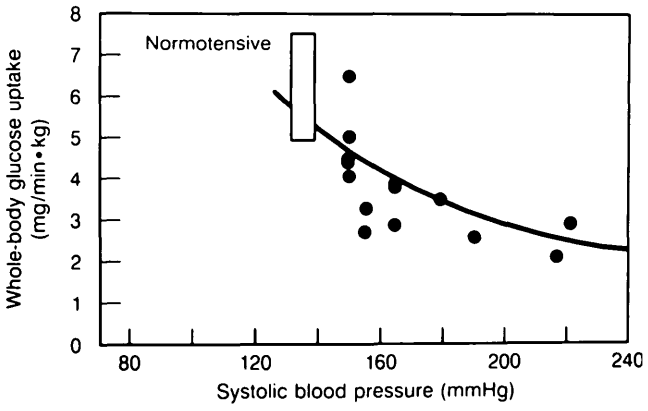

FIG. 7. Relationship between insulin-mediated whole-body glucose uptake and systolic blood pressure in lean hypertensive and control subjects shown in Fig. 6 ($r = -0.76$, $P < 0.001$). From Ferrannini et al. (65).

the cell, and the resultant changes in substrate/energy requirements sensitize, either directly or by altering ion fluxes into the cell, the vascular smooth muscle response to pressor amines such as norepinephrine and angiotensin II. Unfortunately, little is known about such interactions, and they are deserving of further investigation.

An alternative explanation for the link between hypertension and insulin resistance is the development of hyperinsulinemia. The normal β-cell response to insulin resistance is to augment its secretion of insulin (Fig. 1), and individuals with essential hypertension (57–66), obesity (1,12–16,18–20), and NIDDM (18–30) clearly have been shown to be hyperinsulinemic. There are several potential mechanisms by which elevated plasma insulin levels can lead to hypertension (Table 3).

Kidney sodium handling. It long has been recognized that total-body sodium content is increased in obese (67–69) and NIDDM (70–73) subjects with hypertension. Moreover, weight loss is associated with natriuresis, reduction in blood pressure, and decline in fasting/meal-stimulated plasma insulin levels (11,42–46,51,72–79). Conversely, acute carbohydrate ingestion is associated with hyperinsulinemia and sodium retention (72,74,77–79). Similarly, refeeding edema with its associated antinatriuresis has been shown to be related to hyperinsulinemia (72,74,77–79). All of these observations point to an important role for insulin in kidney salt and water reabsorption.

To examine the relationship between insulin and kidney sodium excretion in more detail, euglycemic insulin-clamp studies have been performed in healthy young subjects (80,81). Within 30–60 min after a physiological increment in the plasma insulin concentration, urinary sodium excretion declined, eventually reaching a nadir that was ~50% lower than the basal rate (Fig. 8). Using micropuncture and microperfusion techniques, the antinatriuretic effect of insulin has been shown to be exerted on both the proximal and distal parts of the nephron (82,83). It is important to emphasize that an increment in the plasma insulin concentration of as little as 30–40 μU/ml is capable of eliciting this antinatriuretic effect (82). Such insulin concentrations are within the range of fasting insulin concentrations observed in the obese individuals (12–16) and are considerably less than meal-stimulated insulin levels (Fig. 1). For the compensatory hyperinsulinemia to induce kidney sodium retention, expansion of the extracellular fluid volume, and ultimately hypertension, it is necessary that the kidneys of obese, diabetic, and hypertensive subjects maintain normal sensitivity to the antinatriuretic effect of insulin, even though severe resistance exists regarding carbohydrate metabolism. One study has shown this to be true in obese insulin-resistant subjects (84). The effect of insulin on kidney sodium excretion in patients with NIDDM and essential hypertension has yet to be studied.

TABLE 3
Mechanisms by which hyperinsulinemia may lead to development of hypertension

Increased renal Na^+/water reabsorption
Sympathetic nervous system activation
Decreased Na^+-K^+-ATPase activity
Increased Na^+-H^+ pump activity
Increased cellular Ca^{2+} accumulation
Stimulation of growth factors

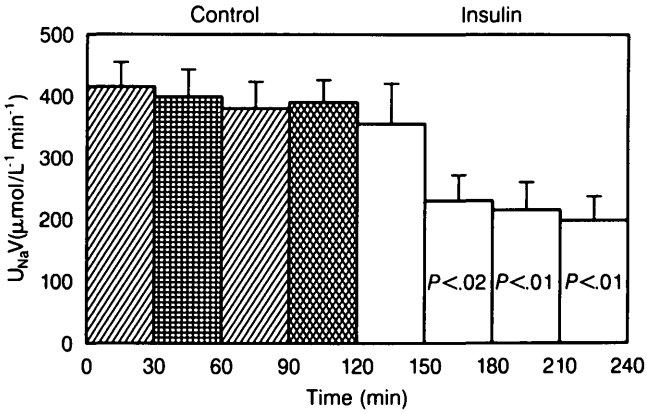

FIG. 8. Effect of euglycemic hyperinsulinemia (~100 μU/ml) on urinary sodium excretion ($U_{Na}V$) in healthy young control subjects. Insulin infusion was begun at 120 min. From DeFronzo et al. (80). © by the American Society for Clinical Investigation.

Sympathetic nervous system (SNS). A second mechanism by which insulin can cause hypertension involves stimulation of the sympathetic nervous system. Various studies in humans (44,85,86) and animals (87–89) have demonstrated that changes in dietary intake have a profound influence on SNS activity. Thus, fasting decreases whereas feeding activates the SNS (85–90). In these studies, the change in SNS activity was closely correlated with the change in plasma insulin concentration. With the insulin/glucose-clamp technique, Rowe et al. (91) demonstrated that insulin caused a dose-related increase in the plasma norepinephrine level, whereas hyperglycemia was without effect. The increase in plasma norepinephrine concentration was closely related to an increase in pulse and blood pressure (Table 4). Note that an active-transport system in the neural synapse recaptures the major fraction of norepinephrine released from nerve terminals. Thus, the increase in plasma norepinephrine observed by Rowe et al. (91) grossly underestimates the magnitude of SNS activation by insulin. Studies in dogs (92,93), humans (94,95), and rats (96,97) have provided additional evidence for the role of insulin in stimulation of the SNS.

The SNS can influence the blood pressure by augmenting the cardiac output (increased cardiac contractibility and heart rate), by increasing cardiopulmonary blood volume (constriction of the great veins), by directly vasoconstricting resistant vessels, and by enhanc-

TABLE 4
Activation of sympathetic nervous system by hyperinsulinemia

	Plasma norepinephrine	Pulse	Blood pressure
Saline infusion	0	0	0
Hyperglycemic clamp	±	0	0
Euglycemic insulin clamp			
200 μU/ml	↑	↑	↑
500 μU/ml	↑↑	↑↑	↑↑

Table is based on data from Rowe et al. (91).

ing kidney sodium reabsorption (direct stimulation of renal tubular sodium reabsorption, renal vasoconstriction, and stimulation of renin secretion) with expansion of the extracellular fluid volume. For a more detailed review of the relationship between the SNS and hypertension, the reader is referred to several recent excellent reviews (90,98,99). In addition to the effects of catecholamines on the cardiovascular system, it is well recognized that epinephrine is a powerful insulin antagonist (100,101). It inhibits insulin-mediated glucose uptake by muscle and blocks the suppressive action of insulin on hepatic glucose production. Both of these defects are characteristic of obesity and NIDDM (18).

The relationship between insulin resistance, plasma insulin concentration, SNS activity, and hypertension is summarized in Fig. 9. If insulin resistance represents the primary metabolic defect that is inherited (NIDDM, essential hypertension) or acquired (obesity, aging), the β-cell will respond to this by augmenting its secretion of insulin. The resultant hyperinsulinemia has two important effects: first, insulin directly enhances kidney sodium reabsorption, leading to extracellular volume expansion and hypertension; second, insulin activates the SNS, and this in turn causes hypertension through various mechanisms (enhanced kidney sodium reabsorption and volume expansion, peripheral vasoconstriction, increased cardiac output). Of particular importance, SNS activation can induce or worsen preexisting insulin resistance, closing a feedback loop, which ensures the perpetuation of both the insulin resistance and hypertension. It should be emphasized that we need not assume that the primary metabolic abnormality that initiates the sequence of events outlined above is insulin resistance. It is possible that the basic disturbance is primary central nervous system overdrive, leading to excessive SNS activity. This in turn can lead to hypertension and, secondarily, to insulin resistance.

Altered cellular electrolyte transport and composition. For insulin to act, it first must bind to specific receptors present on the cell surface of all insulin target tissues (102; Fig. 10). Once insulin has bound to its receptor, the second messenger for insulin action is activated (103,104). There is considerable controversy concerning the precise identification of the second messenger for insulin's many varied effects. However, many authorities believe that tyrosine kinase, which is an integral part of the β-subunit of the insulin receptor, is a prime candidate for insulin's second messenger (105,106; Fig. 10). Once the second messenger has been generated, it stimulates glucose transport via a complex mechanism that involves the translocation of glucose-transport units from within the cell and their insertion into the cell membrane (107; Fig. 10). Once inserted into the cell membrane, the glucose-transport units are activated by insulin, and glucose fluxes into the cell. However, free glucose does not accumulate intracellularly because it is rapidly oxidized or converted to glycogen (18). The basic cellular metabolic defects responsible for the insulin resistance of NIDDM, obesity, aging, and hypertension remain unknown. However, considerable evidence suggests that a defect in glucose transport per se or in coupling of the insulin receptor with the glucose-transport system is responsible for the impairment in insulin action (18,108–113), although several publications implicate a primary abnormality in glycogen synthesis in NIDDM (35,114). Whatever genetic defect represents the inherited metabolic disturbance responsible for the insulin resistance in these common

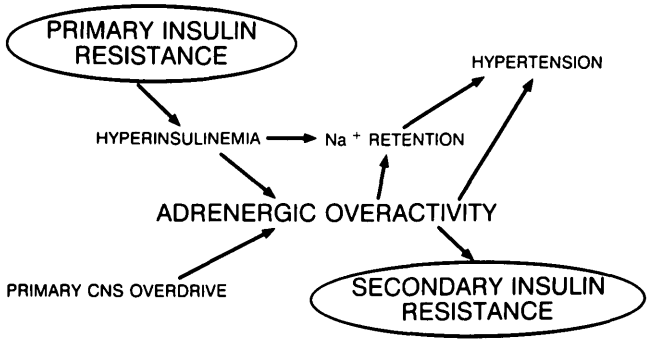

FIG. 9. Relationship between insulin resistance, plasma insulin concentration, sympathetic nervous system activity, and hypertension.

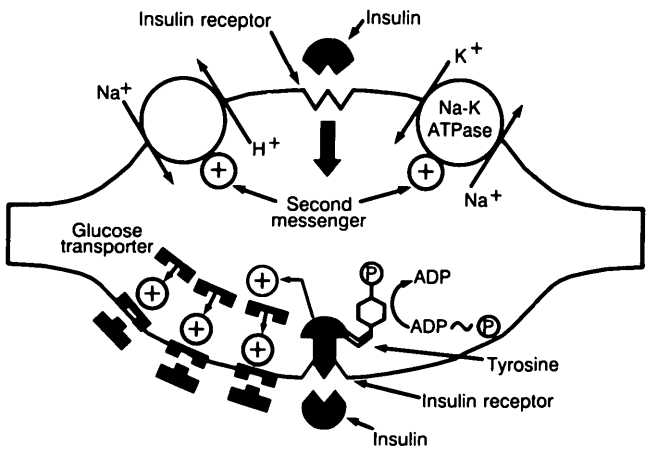

FIG. 10. Schema of mechanism of insulin action on glucose and Na^+ metabolism in muscle.

disorders (diabetes, obesity, hypertension, normal aging), the pancreatic β-cell responds by augmenting its secretion of insulin (Figs. 1 and 3). The resultant hyperinsulinemia can in turn alter the activity of several sodium pumps, which are present in all cell membranes, including the arteriolar smooth muscle cells (Fig. 10). This will lead to the intracellular accumulation of sodium, which in turn sensitizes the arteriolar smooth muscle cells to the pressor effects of norepinephrine and angiotensin II (70,115–121). Such a sequence of events could explain the frequent association between hyperinsulinemia and hypertension.

Na^+-K^+-ATPase represents a key insulin-regulated enzyme, which plays a critical role in maintaining the normal intracellular electrolyte milieu (122–124; Fig. 10). This pump extrudes Na^+ in exchange for K^+ in a ratio of 3:2 and is thus electrogenic. Obesity, diabetes, and hypertension all represent insulin-resistant states with respect to glucose metabolism. If this insulin resistance were to extend to the enzyme Na^+-K^+-ATPase, Na^+ would be expected to accumulate within the cell. In patients with essential hypertension, there is evidence that both the intracellular Na^+ content and transmembrane Na^+ transport rate are diminished in leukocytes (125–128); similar but less consistent results have been reported in erythrocytes (129–132). An excellent review of this subject has been published by Hilton (133). The activity of the Na^+-K^+-ATPase also has been reported to be reduced in various cell systems in both human essential hypertension and experimental animal models of hypertension (115,134). Reduced activity of the Na^+ pump also has been reported in other insulin-resistant states, including obesity (135,136), human insulin-dependent-diabetes mellitus (137), and experimental models of diabetes (138). Consistent with this, the ability of insulin to enhance K^+ uptake in human obesity has been shown to be reduced (139). We are unaware of studies that have examined Na^+-K^+-ATPase activity in NIDDM in humans. The studies reviewed above are consistent with the hypothesis that in certain insulin-resistant states (i.e., obesity and some types of diabetes) in humans and animals, the Na^+-K^+ pump may not be normally responsive to insulin.

Several recent observations, however, suggest that an abnormality in the Na^+-K^+-ATPase pump is unlikely to explain the elevation in blood pressure in patients with essential hypertension. First, with the euglycemic insulin-clamp technique, it has been shown that the ability of a physiological increment in the plasma insulin concentration to promote K^+ uptake is normal in essential hypertensive subjects (65). Second, it is well established that insulin-stimulated K^+ uptake in vivo and in vitro is unrelated to its stimulatory effect on glucose metabolism in muscle and other insulin-dependent tissues (140–142). This latter issue has been evaluated more directly with the forearm-catheterization technique combined with intra-arterial insulin infusion to quantitate glucose and K^+ uptake by muscle (143). In healthy subjects, physiological hyperinsulinemia markedly enhanced both glucose and K^+ uptake by muscle (Fig. 11). When oubain, a potent inhibitor of the Na^+-K^+-ATPase pump, was infused with insulin, forearm muscle K^+ uptake was completely abolished, whereas glucose uptake remained unaffected. These results demonstrate that, in vivo in humans, the effects of insulin on K^+ and glucose uptake by muscle, the primary tissue responsible for glucose (18,144) and K^+ (145) disposal, are readily dissociable. There is therefore no a priori reason to expect that the insulin resistance documented with respect to glucose metabolism should extend to K^+. Third, forearm K^+ and glucose uptake have been directly quantitated in patients with essential hypertension over a wide range of plasma insulin concentrations. Although insulin-mediated glucose uptake by forearm muscle was reduced by 30–40% at all insulin doses spanning the physiological and pharmacological range, K^+ uptake was normal (E.F., unpublished observations). Fourth, it is uncertain whether changes in leukocyte/erythrocyte (as opposed to muscle) Na^+ and K^+ content can be causally related to the development of hypertension. On the contrary, most authorities believe that such changes are genetic, rather than pathogenetic markers (133).

Another cell membrane pump that has received considerable attention in the pathogenesis of essential hypertension is the Na^+-H^+ exchanger (146–148; Fig. 10), which is considered to be equivalent to the Na^+-Li^+–cotransport system (147). This transport system is found in various cell types, has a 1:1 stoichiometry for Na^+-H^+ (i.e., it is electrically neutral), and is specifically inhibited by amiloride (147). Significantly, insulin has been shown to stimulate the activity of the Na^+-proton exchanger in skeletal muscle and adipocytes (149–154). This Na^+-H^+ pump has also been shown to be linked to Ca^{2+} exchange (115,121,155,156) and to play a

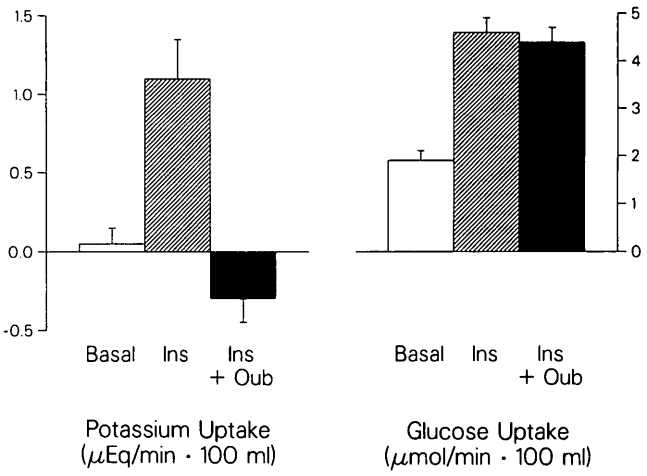

FIG. 11. Glucose and K^+ uptake by forearm muscle during basal postabsorptive conditions, after intra-arterial insulin infusion directly into brachial artery (Ins), and after combined intra-arterial insulin/oubain (Ins & Oub) infusion. From Ferrannini et al. (143).

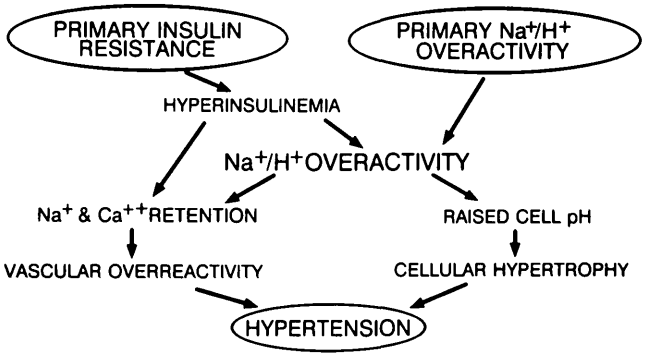

FIG. 12. Relationship between insulin resistance, plasma insulin concentration, activity of Na^+-H^+ exchanger in arterial smooth muscle cells, and hypertension.

critical role in the maintenance of intracellular pH (157,158).

The physiological functions of the Na^+-proton exchanger make it an attractive candidate to explain the elevation in blood pressure observed in insulin-resistant states such as essential hypertension, diabetes mellitus, and obesity (Fig. 12). As discussed previously, a primary defect in insulin action will be counterbalanced by enhanced secretion of insulin. The resultant hyperinsulinemia will augment Na^+-H^+ exchange (149–154), assuming that this pump retains normal sensitivity to insulin (Fig. 12). The intracellular accumulation of Na^+ and Ca^{2+} would be expected to enhance the sensitivity of the vascular smooth musculature to the pressor effects of norepinephrine, angiotensin, and NaCl loading (70,115–121,155,156). Enhanced Na^+-H^+ exchange also will lead to an increase in cell pH (157,158). Intracellular alkalosis is a known stimulator of protein synthesis and cell proliferation (Fig. 12) and eventually could lead to the characteristic hypertrophy of resistance vessel walls that is observed in established hypertension (159,160). Intracellular alkalinization also is known to directly increase smooth muscle contractility (161). Consistent with this, Ng et al. (162) have demonstrated increased leukocyte intracellular pH and Na^+-Ha^+–antiport activity in patients with essential hypertension. In addition, Na^+-H^+ exchange has been implicated as a transmembrane signal for various growth factors (163–166) known to be stimulated by insulin (167).

Several clinical observations are consistent with the above hypothesis. First, the Na^+-H^+ exchanger is the only known genetic marker for essential hypertension (127,168–172). Second, many investigators have demonstrated increased erythrocyte Na^+-H^+ countertransport in hypertensive versus nonhypertensive individuals (148,172–176). Third, increased Na^+-H^+ activity has also been demonstrated in platelets and leukocytes of patients with essential hypertension (162,177,178). Fourth, intracellular free Ca^{2+} has been shown to be increased in erythrocytes of patients with essential hypertension (115,179,180). Fifth, increased Na^+-Li^+ countertransport activity has been reported in erythrocytes of hypertensive versus normotensive insulin-dependent diabetic subjects (181) and in normotensive children of hypertensive diabetic parents (168). Similar studies have yet to be carried out in NIDDM subjects.

Note that the sequence of events discussed above was initiated with a single primary cellular defect: insulin resistance. In this scheme, the Na^+-H^+ exchanger can be viewed as an innocent bystander manipulated by hyperinsulinemia. Conversely, we could postulate that the metabolic cascade starts with a primary genetic defect in the Na^+-proton exchanger (Fig. 12). Last, these two pathogenetic sequences are not mutually exclusive. We could postulate that excessive Na^+-H^+ pump activity is an inherited trait but in itself is not sufficient to cause hypertension. Only in individuals with insulin resistance and secondary hyperinsulinemia will the phenotypic expression (i.e., hypertension) of the Na^+-H^+ exchanger become manifest.

Enhanced growth factor activity. Insulin acting directly (167,182,183) or indirectly through the stimulation of growth factors, such as insulinlike growth factor I (IGF-I; 167,183–189), also may contribute to the development of hypertension by causing hypertrophy of the vascular wall and narrowing of the lumen of the resistance vessels involved in the regulation of systemic blood pressure (159,160,190). The components of vascular hypertrophy include increases in the size and number of myocytes (191) and in the amount of contractile protein, DNA, and collagen (192,193), all of which can be increased by the actions of insulin and IGF-I. Consistent with this, receptors for IGF-I and insulin have been identified on blood vessels (183,194). Further support for the growth factor hypothesis comes from the classic experiment of Cruz et al. (195), who demonstrated that chronic insulin infusion into one femoral artery of the dog causes vascular hypertrophy only on the ipsilateral side.

In summary, much evidence exists supporting the hypothesis that hyperinsulinemia may play an important pathogenetic role in the development of hypertension in several insulin-resistant states, including obesity, diabetes mellitus, and essential hypertension. Insulin can elevate the blood pressure via various mechanisms: kidney Na^+ retention; SNS activation; enhanced fluxes of Na^+ and Ca^+ into vascular smooth muscle cells, leading to an increased vascular sensitivity to the vasoconstrictor effect of pressor amines; and proliferation of arteriolar smooth muscle cells.

INSULIN RESISTANCE, HYPERINSULINEMIA, AND HYPERLIPIDEMIA

The characteristic lipid profile in an individual with NIDDM includes *1*) decreased serum HDL-chol; *2*) increased serum very-low-density lipoprotein (VLDL); and *3*) less commonly, an increase in LDL-chol (196–202). A decrease in HDL-chol (203–208) and an increase in

LDL-chol are well-established risk factors for coronary artery disease (CAD) in both nondiabetic and diabetic subjects (203–213). Although less commonly appreciated, evidence is mounting that elevated VLDL levels also are a risk factor for the development of CAD in both nondiabetic (7,214–219) and NIDDM (197,201, 220–223) subjects.

According to current concepts, LDL is synthesized from hepatic-derived VLDL by the progressive elimination of lipids and apolipoproteins (apoAI and apoAII) and the accumulation of apoC and apoE (224). Intermediate-density lipoprotein (IDL) represents an intermediate, which is formed during the conversion of VLDL to LDL (224), and these IDL particles are particularly atherogenic (225). From these interconversions, it can be anticipated that factors that enhance VLDL synthesis also will increase the formation of IDL and LDL and predispose to accelerated atherogenesis.

The plasma VLDL concentration is determined by two factors: *1*) the rate of VLDL synthesis by the liver and *2*) the rate of VLDL removal by peripheral tissues (197). The former in turn is regulated by the ambient plasma insulin concentration and substrate availability (197,226–28). In obese nondiabetic subjects, individuals with impaired glucose tolerance, and NIDDM patients with mild to moderate fasting hyperglycemia, insulin resistance is universally present (18). However, this is offset by enhanced pancreatic insulin secretion, and the resultant hyperinsulinemia in turn augments hepatic VLDL synthesis (196,229,230). Note that a close relationship between hyperinsulinemia and hypertriglyceridemia has also been described in population-based studies in healthy normal-weight subjects (61,231–234). The association between plasma insulin and triglyceride levels has also been demonstrated in normoinsulinemic individuals (61). In addition to elevated insulin levels, NIDDM subjects, especially if they are obese, have increased plasma free fatty acid and glucose concentrations (14,18,196,229,230), providing an abundant substrate supply to drive VLDL formation. Resistance to the action of insulin on lipoprotein lipase has also been described in obesity and diabetes, and a defect in VLDL removal has been shown to contribute to the hyperlipidemia in these disorders (235–237).

In summary, there is much evidence that suggests that insulin resistance, working through hyperinsulinemia, enhances hepatic VLDL synthesis and contributes to the elevated plasma triglyceride levels observed in normal-weight healthy subjects, obese nondiabetic subjects, and NIDDM subjects. Resistance to the action of insulin on lipoprotein lipase also contributes to the hypertriglyceridemia in some obese and diabetic people.

Reduced HDL-chol concentration is a well-established risk factor for CAD in nondiabetic and diabetic individuals (203–209,213,238–241). Many epidemiological studies have demonstrated an inverse correlation between the plasma insulin and HDL concentrations in otherwise healthy subjects (57,196,231–234,242–245). A similar inverse relationship has been demonstrated in obese and NIDDM patients (196,234,243). Golay et al. (246) have provided insight into the mechanism of the reduced HDL levels in NIDDM. With [^{3}H]apoAI (apoAI is the major lipoprotein in HDL), Golay et al. demonstrated that, despite enhanced HDL synthesis (Fig. 13), the plasma HDL concentration was significantly reduced in NIDDM versus control subjects. This decrease in plasma HDL was entirely accounted for by an increase in the rate of apoAI/HDL degradation, which exceeded an enhanced rate of apoAI/HDL synthesis (Fig. 13). Within both the control and NIDDM groups, the plasma insulin concentration and the plasma HDL concentration (and apoAI clearance rate) were strongly and inversely correlated. Although the precise cellular mechanisms by which insulin regulates HDL metabolism remain to be defined, it is nonetheless clear that hyperinsulinemia is associated with a decline in circulating HDL levels and an increased risk for CAD.

In summary, there is abundant evidence that now implicates hyperinsulinemia with various lipid abnormalities (increased VLDL/IDL/LDL and decreased HDL), which are known risk factors for CAD and other macrovascular complications. Although hyperinsulinemia may be the final common denominator ultimately responsible for the abnormal plasma lipid profile, it is important to recognize that insulin resistance represents the basic underlying metabolic defect.

INSULIN RESISTANCE, HYPERINSULINEMIA, AND ATHEROSCLEROSIS

Epidemiologists interested in atherosclerosis have long recognized that insulin is a major risk factor for the development of CAD and that the effect is independent of blood pressure and plasma lipid levels (247–255). A

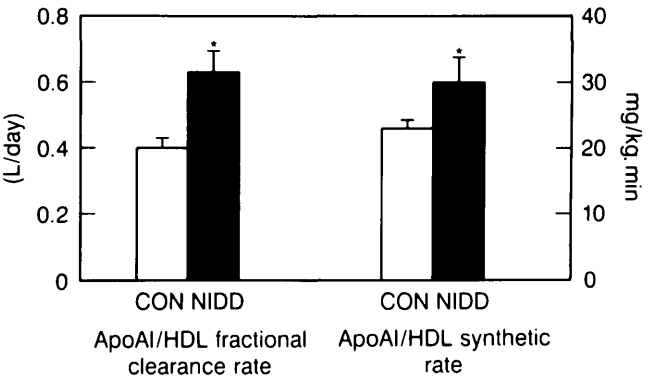

FIG. 13. High-density lipoprotein (HDL) metabolism in non-insulin-dependent diabetic (NIDD) and control (CON) subjects. Apolipoprotein A-I (ApoAI)/HDL synthetic rate was significantly increased in diabetic versus CON subjects. However, plasma HDL levels were significantly reduced in NIDD subjects because of proportionately greater increase in ApoAI/HDL fractional clearance rate. Based on data from Golay et al. (246).

growing body of experimental evidence has accumulated to support this association (182). The major effects of insulin on arterial tissues are summarized in Table 5. The atherosclerotic plaque is characterized by excessive amounts of lipid and collagen, foam macrophages, and proliferated smooth muscle cells (256). All of these constituents are affected by the plasma insulin concentration. In a now classic experiment, Cruz et al. (195) demonstrated that chronic insulin infusion into one femoral artery of the dog resulted in marked intimal and medial proliferation and the accumlation of cholesterol and fatty acids on the insulin-infused side but was without effect on the contralateral femoral artery. Subsequent studies have shown that adding insulin to cultured smooth muscle cells markedly stimulates their proliferation (257–259). Enhanced LDL-receptor activity and increased cholesterol and triglyceride synthesis have been demonstrated in arterial smooth muscle cells, fibroblasts, and mononuclear cells both in vivo and in vitro after the addition of insulin (260–265). The effect of insulin to augment lipid synthesis by vascular smooth muscle cells probably results from its stimulatory action on the lipogenic enzymes glucose-6-phosphate dehydrogenase, malic enzyme, and 3-hydroxyacyl-CoA dehydrogenase (266,267). In addition to fostering the development of the atherosclerotic plaque, hyperinsulinemia has been shown to inhibit the reabsorption of plaques once formed (268,269). Collagen is an integral component of the atherosclerotic lesion (256), and it is well established that collagen synthesis is augmented by insulin and insulinlike growth factors (270,271). Last, not only is insulin itself a growth-promoting substance, but it stimulates various other growth factors, including IGF-I, which cause cells to proliferate and thereby contribute to the atherosclerotic process (167,182–189).

In summary, various different sorts of evidence have implicated insulin, independent of changes in plasma lipid levels or blood pressure, in the pathogenesis of atherosclerosis. Although this relationship was initially promulgated by epidemiological observations (247–255), a significant body of experimental data has accumulated to provide the biochemical/cellular basis of this association.

One of the great paradoxes in medicine is the inability of effective antihypertensive therapy to diminish the increased incidence of coronary artery disease in patients with hypertension. Normalizing blood pressure in hypertensive individuals reduces the incidence of stroke, kidney failure, congestive heart failure, and accelerated hypertension but has never been shown to prevent CAD (272–276). This paradox may be explained by the failure of antihypertensive therapy to reverse the basic underlying metabolic problem: insulin resistance with its compensatory hyperinsulinemia. In fact, most antihypertensive regimens exacerbate the existing insulin resistance/hyperinsulinemia and promote a more atherogenic plasma lipid profile. This is particularly true of β-adrenergic antagonists and diuretics (277–281) (see subsequent discussion).

TABLE 5
Effect of insulin on arterial tissues

Proliferation of smooth muscle cells
Enhanced cholesterol synthesis and low-density lipoprotein–receptor activity
Increased formation and decreased regression of lipid plaques
Stimulation of connective tissue synthesis
Stimulation of growth factors

TABLE 6
Defects in insulin-mediated glucose metabolism in obese, non-insulin-dependent diabetes mellitus (NIDDM), elderly, and essential hypertensive individuals assessed by euglycemic insulin-clamp technique

	Obesity	NIDDM	Elderly	Hypertension
Whole-body glucose uptake	↓↓↓	↓↓↓	↓↓	↓↓
Glucose oxidation	↓	↓	↓↓	0
Nonoxidative glucose disposal	↓↓	↓↓	0	↓↓
Suppression of hepatic glucose production	↓	↓	0	0

For detailed discussion see text. Nonoxidative glucose disposal primarily represents glycogen synthesis.

WHICH IS THE CULPRIT: INSULIN RESISTANCE OR HYPERINSULINEMIA?

An important question that arises from the preceding discussion is whether the abnormalities in blood pressure regulation, plasma lipid profile, and/or susceptibility to atherogenesis observed in obese, diabetic, elderly, and hypertensive individuals are related to the insulin resistance per se or to the compensatory increase in plasma insulin concentration. This is a difficult issue to address, because the two conditions usually go hand in hand (Fig. 1). However, the question may be approached indirectly by examining the mechanism(s) responsible for the insulin resistance in these four common clinical disorders. As shown in Table 6, a defect in total-body glucose metabolism could result from an abnormality in glucose oxidation, nonoxidative glucose disposal (glycogen formation), or suppression of hepatic glucose production. If one metabolic abnormality could be shown to be related consistently to the clustering of hypertension, lipid abnormalities, and atherosclerosis, the case for insulin resistance as a primary etiological factor would be strengthened. If, on the other hand, a variety of different metabolic abnormalities are shown to contribute to the defect in insulin action, it becomes more difficult to argue that the clustering of hypertension, hyperlipidemia, and atherosclerosis is due to the

insulin resistance per se. Rather, a stronger argument could be made for the pathogenetic role of hyperinsulinemia, which is a consistent feature of all insulin-resistant states. A quick perusal of Table 6 shows that defects in glucose oxidation, nonoxidative glucose disposal, and suppression of hepatic glucose production all contribute, in varying amounts, to the insulin resistance in obesity, NIDDM, aging, and hypertension. Although certainly not conclusive, these observations favor the primacy of hyperinsulinemia rather than insulin resistance in the pathogenesis of the hyperlipidemia, elevated blood pressure, and accelerated atherogenesis. In support of this, there are several well-established mechanisms by which insulin can lead to hypertension, diminished HDL-chol, elevated VLDL, and atherosclerosis. However, we cannot avoid being impressed by the rather striking decrease in nonoxidative glucose disposal that occurs in individuals with obesity, NIDDM, and essential hypertension (Table 6). Therefore, it behooves the investigator to gain a more in-depth appreciation of the potential mechanisms by which a defect in glycogen synthesis might be related to an abnormality in blood pressure regulation, lipid metabolism, and atherogenesis.

INSULIN RESISTANCE: A MULTIFACETED SYNDROME

From the preceding discussion, it appears that insulin resistance is a multifaceted syndrome that can express itself in many ways, depending on a particular individual's genetic background. Insulin resistance is a common disorder, which occurs with high frequency in the general population. As shown in Fig. 14, there is a clear-cut age-related decline in the body's sensitivity to insulin (282,283). However, within any given age-group, i.e., young, middle aged, and elderly, there is a wide range of insulin sensitivity. For instance, within the young group, the most insulin-sensitive individual uses glucose at a rate that is four times that of the most insulin-resistant

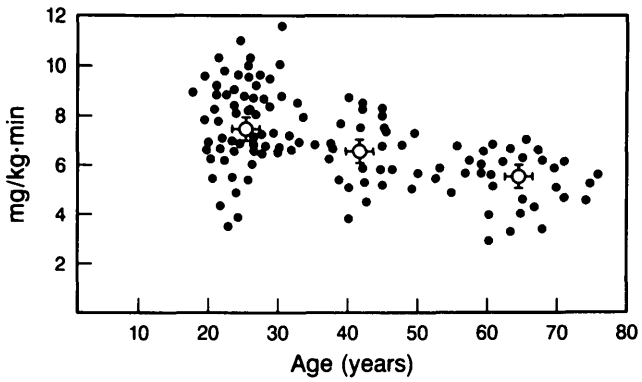

FIG. 14. Age-related decline in insulin-mediated glucose disposal (insulin-clamp technique) in healthy normal-weight subjects. Mean ± SE for young, middle-aged, and elderly subjects is shown ($r = -0.720$, $P < 0.001$).

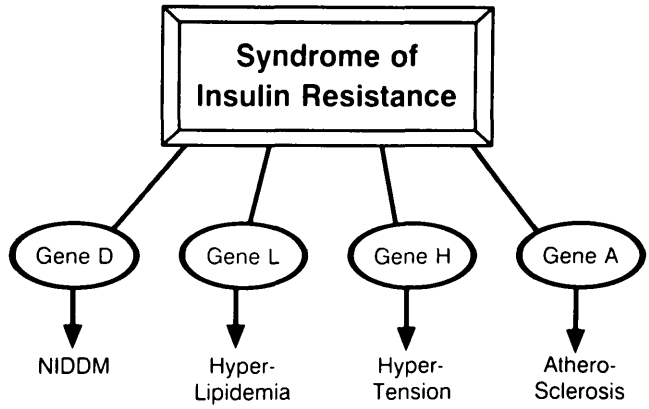

FIG. 15. Interaction between insulin-resistance gene and genes for non-insulin-dependent diabetes mellitus (NIDDM; D), lipid dyscrasias (L), hypertension (H), and atherosclerosis (A). In this schema, insulin resistance, acting directly or indirectly through compensatory hyperinsulinemia, amplifies genetic predisposition for diabetes, hyperlipidemia, hypertension, or atherosclerosis, leading to clinically manifest phenotype.

person. To compensate for this defect in insulin-mediated glucose metabolism, the β-cell must augment its secretion of insulin. In a sense, this is an adaptive process in that the hyperinsulinemia prevents the development of glucose intolerance and frank diabetes mellitus. However, in other ways, this adaptive process is maladaptive. In most people, the increase in plasma insulin concentration probably has little or no consequence. However, in genetically predisposed individuals, the hyperinsulinemia may have important clinical ramifications (Fig. 15). For instance, in individuals who have simultaneously inherited a gene that limits the β-cell's ability to augment insulin secretion (i.e., the diabetic gene; Fig. 15), the presence of insulin resistance presents a major problem. Because insulin secretion cannot be augmented sufficiently to offset the insulin resistance, the phenotypic expression is that of NIDDM (Fig. 1). If, in other individuals, the Na^+-H^+ gene is overexpressed, the simultaneous presence of hyperinsulinemia (i.e., secondary to the insulin resistance) will lead to the intracellular accumulation of sodium, enhanced sensitivity to angiotensin-norepinephrine, and eventually hypertension. Still, in others who have inherited a primary abnormality in lipid metabolism, hyperinsulinemia may interact with this gene to cause a phenotype characterized by high plasma VLDL or decreased HDL levels (Fig. 15). Similarly, in individuals who have inherited a gene or set of genes that predispose to atherosclerosis, the simultaneous presence of hyperinsulinemia will manifest itself as CAD. Note that excessive caloric intake and the development of obesity, although an acquired form of insulin resistance, can be viewed in the same light as the inherited form of insulin resistance.

In summary, the gene(s) for insulin resistance is (are) endemic in the general population (Fig. 14). However,

in most individuals, the phenotypic expression of this gene(s) goes undetected, and rarely is its biochemical counterpart (i.e., hyperinsulinemia) picked up because measurement of the plasma insulin concentration is not routinely performed. When the insulin-resistance gene coexists with some other gene, i.e., the hypertension gene, the diabetes gene, the hyperlipidemia gene, or the atherogenesis gene, the phenotypic expression assumes the characteristic of the latter (Fig. 14). Thus, a "touch" of the hypertension gene may in itself be insufficient to elevate blood pressure. However, in the presence of hyperinsulinemia (which is a compensatory response to the insulin resistance), the expression of the hypertension gene can be amplified, and the phenotypic result is essential hypertension. The same scenario can be postulated for diabetes, hyperlipidemia, and atherosclerosis. This pathogenetic sequence may help explain the common clustering of diabetes, obesity, hypertension, elevated VLDL, decreased HDL, and atherosclerosis in the same individual.

CLINICAL IMPLICATIONS OF INSULIN RESISTANCE

Diabetes and hypertension are common clinical disorders that affect ~10 and ~40%, of the elderly population, respectively (1,3,41,284,285). The treatment of both of these disorders involves the choice of medications that have the potential to adversely affect the body's sensitivity to insulin. Exercise (286–289) and weight loss (51,287,289) represent the cornerstones of diabetic management for NIDDM patients. However, these therapeutic interventions are often insufficient to restore normoglycemia, and pharmacological approaches are required. In the United States, sulfonylureas represent the only class of oral agents available for the treatment of NIDDM. Acutely, these drugs improve glucose tolerance by enhancing insulin secretion. Fortunately, their beneficial long-term effects are related to an improvement in insulin sensitivity (290,291), and the initially elevated plasma levels usually, but not always, return to pretreatment values (287). If insulin resistance with its compensatory hyperinsulinemia plays a role in the development of atherosclerosis, hypertension, and abnormal serum lipid profile (Fig. 4), it makes sense to develop antidiabetic drugs whose primary mechanism of action is to improve the body's sensitivity to insulin. We also must be concerned about the use of insulin to treat the patient with NIDDM. There are many data to support the concept that hyperglycemia and poor metabolic control play an important role in the development of the chronic microvascular complications (neuropathy, nephropathy, retinopathy) of diabetes mellitus (292). Therefore, the American Diabetes Association has advocated that physicians strive for the best possible glycemic control without untoward side effects from hypoglycemia (293). On the other hand, evidence reviewed in the preceding sections of this article suggest that hyperinsulinemia may be deleterious to various organ systems and may lead to macrovascular disease. To place this controversy in perspective, some quantitative considerations are helpful. The normal β-cell secretes ~30 U insulin/day (294). To normalize the plasma glucose profile in NIDDM patients, especially if they are obese, >100 U insulin/day is required (295,296). Thus, the physician is faced with a dilemma. Does he/she aggressively treat the abnormal plasma glucose profile with the aim of achieving normoglycemia if this can only be achieved at the expense of marked hyperinsulinemia? This is a difficult issue to resolve, because the relationship between glycemic control and microvascular complications is difficult to quantitate, whereas the relationship between insulin and macrovascular disease is even more elusive. Obviously, the best approach would be to use drugs that improve glucose tolerance by enhancing tissue sensitivity to insulin, thereby lowering the plasma insulin concentration. Unfortunately, such drugs are not yet available in the U.S.

Treatment of hypertension has been shown to effectively reduce the incidence of stroke, congestive heart failure, kidney insufficiency, and accelerated/malignant hypertension but not the incidence of CAD (272–276). It has become apparent that several categories of drugs that have gained widespread use in the treatment of hypertension are associated with worsening glucose tolerance and a more atherogenic plasma lipid profile. In particular, both diuretics (277–279,281,297–299) and β-adrenergic antagonists (277,279,280,298,300) have been shown to cause insulin resistance and worsening glucose tolerance despite an increase in circulating insulin levels. When diuretics and β-blockers are used in combination, the deleterious effects on insulin resistance, glucose metabolism, and plasma lipid profile are even more pronounced (301). Of particular concern is the recent observation that the insulin resistance and glucose intolerance persists for many months after discontinuation of diuretics and β-blocking agents (299,300,302). Because insulin resistance, hyperinsulinemia, impaired glucose tolerance, and hyperlipidemia are all components of the insulin-resistance syndrome, we must be concerned about the atherogenic potential of these antihypertensive drugs, particularly in diabetic patients. Given the choice, it would seem preferable to select antihypertensive medications that are metabolically inert. The closest approximation to such an ideal drug are the Ca^{2+}-channel blockers (277,300,303,304) and the converting enzyme inhibitors (277,299,303,305–307). Neither have any known adverse effects on glucose or lipid metabolism, and there is even the suggestion that the converting enzyme inhibitors may enhance insulin sensitivity and improve glucose tolerance (299,305–307).

SUMMARY

Insulin resistance with respect to glucose utilization no longer can be considered an uncommon metabolic dis-

order. In addition to NIDDM and obesity, insulin resistance has been shown to be a characteristic feature of the normal aging process and essential hypertension. Moreover, within the normal healthy adult population, there is a wide (3- to 4-fold) spectrum of insulin sensitivity (Fig. 14). In fact, a small but significant percentage of the normal population is as resistant as individuals with diabetes mellitus or obesity. Nonetheless, glucose tolerance remains unaltered in such individuals, because the pancreatic β-cells are capable of augmenting their secretion of insulin to precisely offset the insulin action. However, much evidence has begun to accumulate that chronic day-long hyperinsulinemia is associated with the development of hypertension, hyperlipidemia, and atherosclerosis. In a sense, insulin resistance can be viewed as a large iceberg submerged just below the surface of the water. The physician recognizes only the tips of the iceberg—diabetes, obesity, hypertension, hypertriglyceridemia, diminshed HDL-chol, and atherosclerosis—which extrude above the surface, and the complete insulin-resistance syndrome may be missed. With the recognition that insulin resistance consists of a cluster of disorders and biochemical abnormalities, it is important for the various subspecialties (diabetes, metabolism, lipidology, hypertension, cardiology) to interact more closely and to focus their attention on defining the mechanism(s) responsible for the defect in insulin-mediated glucose metabolism. Such an understanding may lead to the development of a new class of drugs, "insulin sensitizers." By lowering the elevated plasma insulin concentration, such agents may provide a wide spectrum of beneficial metabolic effects, which not only improve glucose utilization but normalize the plasma lipid profile and decrease the risk for CAD.

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