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Role of Insulin Resistance in Human Disease

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Resistance to insulin-stimulated glucose uptake is present in the majority of patients with impaired glucose tolerance (IGT) or non-insulin-dependent diabetes mellitus (NIDDM) and in ~25% of nonobese individuals with normal oral glucose tolerance. In these conditions, deterioration of glucose tolerance can only be prevented if the β -cell is able to increase its insulin secretory response and maintain a state of chronic hyperinsulinemia. When this goal cannot be achieved, gross decompensation of glucose homeostasis occurs. The relationship between insulin resistance, plasma insulin level, and glucose intolerance is mediated to a significant degree by changes in ambient plasma free-fatty acid (FFA) concentration. Patients with NIDDM are also resistant to insulin suppression of plasma FFA concentration, but plasma FFA concentrations can be reduced by relatively small increments in insulin concentration. Consequently, elevations of circulating plasma FFA concentration can be prevented if large amounts of insulin can be secreted. If hyperinsulinemia cannot be maintained, plasma FFA concentration will not be suppressed normally, and the resulting increase in plasma FFA concentration will lead to increased hepatic glucose production. Because these events take place in individuals who are quite resistant to insulin-stimulated glucose uptake, it is apparent that even small increases in hepatic glucose production are likely to lead to significant fasting hyperglycemia under these conditions. Although hyperinsulinemia may prevent frank decompensation of glucose homeostasis in insulin-resistant individuals, this compensatory response of the endocrine pancreas is not without its price. Patients with hypertension, treated or untreated, are insulin resistant,

hyperglycemic, and hyperinsulinemic. In addition, a direct relationship between plasma insulin concentration and blood pressure has been noted. Hypertension can also be produced in normal rats when they are fed a fructose-enriched diet, an intervention that also leads to the development of insulin resistance and hyperinsulinemia. The development of hypertension in normal rats by an experimental manipulation known to induce insulin resistance and hyperinsulinemia provides further support for the view that the relationship between the three variables may be a causal one. However, even if insulin resistance and hyperinsulinemia are not involved in the etiology of hypertension, it is likely that the increased risk of coronary artery disease (CAD) in patients with hypertension and the fact that this risk is not reduced with antihypertensive treatment are due to the clustering of risk factors for CAD, in addition to high blood pressure, associated with insulin resistance. These include hyperinsulinemia, IGT, increased plasma triglyceride concentration, and decreased high-density lipoprotein cholesterol concentration, all of which are associated with increased risk for CAD. It is likely that the same risk factors play a significant role in the genesis of CAD in the population as a whole. Based on these considerations the possibility is raised that resistance to insulin-stimulated glucose uptake and hyperinsulinemia are involved in the etiology and clinical course of three major related diseases—NIDDM, hypertension, and CAD. *Diabetes* 37:1595–607, 1988

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Resistance to insulin-stimulated glucose uptake is a common phenomenon and plays a central role in the pathogenesis and clinical course of several important human diseases. The fact that a large number of patients with diabetes are "insulin insensitive" was first demonstrated by Himsworth (1) ~50 yr ago; on the basis of this finding, he suggested that patients with diabetes should be divided into two categories—insulin sensitive and

insulin insensitive. This point of view became institutionalized when the National Diabetes Data Group came to the same conclusion ~40 yr after Himsworth's original observations (2), and we now use the terms insulin-dependent and non-insulin-dependent diabetes mellitus (NIDDM). The fact that resistance to insulin-stimulated glucose uptake is a characteristic finding in patients with NIDDM and impaired glucose tolerance (IGT) was emphasized by reports published from our laboratory ~20 yr ago (3–5). Our initial findings have been subsequently confirmed by many investigators using various techniques to quantify *in vivo* insulin action (6). Thus, it is now generally recognized that resistance to insulin-stimulated glucose uptake is characteristic of patients with either IGT or NIDDM. However, controversy continues as to the role of insulin resistance in the pathogenesis and clinical course of NIDDM and, in particular, the relationship between this abnormality and the changes in β -cell function that also exist in patients with this syndrome (7). First, I will address this issue and develop a hypothesis to account for the development of fasting hyperglycemia in patients with NIDDM, taking into consideration the changes in both insulin action and secretion that have been described. In this effort, the focus will be on the physiological events that result from the presence of resistance to insulin-stimulated glucose uptake. This approach is based on the premise that it is the manner in which the individual responds to insulin resistance, regardless of its cause, that determines the degree to which glucose tolerance will deteriorate. In other words, resistance to insulin-stimulated glucose uptake is necessary for the development of NIDDM, but insulin resistance, by itself, is not sufficient to produce the full-blown syndrome.

Second, I will explore the implications of resistance to insulin-stimulated glucose uptake in individuals who do not become frankly hyperglycemic. The fact that an insulin-resistant subject may not become diabetic does not mean that they suffer no untoward consequences. Indeed, an argument can be made that the more insulin sensitive an individual, the better off he or she is, and that the attempt to

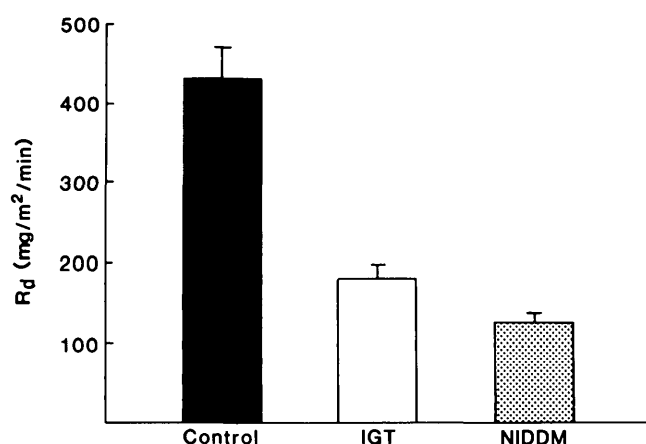


FIG. 1. Mean \pm SE values for glucose uptake (R_d) during glucose-clamp studies in individuals with normal glucose tolerance (solid bar), impaired glucose tolerance (open bar), or NIDDM (stippled bar). Experimental groups differed significantly from control at $P < .001$. Groups were well matched for other relevant variables. Clamp studies were conducted at steady-state plasma insulin levels of $\sim 60 \mu\text{U/ml}$. From Golay et al. (8) with permission.

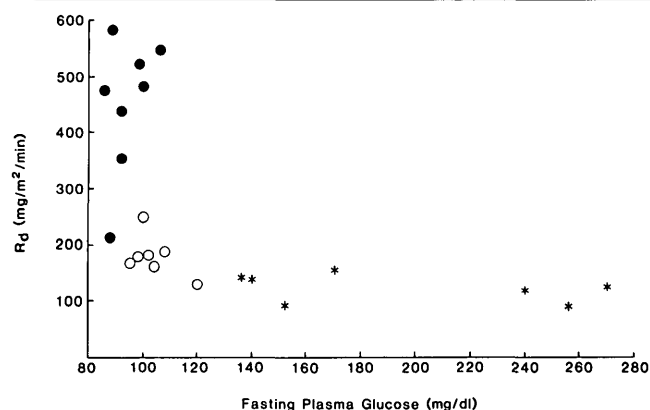


FIG. 2. Relationship between glucose uptake (R_d) during glucose-clamp studies and fasting plasma glucose concentration in individuals with normal glucose tolerance (●), impaired glucose tolerance (○), or NIDDM (*). These are individual values for groups shown in Fig. 1. From Golay et al. (8) with permission.

compensate for insulin resistance sets in motion a series of events that play an important role in the development of both hypertension and coronary artery disease (CAD). Because CAD is also the major cause of morbidity and mortality in patients with NIDDM, it is necessary to consider the possibility that variations in insulin-stimulated glucose uptake determine to an enormous degree the likelihood that an individual will develop premature atherosclerotic vascular disease. Whether this generalization proves to be true remains to be determined, but the evidence in its support is too great to ignore. I hope to effectively summarize this evidence and set forth a hypothesis that is coherent, consistent with available data, and testable by available techniques.

ROLE OF INSULIN RESISTANCE IN PATHOGENESIS OF NIDDM

Relationship between insulin resistance and degree of glucose intolerance. The data in Fig. 1 show measurements of insulin-stimulated glucose uptake (R_d) measured by the glucose clamp in individuals with normal glucose tolerance, IGT, or NIDDM (8). It is obvious from these results that insulin-stimulated glucose uptake is lower than normal in patients with either IGT or NIDDM. It is also clear that glucose uptake is reduced to almost the same degree in IGT and NIDDM. This latter point is more dramatically evident from the results shown in Fig. 2, which indicate that there is essentially no relationship between fasting plasma glucose concentration and insulin resistance in patients with IGT and NIDDM. They are all insulin resistant, whether their fasting plasma glucose concentration is 100 or 250 mg/dl . Thus, resistance to insulin-stimulated glucose uptake, by itself, cannot account for differences in the degree to which glucose tolerance deteriorates in patients with IGT or NIDDM. Essentially identical results and the same conclusion was reached as the result of similar studies carried out in Pima Indians (9). Thus, some factor other than insulin resistance must be implicated to explain why fasting plasma glucose is 125 mg/dl in one patient with NIDDM and 250 mg/dl in another.

Another obvious conclusion from the data shown in Fig. 2 is that insulin-stimulated glucose uptake can vary almost threefold in individuals with normal glucose tolerance. Furthermore, it can be seen that some subjects with normal oral

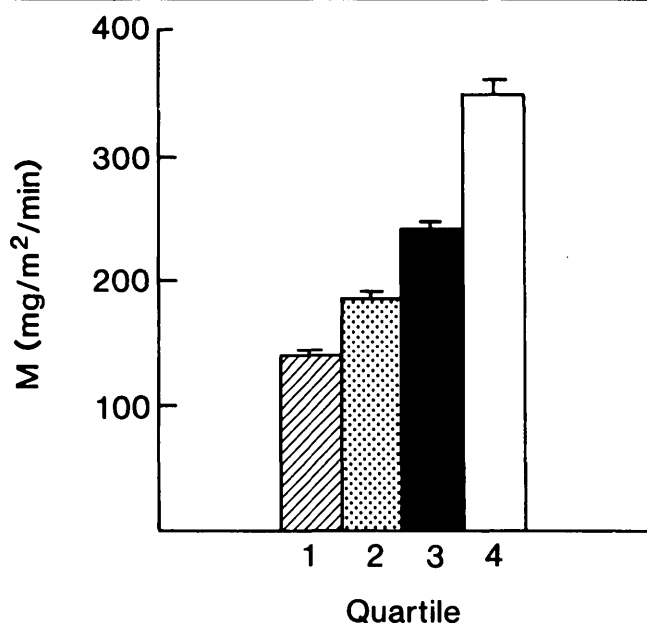


FIG. 3. Mean \pm SE values for glucose uptake (M) during glucose-clamp studies in 100 individuals with normal glucose tolerance. Study population was divided into 4 quartiles on basis of glucose uptake rate and were well matched for other relevant variables. Clamp studies were conducted at steady-state plasma insulin levels of ~ 100 μ U/ml. From Hollenbeck and Reaven (10) with permission.

glucose tolerance are approximately as insulin resistant as patients with IGT or NIDDM. To define this phenomenon more clearly, we performed glucose-clamp studies in 100 non-obese individuals with normal oral glucose tolerance. The results of these experiments are seen in Fig. 3 (10). The 100 subjects were divided into four quartiles on the basis of the glucose-clamp results, and the data in Fig. 3 indicate that glucose uptake (M) in quartile 1 was $\sim 33\%$ of the value in quartile 4. Thus, the threefold variation between the most insulin-sensitive and most insulin-resistant normal subjects, seen in Fig. 2, was confirmed when similar measurements were carried out in a large population of individuals with normal oral glucose tolerance. Furthermore, the absolute value for glucose uptake in the subjects in quartile 1 (who were most insulin resistant) was comparable in degree with that of patients with IGT and NIDDM shown in Fig. 1. Thus, resistance to insulin-stimulated glucose uptake of a similar degree of severity exists in patients with IGT or NIDDM, regardless of magnitude of hyperglycemia, and in at least 25% of the normal population. The obvious question, which is addressed in the next section, is how can degrees of

glucose tolerance vary so dramatically in individuals with comparable degrees of resistance to insulin-stimulated glucose uptake?

β -Cell compensation for insulin resistance. Plasma glucose and insulin responses to a 75-g oral glucose load in four groups of 25 individuals with normal oral glucose tolerance are shown in Fig. 4 (10). These are the same individuals whose glucose-clamp results are seen in Fig. 3. The plasma glucose response of the four groups were comparable and within normal limits. In contrast, the insulin responses of the four groups were quite different. The highest insulin levels were seen in quartile 1 (those with the greatest degree of insulin resistance). At the other extreme, normal individuals who were most insulin sensitive (quartile 4) had the lowest insulin response. The other two groups were intermediate in respect to both insulin response and insulin action, and there was an overall correlation ($r = .65$, $P < .001$) between degree of insulin resistance and insulin response to the oral glucose challenge.

Based on the data in Figs. 3 and 4, it seems reasonable to suggest that the reason why glucose tolerance is normal in quartile 1, despite their severe degree of insulin resistance, is because they can secrete enough insulin to compensate for the insulin resistance. Thus, it is the ability of the β -cell to modify the rate of insulin secretion that enables individuals with widely varying degrees of insulin resistance to have similar degrees of glucose tolerance. Variations in β -cell response also seem to account for the differences in glucose tolerance that occur in patients with IGT and NIDDM, shown previously to have comparable degrees of insulin resistance. Support for this point of view can be seen in Fig. 5, which displays the plasma glucose and insulin responses to meals in normal individuals and patients with NIDDM and progressive degrees of hyperglycemia (11). Subjects in these studies ate breakfast at 0800 (20% of total daily calories) and lunch at 1200 (40% of total calories), and plasma glucose and insulin concentration were determined hourly from 0800 to 1600. It can be seen that patients with NIDDM and the lowest levels of glycemia had the highest insulin levels and that the progressive increase in ambient glucose level seen in patients with NIDDM was associated with a decline in plasma insulin concentration. Thus, patients with NIDDM and a relatively mild degree of hyperglycemia were hyperinsulinemic compared with normal individuals, and the inability to sustain the hyperinsulinemic state was associated with the development of severe hyperglycemia.

Based on the data presented to this point, it seems clear that the more insulin sensitive an individual, the better off he

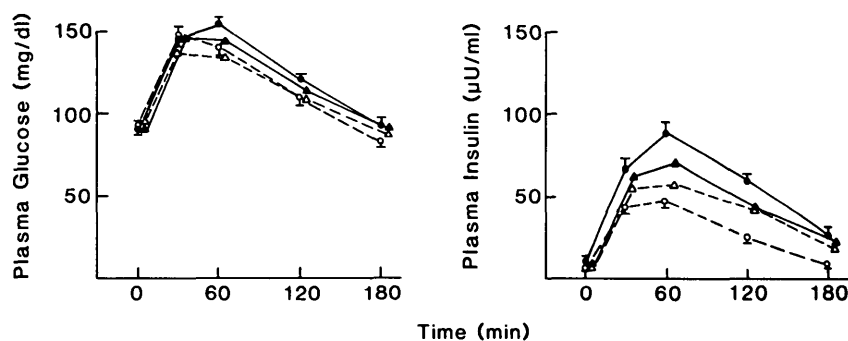


FIG. 4. Plasma glucose (left) and insulin (right) responses to 75-g oral glucose challenge in study population whose glucose-clamp results are shown in Fig. 3. Group was divided into 4 quartiles (1, ●; 2, ▲; 3, △; 4, ○) on basis of glucose-clamp determinations. From Hollenbeck and Reaven (10) with permission.

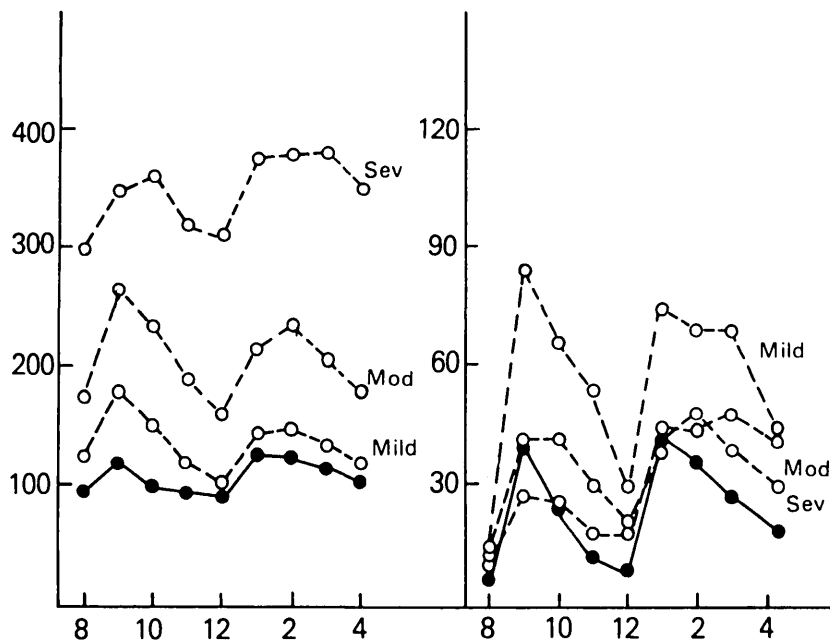


FIG. 5. Mean \pm SE plasma glucose (mg/dl; left) and insulin ($\mu\text{U/ml}$; right) concentrations at hourly intervals from 0800 to 1600 in normal individuals (●) and patients with NIDDM (○). Patients with NIDDM were divided into 3 groups on basis of degree of glucose intolerance: mild (fasting glucose <140 mg/dl), moderate (fasting glucose 140–250 mg/dl), and severe (fasting glucose >250 mg/dl). Meals were eaten at 0800 (20% of daily calories), 1200 (40% of daily calories), and 1800 (40% of daily calories). Each meal contained (as percentage of total calories) 15% protein, 40% fat, and 45% carbohydrate. Adapted from Fraze et al. (11).

or she is. In this situation, glucose is disposed of efficiently, the β -cell is not stressed, and glucose tolerance can be maintained at low plasma insulin levels. Unfortunately, this desirable situation is not present in all individuals, and if they are insulin resistant, versus insulin sensitive, their ability to compensate for this defect will largely determine the degree to which their glucose tolerance can be prevented from deteriorating. If the β -cell is able to respond to insulin resistance by secreting large amounts of insulin, gross decompensation of glucose tolerance can be prevented, and individuals will have either normal glucose tolerance, IGT or NIDDM with mild fasting hyperglycemia. However, when hyperinsulinemia cannot be sustained and circulating insulin levels are "normal" in absolute terms, severe hyperglycemia develops in individuals who are insulin resistant. This formulation emphasizes the importance of the ability of the β -cell to compensate for insulin resistance in the development of fasting hyperglycemia and focuses on the many fundamental issues that need resolution. For example, Why can some individuals secrete greater than normal amounts of insulin, whereas others cannot? Is the inability to maintain hyperinsulinemia a primary defect or an acquired one, possibly secondary to chronic hyperglycemia? Were patients with NIDDM and severe fasting hyperglycemia hyperinsulinemic initially? These and other questions need to be answered before we fully understand the role of the β -cell in the pathogenesis of NIDDM. However, the lack of this fundamental information does not prevent us from concluding that the ability of the β -cell to compensate for resistance to insulin-stimulated glucose uptake plays a crucial role in determining the degree to which glucose homeostasis can be maintained.

Abnormal regulation of free-fatty acid (FFA) metabolism in NIDDM. If we assume that the inability to maintain hyperinsulinemia explains why severe hyperglycemia develops in patients with NIDDM, the next question is What regulatory function of insulin has failed when circulating insulin levels are no longer elevated? To answer this question, it is necessary to define a process that can be significantly modified

by a small change in plasma insulin concentration. This criterion must be met because it is apparent from the data in Fig. 5 that relatively small differences in absolute insulin level exist between NIDDM individuals with markedly different levels of glycemia. In this regard, recent results from our laboratory seem to be relevant (12). In these experiments, we quantified the ability of insulin to suppress plasma FFA concentrations in normal subjects and patients with mild (fasting glucose <175 mg/dl) or severe (fasting glucose >250 mg/dl) NIDDM. These experiments measured the fall in plasma FFA concentration seen when plasma insulin concentration was raised by infusing insulin at increasing rates while plasma glucose concentration was maintained constant. The entire study lasted 280 min, with the rate of insulin infusion increased every 70 min. The mean \pm SE plasma insulin concentration achieved at the end of each 70-min period was 6.0 ± 0.6 , 13.5 ± 0.5 , 27.3 ± 1.1 , and $51.2 \pm 0.4 \mu\text{U/ml}$. The results of these studies indicate that plasma FFA concentrations fell progressively in all three groups when plasma insulin concentrations were raised from ~ 6 to $50 \mu\text{U/ml}$ while plasma glucose concentration was held constant (Fig. 6; 12). Furthermore, relatively small increments in plasma insulin concentration led to substantial decreases in plasma FFA concentration, and half-maximal suppression of basal plasma FFA level was achieved at an insulin concentration of $\sim 20 \mu\text{U/ml}$. These data clearly document the fact that small differences in plasma insulin concentration profoundly modulate plasma FFA concentration. Note that the dose-response curve relating plasma insulin concentration to glucose uptake has quite different characteristics. For example, it has been estimated that maximal stimulation of glucose uptake takes place at a plasma insulin concentration of $\sim 675 \mu\text{U/ml}$, with half-maximal stimulation at an insulin level of $60 \mu\text{U/ml}$ or three times the level required for half-maximal suppression of plasma FFA concentration (13). With these considerations, it seems unlikely that significant changes in insulin-stimulated glucose uptake can result from the small differences in plasma insulin concentration that

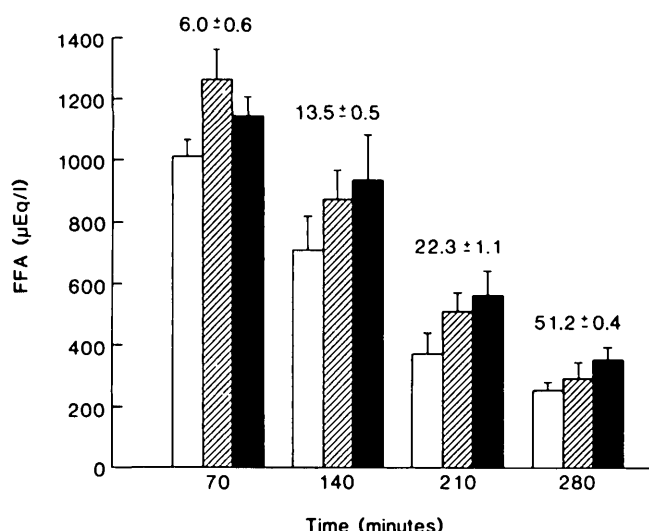


FIG. 6. Mean \pm SE plasma free-fatty acid (FFA) concentrations in normal individuals (open bars) and patients with either mild (hatched bars, fasting plasma glucose concentration <175 mg/dl) or severe (solid bars, fasting plasma glucose concentration >250 mg/dl) NIDDM in response to progressive increases in steady-state plasma insulin (SSPI) concentration. Entire study lasted 280 min, with insulin infused at different rate during each 70-min period. Plasma glucose concentration was kept constant throughout, and FFA concentration at end of each 70-min period is shown. Mean \pm SE SSPI concentration achieved during each 70-min period is shown at top of each set of 3 bars. Adapted from Swislocki et al. (12).

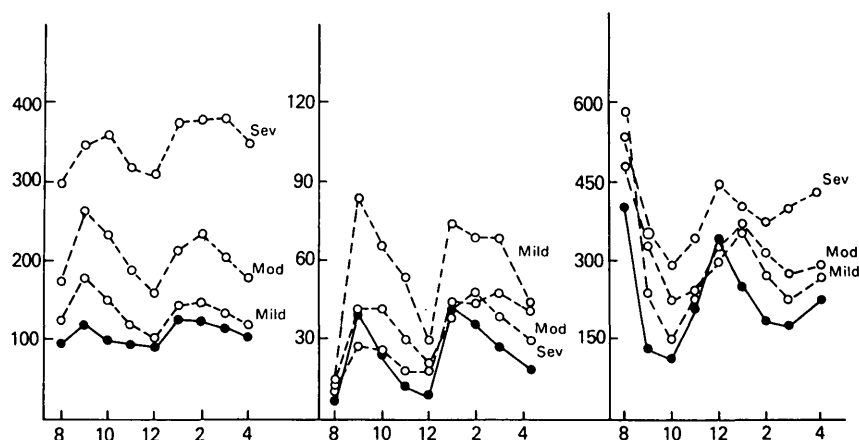
exist between insulin-sensitive subjects with normal glucose tolerance and insulin-resistant patients with severe hyperglycemia. However, it is obvious that the differences in plasma insulin concentration that exist between experimental groups with varying degrees of glucose tolerance depicted in Fig. 5 could lead to profound changes in circulating plasma FFA levels.

The results shown in Fig. 6 indicate that plasma FFA levels were higher at every plasma insulin concentration in both groups of patients with NIDDM compared with the control population. Based on these data, it appeared that there is also resistance to insulin suppression of plasma FFA concentration in patients with NIDDM. This defect in the ability of insulin to regulate plasma FFA concentration in patients with NIDDM was also demonstrated in response to conventional meals (Fig. 7). These plasma glucose and insulin responses have been seen previously (Fig. 5); Fig. 7 illustrates

the relationship between these two variables and the FFA response from 0800 to 1600. It can be seen that both plasma glucose and FFA levels of patients with NIDDM increased progressively as plasma insulin declined. Thus, it appears that hyperinsulinemia in patients with mild NIDDM was able to maintain near-normal plasma glucose and FFA levels, whereas insulin levels that were equivalent to those of normal individuals were associated with extreme elevations in plasma glucose and FFA concentrations in patients with severe NIDDM. These results provide further evidence that insulin is not able to regulate plasma FFA metabolism normally in patients with NIDDM and that resistance to insulin suppression of plasma FFA concentration also exists in this situation. Indeed, we have shown that resistance to insulin-stimulated glucose uptake is significantly correlated with resistance to insulin suppression of plasma FFA concentration (14). In addition, the fact that both plasma FFA and glucose concentrations seem to rise when hyperinsulinemia cannot be maintained permits us to speculate that patients with NIDDM develop fasting hyperglycemia because they cannot sustain the increased insulin secretory response needed to prevent elevations of circulating FFA concentration.

Elevated FFA concentration and development of fasting hyperglycemia. If the loss of insulin's ability to maintain normal plasma FFA concentration is responsible for the development of fasting hyperglycemia in NIDDM, there are at least two reasons that explain how this could happen. First, there is evidence that elevated plasma FFA levels can inhibit insulin-stimulated glucose uptake (15). Although this mechanism may contribute to the development of fasting hyperglycemia, we do not believe it is the major pathophysiological effect of high plasma FFA levels. The logic of this decision can be discerned from consideration of the results shown in Figs. 1 and 2. These data show that resistance to insulin-stimulated glucose uptake is comparable in patients with IGT and NIDDM over a wide range of fasting plasma glucose concentrations. Thus, it does not seem reasonable to suggest that an increase in insulin resistance, secondary to elevated plasma FFA levels, can account for the development of severe fasting hyperglycemia. On the other hand, there are several reasons to believe that elevated plasma FFA levels might be responsible for stimulating hepatic glucose production, an event that would certainly be consistent with the development of significant hyperglycemia in situations characterized by resistance to insulin-stimulated glucose

FIG. 7. Mean \pm SE plasma glucose (mg/dl; left), insulin (μ U/ml; center), and free-fatty acid (μ Eq/L; right) concentrations in individuals with either normal glucose tolerance (●) or NIDDM (○) by degree of glucose intolerance: mild, moderate, or severe. Study group and experimental condition were as described in Fig. 5. From Frazee et al. (11) with permission.



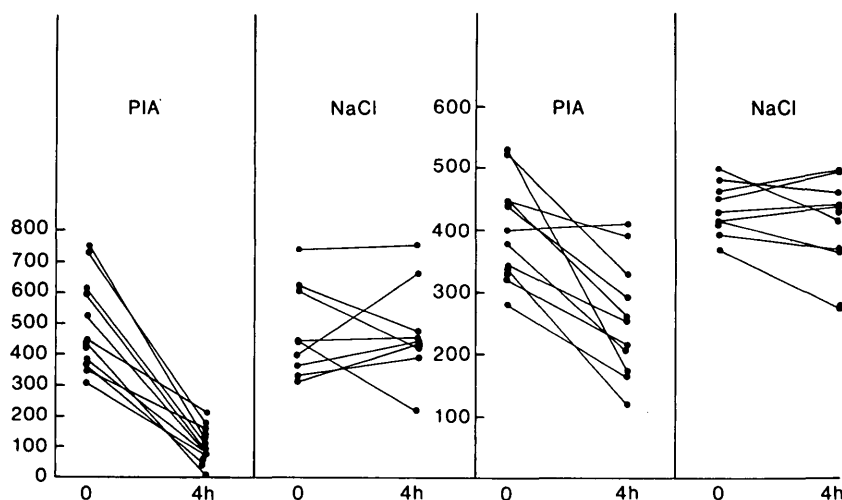


FIG. 8. Plasma free-fatty acid ($\mu\text{eq/L}$; 2 left panels) and glucose (mg/dl ; 2 right panels) concentrations in diabetic rats before and 4 h after administration of either $0.15 \mu\text{mol/kg}$ phenylisopropyladenosine (PIA) or equal volume of 0.9% NaCl. Adapted from Reaven et al. (20).

uptake. For example, there is a significant direct relationship between plasma FFA concentration and both hepatic glucose production and fasting plasma glucose concentration (16). In addition, a significant correlation has been demonstrated between magnitude of hyperglycemia and 8-h plasma FFA response (11). The presence of a significant correlation coefficient between variables does not prove they are causally related, but the likelihood of this possibility can be increased if there are theoretical reasons in support of the putative relationship. In this context, note that an increase in FFA flux to the liver has been shown to augment hepatic glucose production in intact humans (15) and perfused rat liver (17). Increased FFA oxidation by the liver has been associated with stimulation of hepatic gluconeogenesis, possibly due to the ability of the acetyl-CoA generated to activate pyruvate carboxylase, a key gluconeogenic enzyme (18). In addition, acetyl-CoA appears to reduce the activity of pyruvate dehydrogenase (19). As a result, an increase in the rate of hepatic and muscle fatty acid oxidation in diabetes, secondary to a rise in plasma FFA level, would be expected to lead to a decrease in activity of pyruvate dehydrogenase, resulting in an increase in both conversion of glucose to lactate in muscle and in hepatic gluconeogenesis. In addition to these considerations, we have recently conducted experiments that indicate that modulation of FFA metabolism can lower plasma glucose concentration in an ani-

mal model of NIDDM (20,21). Old Sprague-Dawley rats are insulin resistant and hyperinsulinemic and when treated with relatively small doses of streptozocin (20–30 mg/kg), they develop significant increases in plasma glucose, FFA, and triglyceride concentration. Diabetic rats are not catabolic and have plasma insulin concentrations that are only slightly lower than control rats, and we believe they serve as a good model for NIDDM.

When such rats are injected with phenylisopropyladenosine (PIA), an adenosine agonist that is antilipolytic *in vitro*, there is an acute fall in plasma FFA concentration (20). The data in Fig. 8 show that the acute fall in plasma FFA concentration after the administration of PIA to diabetic rats was associated with a significant fall in plasma glucose concentration. Nicotinic acid (NA) can also lower plasma FFA concentration, and the data in Fig. 9 indicate that its administration to rats with our experimental form of NIDDM leads to the same fall in plasma glucose and FFA concentration as does PIA (20). Neither PIA nor NA administration was associated with an increase in plasma insulin concentration, indicating that the fall in plasma glucose concentration that they produce is not mediated by an increase in β -cell function. Although PIA and NA are both antilipolytic agents, they bind to different receptors, suggesting that it is their ability to inhibit lipolysis that accounts for their hypoglycemic effect in diabetic rats. We have also shown that the fall in plasma

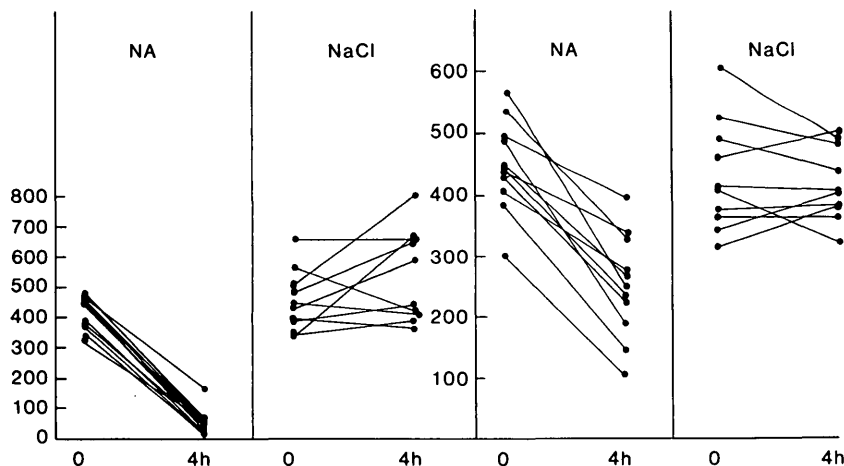


FIG. 9. Plasma free-fatty acid ($\mu\text{eq/L}$; 2 left panels) and glucose (mg/dl ; 2 right panels) concentrations in diabetic rats before and 4 h after administration of either $200 \mu\text{mol/kg}$ nicotinic acid (NA) or equal volume of 0.9% NaCl. Adapted from Reaven et al. (20).

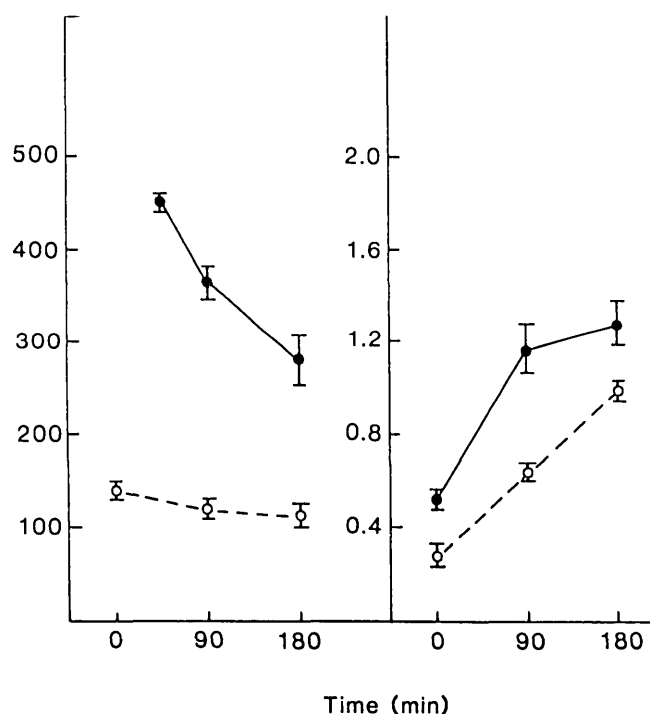


FIG. 10. Mean \pm SE plasma glucose (mg/dl; left) and free-fatty acid (meq/L; right) concentrations before (0 min) and 90 and 180 min after administration of 50 mg/kg etomoxir to normal (○) or diabetic (●) rats. Adapted from Reaven et al. (21).

glucose concentration after NA administration to diabetic rats was associated with a significant fall in hepatic glucose output, consistent with the view that elevated plasma FFA concentrations cause hyperglycemia by stimulating gluconeogenesis (20).

Evidence has been published that suggests that agents that interfere with hepatic fatty acid oxidation are also capable of lowering plasma glucose concentration (21). Documentation of this phenomenon can be seen in Fig. 10, which demonstrates that the administration of etomoxir, a potent inhibitor of the hepatic carnitine palmitoyl transferase (CPT) system, can also lower plasma glucose concentration in rats with experimental diabetes (21). Plasma insulin concentration did not increase after administration of etomoxir, supporting the view that the fall in glucose concentration was not due to enhanced β -cell function, but rather to the inhibition of hepatic FFA oxidation. Note that plasma FFA concentration also increased after etomoxir administration.

The results in Figs. 8–10 suggest that inhibition of hepatic FFA oxidation, either directly by reducing hepatic CPT activity or indirectly by suppressing FFA release from adipose tissue, will lower plasma glucose concentration in rats with an experimental form of NIDDM. The obvious prediction from this formulation is that the combined effect on plasma glucose concentration of administering an antilipolytic agent and an agent that inhibits hepatic CPT would be additive. The results shown in Fig. 11 indicate that this prediction was borne out and that the fall in plasma glucose concentration was greater when etomoxir and NA were given together than when either one was given alone (21). These results provide support for the view that acute modulation of FFA metabolism, specifically hepatic FFA oxidation, either directly or

indirectly, can lead to a significant reduction in plasma glucose concentration in rats with an experimental form of NIDDM. Whether this phenomenon can be replicated in patients with NIDDM remains to be evaluated.

Summary of role of insulin resistance in pathogenesis of NIDDM.

Resistance to insulin-stimulated glucose uptake is present in the majority of patients with IGT or NIDDM (3–9). However, insulin resistance is not confined to individuals with abnormal glucose tolerance, and resistance to insulin-stimulated glucose uptake of a degree comparable to that seen in patients with NIDDM exists in ~25% of nonobese individuals with normal oral glucose tolerance (10). The difference in the degree to which glucose tolerance deteriorates in these various groups appears to be a function of the ability of the β -cell to compensate for the defect in insulin action. Significant fasting hyperglycemia occurs in patients with insulin resistance in association with circulating plasma insulin concentrations that are comparable in absolute terms to those of normal individuals. The most desirable situation is to be an insulin-sensitive individual, thereby not dependent on the ability of the β -cell to secrete large amounts of insulin. If resistance to insulin-stimulated glucose uptake is present, deterioration of glucose tolerance can only be prevented if the β -cell is able to increase its insulin secretory response and maintain a state of chronic hyperinsulinemia. When this goal cannot be achieved, gross decompensation of glucose homeostasis occurs.

We propose that the relationship between insulin resistance, plasma insulin level, and glucose intolerance summarized above is mediated to a significant degree by changes in ambient plasma FFA concentration. Although patients with NIDDM are also resistant to insulin suppression of plasma FFA concentration, plasma FFA concentration can

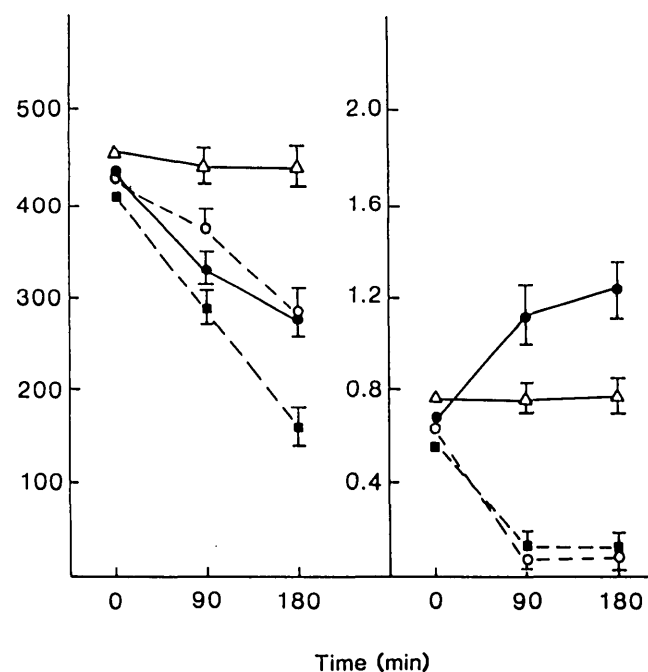


FIG. 11. Mean \pm SE plasma glucose (mg/dl; left) and free-fatty acid (meq/L; right) concentrations before (0 min) and 90 and 180 min after administration to diabetic rats of either vehicle (Δ), nicotinic acid (○), etomoxir (●), or etomoxir plus nicotinic acid (■). Adapted from Reaven et al. (21).

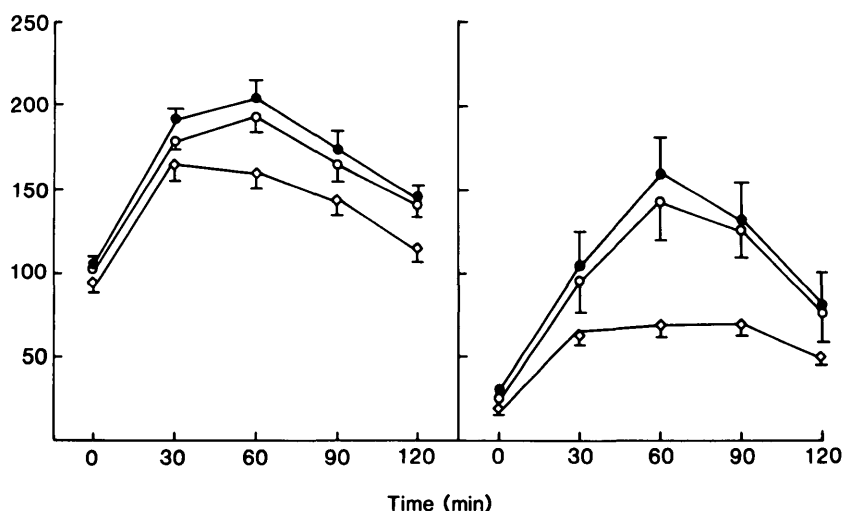


FIG. 12. Mean \pm SE plasma glucose (mg/dl; left) and insulin (μ U/ml; right) concentrations in response to 75-g oral glucose challenge in normal men (\diamond), men with untreated hypertension (\circ), and men receiving treatment for hypertension (\bullet). From Shen et al. (31) with permission.

be suppressed by relatively small increments in insulin concentration (8,11,12,14,15). Consequently, elevation of circulating plasma FFA concentration can be prevented if large amounts of insulin can be secreted (8,11,16). If hyperinsulinemia cannot be maintained, plasma FFA concentration will not be suppressed normally, and the increase in plasma FFA concentration will result in increased hepatic glucose production. Because these events are taking place in individuals who are quite resistant to insulin-stimulated glucose uptake, it is apparent that even small increases in hepatic glucose production are likely to lead to significant fasting hyperglycemia under these conditions.

Finally, note that the apparent ability of ambient hyperinsulinemia to prevent gross decompensation of glucose homeostasis in insulin-resistant individuals does not mean that the resulting state is a benign one. Indeed, in the remaining sections of this presentation, evidence will be presented to support the view that insulin resistance and hyperinsulinemia are involved in the genesis of both hypertension and CAD.

ROLE OF INSULIN RESISTANCE IN PATHOGENESIS OF HYPERTENSION

Insulin resistance and hyperinsulinemia in patients with hypertension. Several reports have indicated that patients with high blood pressure are relatively glucose intolerant compared with individuals with normal blood pressure (22–26). More recently, several groups have demonstrated that untreated patients with high blood pressure are also hyperinsulinemic compared with normotensive individuals (27–30). The combination of glucose intolerance and hyperinsulinemia strongly suggests that a defect in insulin-stimulated glucose uptake exists in some patients with hypertension. To pursue this issue, we compared the plasma glucose and insulin responses to oral glucose and the ability of insulin to promote glucose uptake in normal individuals and patients with high blood pressure. The hypertensive population was further subdivided into two groups—those with untreated hypertension and those whose high blood pressure had been returned toward normal with various forms of antihypertensive medication. The plasma glucose and insulin responses to oral glucose again demonstrate the presence of hyperglycemia and hyperinsulinemia in the two groups with high blood pressure (Fig. 12). Because the

mean blood pressure of the treated group was 145/95 mmHg, it appears that simply lowering blood pressure does not necessarily reduce the degree of glucose intolerance and hyperinsulinemia.

In vivo insulin action was estimated by a modification of the insulin-suppression test, in which subjects receive a continuous intravenous infusion of somatostatin, insulin, and glucose. Endogenous insulin secretion is suppressed by somatostatin, and exogenous insulin infusion leads to a similar steady-state plasma insulin (SSPI) concentration in all subjects, both qualitatively and quantitatively. Because the rate of glucose infusion is also the same, the eventual steady-state plasma glucose (SSPG) concentration provides an estimate of in vivo insulin action, i.e., the higher the SSPG, the more insulin resistant the individual. The results of these measurements demonstrate that SSPG concentrations were significantly higher in both groups of patients with high blood pressure (Fig. 13; 31). Because the SSPI concentrations were the same in all three groups, these results show that patients with hypertension are insulin resistant. Again, whether the patients were being treated for hypertension seemed to be irrelevant, suggesting that it is not high blood pressure per se that is responsible for the defect in insulin-stimulated glucose uptake. Ferrannini et al. (32) carried out somewhat similar studies with the glucose clamp and also concluded that patients with untreated hypertension are insulin resistant.

Based on these considerations, it seems reasonable to conclude at this juncture that resistance to insulin-stimulated glucose uptake, glucose intolerance, and hyperinsulinemia are characteristic of a certain proportion of patients with hypertension. Furthermore, these abnormalities of glucose and insulin metabolism do not necessarily improve when hypertension is controlled by commonly used pharmacological approaches to lower blood pressure.

Relationship between insulin resistance, hyperinsulinemia, and hypertension. It is obvious that the correlations between insulin and blood pressure described above do not prove that the relationship is a causal one. On the other hand, if one postulates that insulin resistance and hyperinsulinemia are involved in the etiology of hypertension, it is possible to find experimental data that provide support for this putative relationship. For example, it has been suggested that the

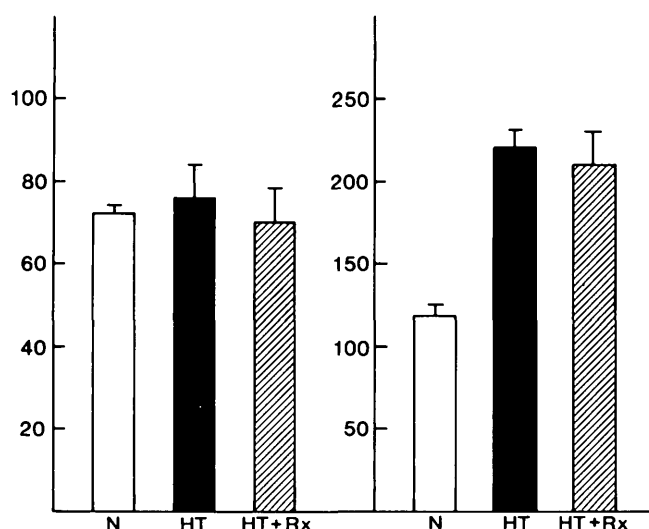


FIG. 13. Mean \pm SE steady-state plasma insulin (μ U/ml; left) and glucose (mg/dl; right) concentrations during last 60 min of 180-min infusion of somatostatin (350μ g/h), insulin ($25 \text{ mU} \cdot \text{m}^{-2} \cdot \text{min}^{-1}$), and glucose ($6 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). N, normal men; HT, hypertensive men; HT + Rx, men receiving treatment for hypertension. From Shen et al. (31) with permission.

reason hypertension is more common in obese individuals may be that they are hyperinsulinemic (33,34). In a similar fashion, the decline in blood pressure associated with exercise training seems to be limited to individuals who were initially hyperinsulinemic and had the greatest fall in plasma insulin level as a result of the training program (33). Furthermore, it has been possible in recent studies to define a statistically significant relationship between plasma insulin concentration and height of blood pressure (27,30).

Available information suggests at least two possibilities by which insulin resistance and hyperinsulinemia could lead to an increase in blood pressure. First, there are reports indicating that increases in plasma insulin concentration are associated with significant increases in plasma catecholamine concentration, independent of any change in plasma glucose concentration (35,36). The potential importance of excessive sympathetic activity in the genesis of hypertension has also been emphasized in studies that show that sucrose feeding of rats with spontaneous hypertension enhances sympathetic nervous system activity and increases blood pressure (37). Interestingly, insulin resistance and hyperinsulinemia also develop in sucrose-fed rats (38). To what extent insulin resistance and hyperinsulinemia contribute to the etiology of hypertension by stimulating sympathetic activity remains to be determined.

The kidney is another possible site at which insulin resistance and hyperinsulinemia might act to raise blood pressure. There is evidence that insulin can act on the isolated toad bladder (39) and in intact dogs (40) and humans (41) to promote renal tubular sodium resorption. More recently, evidence has been published that indicates that insulin acts at the level of the proximal tubule to increase volume reabsorption (42). The fact that insulin has been shown to acutely regulate renal sodium and water metabolism in a manner that could raise blood pressure does not prove that these phenomena occur chronically or that they play a role in the etiology of hypertension. On the other hand, as in the case

of the relationship between insulin and sympathetic activity, available data provide a testable hypothesis to account for a possible causal relationship between insulin resistance, hyperinsulinemia, and high blood pressure in certain individuals.

In an attempt to provide more direct evidence of a link between insulin resistance, hyperinsulinemia, and hypertension, we have taken advantage of results of previous studies from our laboratory that documented insulin resistance and hyperinsulinemia development when normal rats were fed diets high in sucrose (38,43) or fructose (44). Consequently, we evaluated the possibility that an increase in blood pressure would also occur in fructose-fed rats (45). To do this we measured insulin-stimulated glucose uptake, plasma insulin concentration, and blood pressure before and after a 2-wk period in which normal rats were fed either conventional rat chow or chow in which the carbohydrate had been totally replaced by fructose. In vivo insulin action was determined with a variation of the insulin-suppression test described earlier. The data in Fig. 14 compare the SSPG and SSPI values during the insulin-suppression test after 2 wk of feeding a fructose-enriched diet to normal Sprague-Dawley rats with values in chow-fed rats. It is apparent that the SSPG values were higher in the fructose-fed rats, despite the fact that the SSPI levels were somewhat lower in these rats, demonstrating the development of insulin resistance in association with fructose feeding. The results in Fig. 15 indicate that the fructose-fed rats were also hyperinsulinemic compared with chow-fed rats. Finally, Fig. 16 shows that the insulin resistance and hyperinsulinemia of fructose-fed rats were associated with a significant increase in blood pressure. These results demonstrate that blood pressure increases in normal rats in response to a dietary modulation known to produce insulin resistance and hyperinsulinemia. Furthermore, the fructose-induced increase in blood pressure will persist for as long as 3 mo if the rats continue to

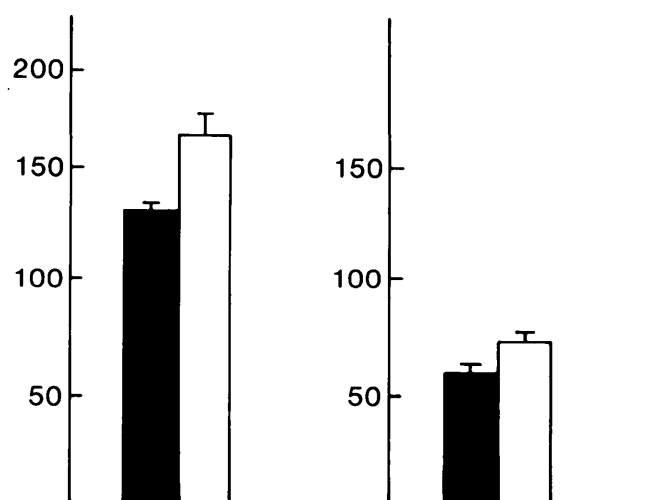


FIG. 14. Mean \pm SE steady-state plasma glucose (mg/dl; left) and insulin (μ U/ml; right) concentrations during last 30 min of 180-min infusion of glucose ($8 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) and insulin ($2.5 \text{ mU} \cdot \text{m}^{-1} \cdot \text{min}^{-1}$). Rats had consumed either conventional rat chow (solid bars) or chow in which carbohydrate had been replaced by fructose (open bars) for preceding 2 wk. $n = 22$ in each group. From Hwang et al. (45) with permission.

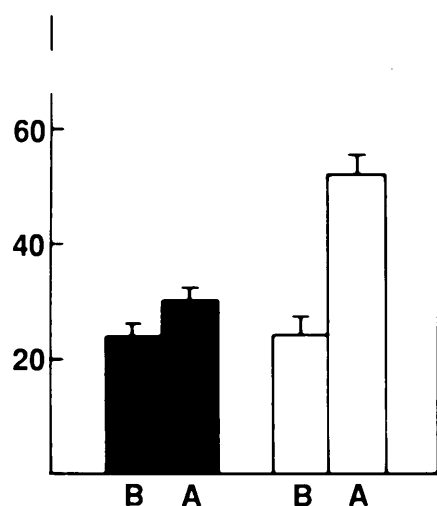


FIG. 15. Mean \pm SE plasma insulin concentration (μ U/ml) before (B) and 2 wk after (A) normal rats were fed either conventional rat chow (solid bars, $n = 24$) or chow in which carbohydrate content had been replaced with fructose (open bars, $n = 21$). Adapted from Hwang et al. (45) with permission.

eat the fructose-enriched diet and will subside promptly once the rats are put back on chow (unpublished observations).

In an effort to further evaluate the role of insulin resistance and hyperinsulinemia in blood pressure regulation, we have taken advantage of the fact that insulin sensitivity is enhanced in exercise-trained rats (46). Consequently, we initiated studies in which two groups of normal rats were fed fructose-enriched diets. One group was maintained in conventional laboratory cages, whereas the other was allowed to run spontaneously. Insulin resistance, hyperinsulinemia, and hypertension developed as before in the sedentary fructose-fed rats, whereas all three of these changes were significantly attenuated in the exercise-trained rats (47).

Summary of role of insulin resistance and hyperinsulinemia in pathogenesis of hypertension. Patients with hypertension, treated or untreated, are insulin resistant, hyperglycemic, and hyperinsulinemic. In addition, a direct relationship between plasma insulin concentration and blood pressure has been noted. The fact that hypertension can be produced in normal rats by an experimental manipulation known to induce insulin resistance and hyperinsulinemia pro-

vides further support for the view that the relationship between the three variables may be more than coincidental. Additional evidence for a causal relationship between the defects in insulin action and high blood pressure can be derived from the observation that prevention of fructose-induced insulin resistance and hyperinsulinemia also significantly reduced the increase in blood pressure associated with the high-carbohydrate diet. On the other hand, great care should be exercised in the extrapolation of results of studies in normal rats to humans with hypertension. Perhaps the best way to summarize the results of feeding high-carbohydrate diets to normal rats is that they are consistent with the speculation that abnormalities of glucose and insulin metabolism may play some role in the etiology of high blood pressure in humans.

RELATIONSHIPS BETWEEN INSULIN RESISTANCE, HYPERINSULINEMIA, AND CAD

Patients with hypertension. Perhaps the best way to begin the discussion of the role of insulin resistance and hyperinsulinemia in the genesis of CAD is to focus on patients with hypertension. Although high blood pressure is a well-recognized risk factor for CAD (48), it has been difficult to demonstrate that treatment of hypertension leads to improved morbidity and mortality from CAD (49–51). This apparent paradox has received a good deal of recent attention, most of which has focused on the fact that conventional treatment of hypertension is often associated with changes in lipid metabolism thought to increase the risk for CAD (52–54). What seems to have been overlooked is the fact that there are multiple risk factors for CAD in patients with hypertension before they receive any drug treatment for hypertension, all of which can be viewed as being secondary to resistance to insulin-stimulated glucose uptake. For example, glucose intolerance is a well-known consequence of insulin resistance, and observations have suggested that relatively minor degrees of glucose intolerance, comparable to those described in many individuals with high blood pressure, significantly increase the risk of developing CAD (55,56). The apparent reason why glucose homeostasis does not grossly decompensate in patients with insulin resistance and high blood pressure is their ability to secrete large amounts of insulin. Although the ensuing hyperinsulinemia minimizes the degree of glucose intolerance in hypertensive individuals,

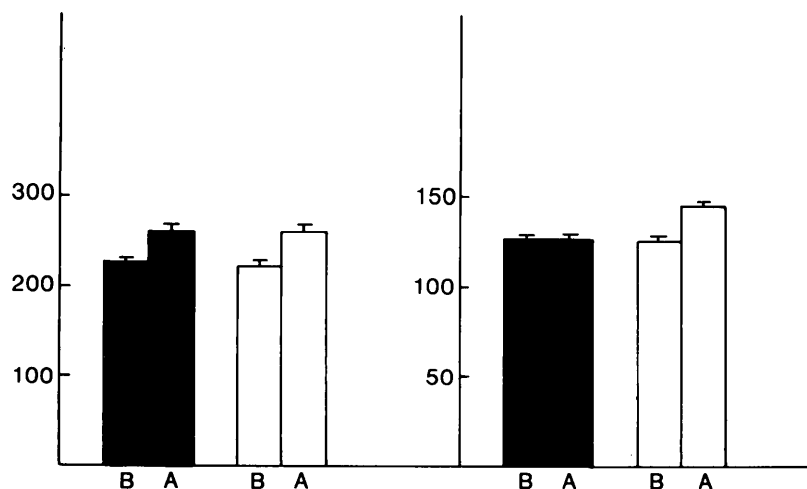


FIG. 16. Mean \pm SE body weight (g; left) and blood pressure (mmHg; right) before (B) and 2 wk after (A) normal rats were fed either conventional rat chow (solid bars, $n = 24$) or chow in which carbohydrate content had been replaced with fructose (open bars, $n = 28$). From Hwang et al. (45) with permission.

this may occur at the expense of increasing risk of CAD. Thus, three prospective epidemiological studies have suggested that hyperinsulinemia is a risk factor for CAD (56–58). The mechanism by which hyperinsulinemia increases the risk of developing CAD is far from clear, and it need not function as a primary risk factor for it to play a role in this regard. Abnormalities of lipoprotein metabolism have also been described in untreated patients with hypertension, including an elevation of plasma triglyceride concentration (54,59). Hypertriglyceridemia appears to be secondary to insulin resistance and hyperinsulinemia, and highly significant correlations have been documented between resistance to insulin-stimulated glucose uptake, hyperinsulinemia, increased very-low-density lipoprotein (VLDL) secretion rate, and hypertriglyceridemia in normal humans and patients with hypertriglyceridemia (60–62). Similar relationships have also been described in rats with various forms of carbohydrate-induced hypertriglyceridemia (44,63,64). Furthermore, when insulin-stimulated glucose uptake is enhanced, either by weight reduction in humans (65) or exercise training in rats (47,64), plasma insulin and triglyceride levels fall. Finally, direct evidence from experiments on perfused rat liver indicate that hepatic VLDL triglyceride secretion is directly related to ambient insulin concentration (66). Thus, there is considerable evidence in support of the hypothesis that hypertriglyceridemia is secondary to hyperinsulinemia and insulin resistance; this mechanism may well account for the appearance of elevated plasma triglyceride concentrations in patients with hypertension.

The view that abnormalities of carbohydrate and lipoprotein metabolism are related in individuals with high blood pressure has received direct support from the results of a recent study in which multiple metabolic variables were measured in a group of untreated patients with hypertension (67). This population was glucose intolerant and hyperinsulinemic compared with a matched group of normal individuals. Direct correlations were noted between degree of both hyperglycemia and hyperinsulinemia and increases in plasma triglyceride concentration. In addition, an inverse correlation was observed between high-density lipoprotein cholesterol (HDL-cholesterol) concentration and glucose intolerance and hyperinsulinemia. These findings emphasize the fact that abnormalities of carbohydrate and lipoprotein metabolism are present in patients with hypertension and that significant relationships exist between the various metabolic variables. None of the patients in this study were receiving antihypertensive medication, which further strengthens the observations that multiple and related abnormalities of carbohydrate and lipid metabolism exist in patients with hypertension. These observations provide further evidence that abnormalities of both carbohydrate and lipoprotein metabolism are prominent in patients with high blood pressure. In addition, these metabolic changes are seen in both treated and untreated patients, are highly related to each other, and may play an important role in the development of CAD in patients with hypertension.

Patients without hypertension. In the previous section, it was indicated that a cluster of risk factors for CAD have been noted in patients with high blood pressure. However, by focusing on the relationship of these metabolic changes to blood pressure, the significance of these findings may

TABLE 1
Syndrome X

Resistance to insulin-stimulated glucose uptake
Glucose intolerance
Hyperinsulinemia
Increased very-low-density lipoprotein triglyceride
Decreased high-density lipoprotein cholesterol
Hypertension

have been somewhat obscured. Based on available data, it is possible to suggest that there is a series of related variables—syndrome X—that tends to occur in the same individual and may be of enormous importance in the genesis of CAD. These changes include resistance to insulin-stimulated glucose uptake, hyperglycemia, hyperinsulinemia, an increased plasma concentration of VLDL triglyceride, a decreased plasma concentration of HDL-cholesterol, and high blood pressure (Table 1). The common feature of the proposed syndrome is insulin resistance, and all other changes are likely to be secondary to this basic abnormality. All five of the proposed consequences of insulin resistance have been shown to increase the risk of CAD, and the fact that all of them may not necessarily be seen in the same individual should not minimize their importance. Based on these considerations, it seems fair to make the suggestion that resistance to insulin-stimulated glucose uptake may play a crucial role in determining who will and who will not develop CAD.

Although it is likely that a significant portion of the variance in insulin resistance observed from person to person is genetically determined (68), insulin action can also be modulated by environmental influence. For example, it has been known for some time that in vivo insulin action will decline with increases in body weight (69,70). More recently, level of habitual physical activity has been shown to be significantly correlated with insulin-stimulated glucose uptake (68,71). Consequently, the more obese and sedentary an individual, the greater the degree of insulin resistance, regardless of genetic influences. Not surprisingly, obesity and decreased physical activity have also been shown to be correlated with hyperinsulinemia, glucose intolerance, increased plasma triglyceride concentration, decreased HDL-cholesterol concentration, and high blood pressure. In light of these considerations, it seems obvious that variations in life-style, in particular avoiding obesity and remaining physically active, provide an approach to minimize the risk factors for CAD associated with resistance to insulin-stimulated glucose uptake.

Summary of role of insulin resistance in etiology of CAD.

Resistance to insulin-stimulated glucose uptake is associated with hyperinsulinemia, glucose intolerance, increased plasma triglyceride and decreased HDL-cholesterol concentrations, and high blood pressure. All of these factors have been shown to increase the risk of CAD. Their presence in patients with high blood pressure and the fact that antihypertensive treatment does not restore to normal and may exacerbate these metabolic changes offer a reasonable explanation why lowering blood pressure has not reduced the risk of CAD. More generally, the fact that the cluster of risk factors for CAD seen in Table 1 is likely to be secondary in insulin

resistance makes the latter abnormality a major factor in the etiology of CAD.

CONCLUSION

Resistance to insulin-stimulated glucose uptake is a common phenomenon. The compensatory response to this defect is to secrete more insulin, and if this can be accomplished the ensuing state of hyperinsulinemia will prevent the development of frank NIDDM. Although NIDDM may not occur if hyperinsulinemia is maintained, unfortunately, this situation is not necessarily benign. First, insulin resistance and hyperinsulinemia are present in patients with hypertension and may play a role in the etiology of this syndrome. It is even more likely that the increased risk of CAD in patients with hypertension and the fact that this risk is not reduced with antihypertensive treatment are due to the clustering of risk factors for CAD, in addition to high blood pressure, associated with insulin resistance. These include hyperinsulinemia, IGT, increased plasma triglyceride concentration, and decreased HDL-cholesterol concentration, all of which have been shown to be associated with increased risk for CAD. In a more general sense, it is also likely that the same risk factors play a significant role in the genesis of CAD in the population as a whole. These conclusions suggest that resistance to insulin-stimulated glucose uptake is involved in the etiology of NIDDM, hypertension, and CAD. Although this concept may seem outlandish at first blush, the notion is consistent with available experimental data.

Approximately 50 yr have elapsed since Himsworth (1) first suggested that human disease could be secondary to a defect in insulin action. It now seems quite clear that he was correct, and the point of view he introduced has become well established. What remains to be seen is the magnitude of the role that resistance to insulin-stimulated glucose uptake plays in the etiology of human disease. I can only hope that this presentation has outlined the possibilities for future efforts to answer this question.

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