

MECHANISMS OF DISEASEFRANKLIN H. EPSTEIN, M.D., *Editor***INSULIN RESISTANCE — MECHANISMS, SYNDROMES, AND IMPLICATIONS**DAVID E. MOLLER, M.D.,
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THE past 20 years have witnessed a remarkable increase in our knowledge of the cellular and molecular mechanisms that underlie the diverse actions of insulin, the central hormone of metabolic regulation. Interest in the molecular details of insulin action has been heightened by the prevalence of insulin resistance and by the fact that insulin resistance has a key role in the pathogenesis of many disorders, including obesity, diabetes mellitus, ovarian hyperandrogenism, and possibly hypertension. In this review, we discuss current concepts of the mechanisms of insulin action and insulin resistance and the implications of insulin resistance for a variety of disorders in humans.

INSULIN ACTION

Through its integrated actions on carbohydrate, protein, and lipid metabolism, insulin exerts a dominant effect on the regulation of glucose homeostasis. These glucoregulatory effects are predominantly exerted in three tissues: liver, muscle, and fat.¹ In the liver, insulin inhibits the production of glucose by inhibiting gluconeogenesis and glycogenolysis and also promotes glycogen storage. In muscle and adipose tissue, insulin stimulates the uptake, storage, and use of glucose. These effects involve a number of tissue-specific and biochemically diverse events that occur over periods ranging from seconds to hours. Important examples include rapid increases in glucose transport through changes in the intracellular distribution and activity of specific transport mechanisms^{2,3}; the activation or inactivation of enzymes responsible for the storage and metabolism of glucose; and changes in the expression of a number of genes.⁴ Insulin also has a major role in the systemic regulation of protein and lipid metabolism through a variety of actions that affect the flux of protein and lipid substrates.¹

Less well known are certain actions of insulin on

classic target organs, such as the stimulation of potassium transport in muscle and cellular differentiation in adipocytes, as well as actions on tissues not usually considered insulin targets, such as the stimulation of ovarian production of androgens and renal retention of sodium. The existence of some of these latter actions of insulin was first suggested by clinical features, such as hirsutism, in patients with marked hyperinsulinemia and resistance to its glucoregulatory effects.⁵

Insulin Signaling

Insulin's diverse actions are initiated by interaction with a specific transmembrane protein receptor. Early studies of the insulin receptor established many of the general principles now accepted as characteristic of most membrane receptors,⁶ and our understanding of the insulin receptor has been dramatically advanced by its cloning and studies of structural and functional relations.^{7,8}

The human insulin receptor is encoded by a single gene composed of 22 exons that is located on chromosome 19.⁹ A single proreceptor precursor of 1382 amino acids that includes a 27-amino-acid signal peptide is synthesized from the messenger RNA. The receptor is subsequently processed by removal of the signal peptide, glycosylation, cleavage into α (molecular weight, 135,000) and β (molecular weight, 95,000) subunits, and assembly as a disulfide-bond-linked tetramer composed of two α and two β subunits (Fig. 1).²⁵ In the mature $\alpha_2\beta_2$ receptor, a 23-residue hydrophobic domain in each β subunit spans the plasma membrane. The extracellular α subunit confers high-affinity insulin binding; mutagenesis studies suggest that specific domains, such as the region encoded by exon 2,²⁶ are critical for ligand binding. The transmembrane component of the β subunit is responsible for transducing the signal of insulin binding to the interior of the cell. After insulin binding, specific tyrosine residues of the intracellular region of the β subunit are rapidly phosphorylated, and the tyrosine kinase intrinsic to this region is activated.^{25,27} The cytoplasmic portion of the β subunit bears strong homology to other transmembrane receptors that have tyrosine kinase activity, including the insulin-like growth factor I (IGF-I) receptor, the receptor for epidermal growth factor, and the products of several proto-oncogenes.²⁸ Receptor autophosphorylation and tyrosyl phosphorylation of other protein substrates require an intact binding site for ATP within the β subunit (Fig. 1). Mutation of a critical lysine residue within this site abolishes insulin-stimulated kinase activity and prevents receptor occupancy from generating insulin-stimulated biologic actions.²⁹ Complete activation of kinase may not be necessary for signaling all the actions of insulin, however, since certain mutant receptors with impaired kinase function appear to signal some effects of insulin normally.^{29,30}

The immediate consequences of the activation of the tyrosine kinase activity of the insulin receptor re-

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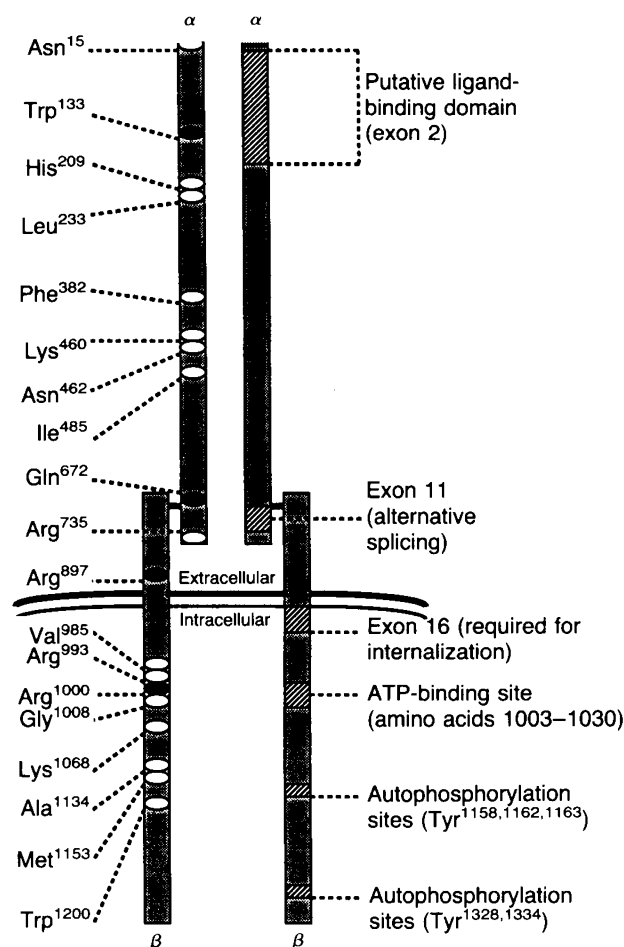


Figure 1. Structure of the Human Insulin Receptor, with Known Point Mutations.

The insulin receptor is depicted as a transmembrane tetrameric protein composed of two α and two β subunits. Several functionally important domains and residues are identified in the right half-receptor. Nineteen known naturally occurring point mutations are identified in the left half-receptor according to the involved amino acid.¹⁰⁻²² The amino acid numbers correspond to the system of Ebina et al.⁸ Mutations that encode amino acid substitutions (missense mutations, open ovals) are distinguished from those that encode stop codons (nonsense mutations, solid ovals). Two large deletions of the insulin-receptor gene are not shown.^{23,24}

main poorly defined. No direct, functionally important tyrosyl phosphorylation of the proteins classically regulated by insulin (e.g., glycogen synthase and glucose transporters) has been described. Many actions of insulin are regulated by phosphorylation or dephosphorylation of serine (or threonine) residues, however, and a "phosphorylation cascade" has therefore been proposed to explain some of the actions of insulin (Fig. 2). In one such model, tyrosyl residues of proximal intermediates are phosphorylated, leading after an unknown number of steps to the activation of serine kinases. Serine kinases then either regulate protein function directly by phosphorylation or indirectly by activating specific phosphatases.³¹ A major goal of current research is to identify signaling intermediates

that participate in the switch from tyrosyl to seryl phosphorylation pathways. The novel peptide pp185 (or IRS-1) is an example of a protein whose tyrosyl residues appear to be phosphorylated by the activated insulin-receptor kinase, and could have such a role.³² Other molecules potentially involved in the generation of insulin effects include a lipid kinase (phosphatidylinositol-3-kinase), and serine kinases such as the *raf-1* kinase and S6 kinase.³¹ The latter enzyme may modify protein synthetic processes by phosphorylating ribosomal S6 protein. By activating a specific phospholipase C, insulin may also generate a soluble phosphatidylinositol-glycan mediator that could then regulate the function of specific enzymes.³³ Some aspects of insulin action may not involve a phosphorylation cascade. Instead, conformational changes in the receptor that occur after binding may facilitate noncovalent interactions of the receptor with signal-transducing G proteins.

Receptor Regulation

Given the key role of insulin receptors in mediating the actions of insulin, one would expect their number and function to be tightly regulated. Occupancy of the receptor by insulin is followed by endocytotic internalization of the hormone-receptor complex, an event that requires the presence of specific amino acids in the cytoplasmic portion of the β subunit adjacent to the membrane and a functionally normal receptor kinase.^{25,29} Once internalized, the receptors may be degraded, but most are recycled to the cell surface. The dose-dependent ability of insulin to reduce the number of receptors by accelerating receptor degradation is called "down-regulation."^{34,35} In addition to insulin itself, other physiologic factors, including exercise, diet, and hormones such as growth hormone and glucocorticoids, can change the number of receptors.³⁴ Another important aspect of the regulation of insulin receptors is the termination of insulin signaling. Dephosphorylation of the insulin receptor by tyrosine phosphatases is one likely mechanism for termination of the signal.³⁶ The identity and regulation of specific phosphatases that act on the insulin receptor are not known, however. The insulin-receptor kinase is also potentially regulated by other cellular signaling systems, such as the protein kinase C pathway, which when activated results in seryl phosphorylation of the receptor and inhibition of its tyrosine kinase activity,³⁷ and other endogenous factors.³⁸

Basis for the Multiple and Tissue-Specific Actions of Insulin

The most obvious determinant of tissue-specific insulin action is the identity of the specific proteins expressed in particular tissues. For example, insulin stimulates lipogenesis in fat largely because the necessary enzymes are expressed in adipocytes. In addition to such tissue-specific factors, there is increasing evidence that a number of distinct signals may emanate

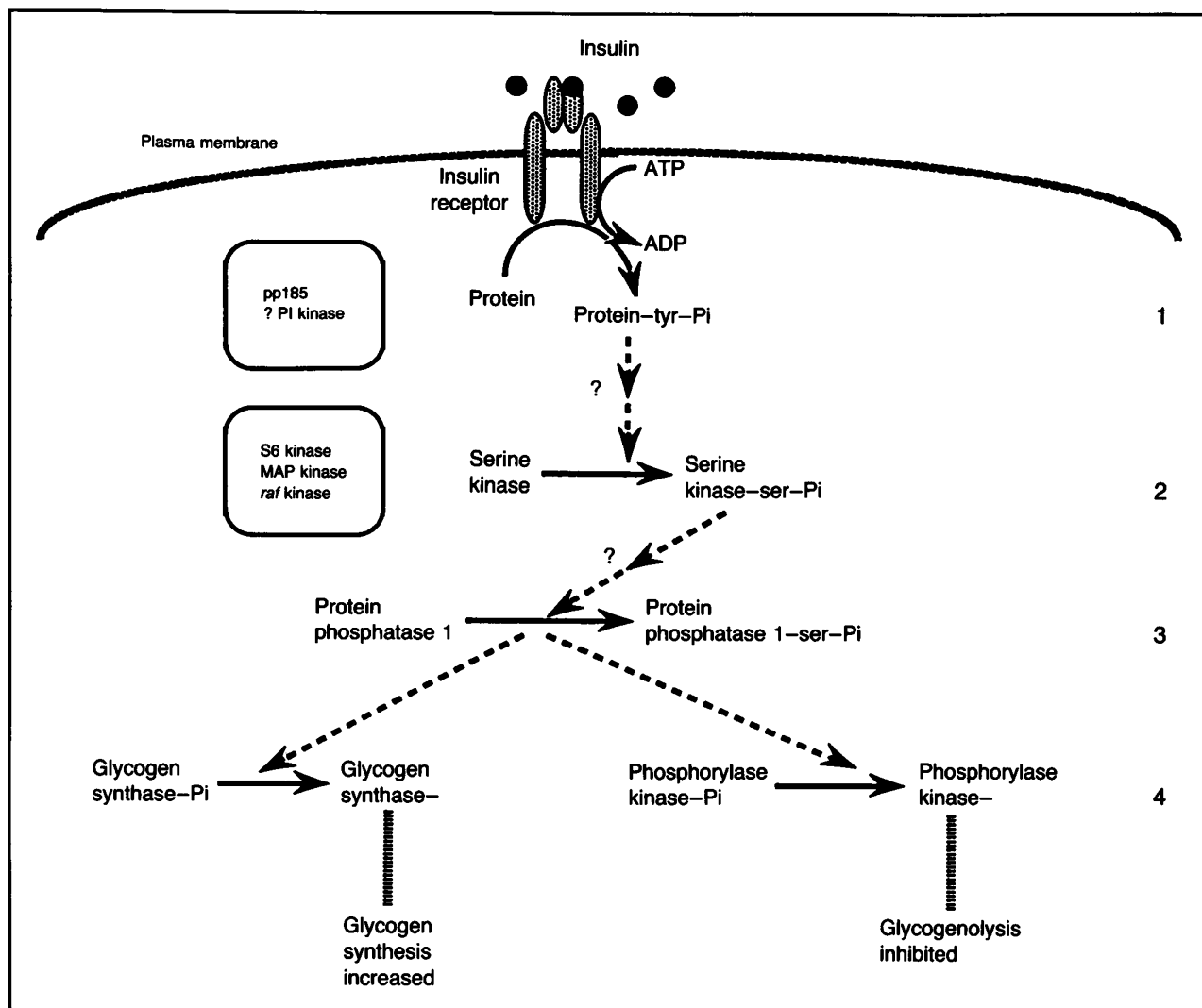


Figure 2. Insulin Signaling through a Phosphorylation Cascade.

With glycogen metabolism as a model, the action of insulin is depicted as involving a cascade of phosphorylation and dephosphorylation reactions, beginning with the activation of the tyrosine kinase of the insulin receptor. Steps 1 and 2 represent the activation of currently unidentified kinases by tyrosine or serine phosphorylation. Candidate signaling intermediates that may be tyrosyl phosphorylated by the receptor (upper box) or serve as insulin-activated serine kinases (lower box) are also shown. With the possible exception of S6 kinase, these potential intermediates have not yet been linked to specific actions of insulin. Step 3 represents the coordinate activation of protein phosphatase 1 by seryl phosphorylation, followed by the activation of glycogen synthase and the inactivation of glycogenolysis by seryl dephosphorylation (step 4). Other potential signaling systems (e.g., G proteins and phospholipases) that may interact with or be regulated by the activated insulin receptor are not shown. PI denotes phosphatidylinositol, Pi inorganic phosphate, and MAP microtubule-associated protein.

directly from the activated insulin receptor within a given cell type. Certain site-directed²⁹ or naturally occurring³⁰ mutations of the insulin receptor thus appear capable of activating some pathways but not others.

Although we commonly refer to *the* insulin receptor, we now know that the binding of insulin to several proteins can generate metabolic signals. First, splicing of the insulin-receptor messenger RNA at alternative sites results in the inclusion or exclusion of one small exon (exon 11) encoding a short segment of the distal region of the α subunit (Fig. 1). The relative abun-

dance of these two splice variants is regulated in a tissue-specific manner.^{39,40} The search for functional differences between the two variants is at an early stage and is currently limited to small differences in insulin-binding affinity and endocytotic rate.⁴¹ Second, at concentrations considerably higher than those required for insulin-receptor occupancy but within the range that occurs in some disorders, insulin can also bind to and activate IGF-I receptors.⁴² Third, recent studies have demonstrated the existence of $\alpha_2\beta_2$ hybrid receptors — receptors composed of one insulin $\alpha\beta$ half-receptor and one IGF-I $\alpha\beta$ half-receptor.⁴³

Although much remains to be learned about the signals such hybrids generate, they could mediate some of the tissue-specific actions of insulin.

INSULIN RESISTANCE

Insulin resistance is defined as a subnormal biologic response to a given concentration of insulin. The clinical spectrum of insulin resistance is broad, and includes patients with diabetes mellitus who require insulin and who continue to have hyperglycemia despite large doses of exogenous insulin as well as severely insulin-resistant people who maintain near-normal blood glucose levels through marked elevations in endogenous insulin secretion. Although insulin's effects are pleiotropic, the term "insulin resistance" typically refers to the actions of insulin on glucose homeostasis. In some disorders selective resistance to insulin may in fact occur, causing the high insulin levels needed to compensate for its decreased glucose-lowering effect to produce increased effects in other pathways. One possible example is the increase in ovarian production of androgens that occurs in patients with hyperinsulinemia who have severe resistance to the glucose-lowering effect of insulin.^{5,44,45}

Virtually all patients with diabetes mellitus, whether they have insulin-dependent diabetes mellitus (IDDM) or non-insulin-dependent diabetes mellitus (NIDDM), have some degree of resistance to the actions of insulin on glucose homeostasis. In patients who require exogenous insulin, doses of more than 100 to 200 units per day may be viewed as evidence of unusually severe insulin resistance. When such increased requirements for insulin result from the now rare occurrence of high titers of antibodies to insulin or the disputed entity of subcutaneous degradation of injected insulin, the insulin dose does not reflect insulin resistance at the level of target cells.

Several methods are used to detect and quantify insulin resistance. In patients treated with exogenous insulin, the administered dose is an imperfect measure of tissue resistance. An elevated circulating level of endogenous insulin is a common feature of insulin resistance, and in the absence of a defect in insulin secretory capacity this level correlates well with more sophisticated measures of insulin sensitivity.⁴⁶ Hyperinsulinemia results not only from increased secretion of insulin by beta cells, but also from impairment of receptor-mediated clearance of insulin by resistant peripheral target cells.⁴⁷ Mutations of the insulin molecule may result in a failure of proinsulin to be cleaved or in diminished affinity of insulin for its receptor, and such mutations can thus cause hyperinsulinemia. Patients with such defects respond normally to exogenous insulin, however, and are not actually insulin-resistant.⁴⁸ Quantitative *in vivo* measurements of insulin sensitivity, such as the euglycemic insulin-clamp technique and computer-modeled analysis of the response of glucose to a bolus dose of insulin, permit the determination of dose-response curves for

in vivo insulin action.⁴⁶ Insulin sensitivity can also be measured *in vitro* in freshly obtained or cultured cells and tissue samples.

Cellular Mechanisms of Insulin Resistance

Intrinsic (Primary) Defects in Target Cells

Intrinsic defects in insulin sensitivity were first suggested by the observation that defects in insulin binding and action persisted in cultured fibroblasts derived from some patients with *in vivo* insulin resistance. Since the action of insulin involves many gene products (Fig. 2), target-cell defects could be due to mutations affecting any protein between the receptor and the final insulin-regulated proteins (Table 1).

The insulin-receptor locus has received the greatest attention, and to date 21 receptor mutations have been identified in 19 patients with insulin resistance.¹⁰⁻²⁴ With two exceptions,^{14,22} each mutation has been detected in only one patient or family. All the mutations so far detected are in the structural gene rather than the gene promoter or other noncoding domains (Fig. 1); with the exception of two gross gene deletions,^{23,24} all are single-nucleotide substitutions. The consequences of these mutations for the expression and function of receptors are diverse; they result in decreased levels of receptor messenger RNA,^{15,19} defective processing of the proreceptor into its α and β subunits,²⁰ impaired transport of receptors to the cell membrane,^{15,18} accelerated receptor degradation,¹⁶ abnormal insulin binding,^{15,17} and impaired receptor tyrosine kinase activity.^{10-14,23,24} These disorders have

Table 1. Causes of Insulin Resistance.

Defects intrinsic to target cells
Mutations of the insulin-receptor gene
Defects in other genes important for insulin action (putative)
Glucose transporters
Substrates for insulin-receptor kinase or signaling intermediates
Cellular inhibitors of insulin-receptor kinase
Secondary factors affecting target cells
Abnormal physiologic states
Stress (e.g., fever, sepsis)
Fasting or starvation
Uremia
Cirrhosis
Ketoacidosis
Obesity
Diabetes or hyperglycemia
Normal physiologic states
Puberty
Advanced age
Pregnancy
Specific hormonal or metabolic factors
Glucocorticoids (e.g., Cushing's syndrome)
Growth hormone (acromegaly)
Catecholamines (e.g., pheochromocytoma)
Glucagon (e.g., glucagonoma)
Thyroid hormone (thyrotoxicosis)
Hyperinsulinemia (e.g., insulinoma)
Hyperglycemia (diabetes)
Free fatty acids (nonesterified fatty acids)
Adenosine
Perhaps islet amyloid polypeptide (amylin)
Autoantibodies to the insulin receptor

both dominant and recessive patterns of inheritance. Some patients¹⁰⁻¹³ with mutations in the cytoplasmic component of the β subunit are simple heterozygotes for the mutant alleles. One likely explanation for the apparent ability of such dominant-negative mutations to impair the function of the receptor encoded by the normal allele relates to the fact that the receptor is an oligomeric protein that will contain products of both normal and defective alleles.¹²

Functionally important defects in other genes that are central to insulin action have not been described. Candidate genes include members of the family of glucose-transporter proteins, in particular the transporter species that appears to be responsible for the insulin-stimulated uptake of glucose in muscle and fat (the type 4 glucose transporter, or GLUT-4),³ and several enzymes involved in the intracellular pathways of glucose metabolism, such as hexokinase, phosphofructokinase, and glycogen synthase. As signaling intermediates between the receptor and downstream pathways are identified and cloned, their role in insulin resistance will need to be defined. The potential role of currently unidentified proteins has been suggested by the recent report of an inhibitor of the insulin-receptor kinase in cultured cells from an insulin-resistant patient.⁴⁹

Secondary Factors Affecting the Sensitivity of Target Tissue to Insulin

Many physiologic states and circulating factors can adversely affect the action of insulin. The secondary nature of these defects is established by the restoration of normal insulin sensitivity after the removal of the factor or state, or the reversal of the defect after cells are removed from the abnormal *in vivo* milieu. Glucocorticoids, glucagon, catecholamines, and growth hormone induce insulin resistance in cases of the excess secretion of individual hormones, which occurs in specific endocrinopathies, and the combined effects of these hormones in the setting of infection and stress.⁵⁰ The anti-insulin effects of glucagon are confined largely to the liver, although impaired glucose transport has also been described in peripheral cells.⁵¹ Other counterregulatory hormones antagonize the actions of insulin in both hepatic and peripheral cells. Although growth hormone increases glucose clearance in the short term,⁵⁰ antagonistic effects may later result from decreases in the number of insulin receptors⁵² or the inhibition of glucose transport, possibly through effects on the expression of glucose-transporter genes.⁵³ Glucocorticoids may induce insulin resistance directly by reducing the number or efficacy of glucose transporters,⁵⁴ and indirectly by increasing the circulating levels of glucagon and free fatty acids.⁵⁰ The decreased cellular use of glucose induced by glucocorticoids does not involve changes at the level of the insulin receptor, since the transcription of the receptor gene is actually stimulated by glucocorticoids in some cell types. Catecholamines antagonize insulin by stimulating gluco-

neogenesis, glycogenolysis, and lipolysis⁵⁰ and by inhibiting peripheral glucose use by a β -adrenergic mechanism that may also involve a decrease in cellular glucose transport.⁵⁵

Hyperinsulinemia itself down-regulates insulin receptors^{34,35} and results in postreceptor cellular desensitization.⁵⁶ Insulin resistance can be demonstrated in patients with insulinomas and in normal subjects after the infusion of exogenous insulin.⁵⁷ Islet amyloid polypeptide, or amylin, a recently identified product of pancreatic beta-cells that is secreted together with insulin, may antagonize the glucose-lowering effect of insulin on peripheral tissues.⁵⁸ The concentrations of amylin shown to result in insulin resistance are as much as 1000 times the physiologic levels, however.⁵⁸ Both *in vitro* and *in vivo*, hyperglycemia is itself an important cause of diminished sensitivity to the glucose-lowering effects of insulin (see below).^{59,60} In certain tissues, adenosine⁶¹ or free fatty acids⁶² may attenuate the action of insulin.

Several complex physiologic states, including diabetic ketoacidosis, uremia,⁶³ cirrhosis,⁶⁴ fasting,² pregnancy, puberty, and aging,⁶⁵ are associated with resistance to insulin. Uremia does not impair insulin binding, insulin-receptor kinase activity, or glycogen synthase activity,⁶³ suggesting that it has a postreceptor effect on the insulin-stimulated transport of glucose. The glucose-lowering effects of insulin are reduced by fasting as a result of decreased glucose-transporter expression, decreased functional activity of glucose transporters, or both.²

Although rare, perhaps the best-characterized secondary factor that can affect the sensitivity of target cells to insulin is spontaneously occurring antibodies to the insulin receptor.⁶⁶⁻⁶⁸ Such antibodies are typically polyclonal IgG and usually develop in the setting of other features of autoimmunity. These antibodies frequently cause steric inhibition of insulin binding, although certain antibodies may bind to the receptor and affect its function without directly blocking insulin binding.^{68,69} Anti-insulin-receptor antibodies may also accelerate the degradation of insulin receptors and cause postreceptor desensitization of target cells. When incubated with target cells *in vitro*, these antibodies usually behave as insulin agonists.⁶⁸ Affected patients can have multiple populations of antibodies that differ in their antagonistic or agonistic properties and in tissue specificity.

SYNDROMES OF INSULIN RESISTANCE

General Consequences of Insulin Resistance

The clinical consequences of insulin resistance can be divided into two broad categories — those that result from deficient insulin action and those that result from excessive insulin action. Impaired glucose tolerance and diabetes are clearly the consequences of deficient insulin action. Other potential consequences of deficient insulin action include growth retardation and lipodystrophy.

The notion that compensatory hyperinsulinemia

can actually produce excessive insulin action was first suggested by two clinical features common to many patients with severe resistance to the glucose-lowering effects of insulin — the skin lesion of acanthosis nigricans and ovarian thecal hyperplasia with hyperandrogenism.^{5,44,45,70} Acanthosis nigricans is characterized by hyperkeratotic epidermal papillomatosis with increased melanocytes; it leads to hyperpigmented, velvety areas of skin, predominantly in apposed and flexural locations.⁷⁰ Mild acanthosis nigricans and moderate insulin resistance have been found to be prevalent in some studies (as high as 7 percent), and their severity is positively correlated.⁷¹ In view of the common association of insulin resistance with acanthosis nigricans and ovarian dysfunction,⁷² the correlation between the severity of these lesions and the circulating level of insulin, and their absence in insulin-deficient states, it is clear that these features are caused by excessive rather than deficient insulin action. Hyperinsulinemia may affect the skin and ovaries by binding to and activating IGF-I receptors or through insulin receptors that remain partially competent for signaling. Human ovarian cells have both insulin and IGF-I receptors, and both ligands can stimulate steroidogenesis and cell growth in ovarian tissue.^{44,45,73}

Genetic Syndromes of Severe Insulin Resistance

Type A Syndrome and Variants

The Type A syndrome of insulin resistance is the prototypic inherited syndrome of severe insulin resistance (Table 2).⁵ The syndrome is characterized by marked endogenous hyperinsulinemia with or without glucose intolerance, acanthosis nigricans, and (in affected postpubertal women) ovarian hyperandrogenism. The classic syndrome occurs in lean or muscular adolescent girls who come to medical attention because of clinical manifestations of hyperandrogenism such as amenorrhea, hirsutism, and virilization. The affected ovaries show stromal hyperplasia and hyperthecosis, such as occurs in women with the polycystic ovary syndrome.^{44,45} Similar degrees of insulin resistance with variable acanthosis nigricans may occur in brothers,⁷⁴ prepubertal sisters, and the fathers¹² of female probands. The Rabson–Mendenhall syndrome,⁷⁵ a variant of the Type A syndrome, is characterized by pineal hyperplasia, dental dysplasia, and other dysmorphic features.

Several patients with the Type A syndrome who had some clinical features of acromegaly, including acral enlargement, coarsened facial features, and widened spaces between the teeth, have been described.⁷⁴ These patients had normal or low circulating levels of growth hormone and IGF-I. Patients with the additional features of obesity, accelerated linear growth, and muscle cramps⁷⁴ have also been described.

Insulin-receptor mutations that cause defects in receptor expression on the cell surface^{15,18} or in the signaling capacity of the receptor^{10-14,18,20,23,24} (or both) have been identified in several patients with the Type

Table 2. Genetic Syndromes of Severe Insulin Resistance.

SYNDROME	CLINICAL FEATURES	MECHANISMS
Type A syndrome		
Classic	Acanthosis nigricans, severe insulin resistance, ovarian hyperandrogenism	Insulin-receptor mutations or other target-cell defects in insulin action
Rabson–Mendenhall	Type A features, perhaps with dental dysplasia, pineal hyperplasia, or other dysmorphic features	Insulin-receptor mutations or other target-cell defects in insulin action; possibly other defects
Pseudoacromegaly	Type A features, perhaps with acral enlargement, muscle hypertrophy, widened teeth spacing, muscle cramps, or other features of acromegaly	Possibly insulin-receptor mutations, other defects
Leprechaunism	Intrauterine growth retardation, dysmorphic facies, perhaps with Type A features, hypertrichosis, lipodystrophy, or phallic enlargement	Insulin-receptor mutations; possible defects in other growth-factor receptors or pathways common to multiple growth factors
Lipodystrophy		
Total congenital lipodystrophy	Total lipodystrophy, perhaps with Type A features, hepatosplenomegaly, cardiomyopathy, features of acromegaly, hypertriglyceridemia, or genital hypertrophy	Possibly insulin-receptor mutations or other defects
Partial congenital lipodystrophy	Adipose-tissue depots variably affected by lipodystrophy or lipohypertrophy, perhaps with Type A features, hepatosplenomegaly, cardiomyopathy, features of acromegaly, or hypertriglyceridemia	Possibly insulin-receptor mutations or other defects

A syndrome^{10-14,18,23,24} or the Rabson–Mendenhall syndrome.^{15,20} Other patients have had defects in insulin-receptor binding (affinity, number, or both) or insulin-stimulated receptor autophosphorylation and kinase activity, although their receptor-gene structure has not yet been determined. All of these findings suggest that genetic defects at the insulin-receptor locus probably account for most cases of the Type A syndrome of insulin resistance. We have found a normal complementary DNA nucleotide sequence for the insulin receptor in one patient with this syndrome (unpublished data), demonstrating that in at least some patients, insulin resistance may be due to mutations in the receptor-gene promoter or other proteins important for insulin action. We stress that in the limited numbers of patients so far studied, the location (Fig. 1) and biochemical consequences of these receptor mutations do not provide an explanation for the heterogeneous clinical phenotype.

Leprechaunism

Leprechaunism is a rare congenital syndrome characterized by intrauterine growth retardation, dysmorphic facies, lipodystrophy, acanthosis nigricans, and ex-

treme insulin resistance.⁷⁶ Like adolescents with the Type A syndrome, affected newborn girls may have cystic ovaries, hirsutism, and clitoromegaly. Studies with cultured cells from several patients have demonstrated defects in insulin binding, insulin-receptor autophosphorylation and kinase activity, and insulin-stimulated biologic actions.⁷⁷ Four patients with leprechaunism had mutations of both alleles of the gene for the insulin receptor, the patients being either compound heterozygotes^{16,19} or homozygotes.^{15,17} Some patients with leprechaunism have apparent abnormalities of other growth-factor receptors including the receptor for epidermal growth factor and the IGF-I receptor.⁷⁸ This suggests that certain insulin-receptor defects may impair the function of other receptors¹⁵ or that leprechaunism may be caused by mutations that affect signaling pathways common to a number of growth factors.⁷⁸

Lipodystrophy

Patients with lipodystrophy may have no adipose tissue (congenital total lipodystrophy, or the Berardinelli-Seip syndrome) or partial lipodystrophy with variable regional lipodystrophy or hypertrophy (or both).⁷⁹ Other components of the Type A syndrome, as well as acromegaloid and dysmorphic features (such as genital hypertrophy and cardiomyopathy), may also be present.⁷⁹ Patients with total lipodystrophy may have marked hypertriglyceridemia with associated hepatosplenomegaly due to fatty infiltration. Heterogeneous defects in insulin binding, receptor expression, receptor kinase function, and postreceptor signaling have been identified in cells from patients with insulin resistance who have congenital lipodystrophy.⁸⁰ The specific mechanism responsible for lipodystrophy or lipodystrophy is unknown. In vivo resistance to the antilipolytic action of insulin has been described,⁸¹ suggesting that certain defects at the level of the insulin receptor or postreceptor pathways can preferentially affect lipid metabolism in a generalized or region-specific manner. Acquired forms of total or partial lipodystrophy have also been described⁷⁹ and are frequently associated with severe insulin resistance.

Type B Syndrome

Insulin resistance due to autoantibodies to the insulin receptor is referred to as the Type B syndrome.^{5,66,67} Typically, patients with the syndrome have uncontrolled diabetes, acanthosis nigricans, and (in premenopausal women) ovarian hyperandrogenism.⁶⁸ Given that antireceptor antibodies can behave as agonists and antagonists, patients may have fasting hypoglycemia⁶⁸ with or without postprandial hyperglycemia or may alternate among insulin-resistant diabetes, remission, and hypoglycemia.⁸² Most patients with the Type B syndrome have clinical or laboratory evidence of systemic autoimmune disease. Systemic lupus erythematosus, primary biliary cirrhosis, and other defined disorders have been described; more

often the signs of autoimmunity are limited to laboratory abnormalities such as leukopenia and high titers of anti-DNA antibodies.^{68,83} The Type B syndrome has also been associated with ataxia-telangiectasia.⁸⁴ Whether the predominant metabolic disorder is insulin-resistant hyperglycemia or refractory hypoglycemia, the treatment options are limited. Patients have benefited from glucocorticoids, immunosuppressive agents, and plasmapheresis.^{68,82,83} A single report suggests that insulin-receptor autoantibodies of unknown functional consequence can be detected in a small minority of patients with typical NIDDM.⁶⁹

Obesity and NIDDM

Insulin resistance is one of two physiologic defects involved in the pathogenesis of NIDDM, the other being a defect in the functional capacity of pancreatic beta cells to secrete insulin. This defect in insulin secretion is found in virtually all patients and is undoubtedly necessary to the development of overt hyperglycemia.⁸⁵ The relation between insulin resistance and diabetes is illustrated in some patients with insulin-receptor mutations in whom mildly impaired or even normal glucose tolerance may persist for years as long as hyperinsulinemia is maintained, despite insulin resistance far exceeding that in typical NIDDM. The ability of insulin resistance to provoke a failure of beta-cell compensation in susceptible people could be a critical step in the pathogenesis of NIDDM.

Insulin resistance is ubiquitous in obese people and in lean or obese patients with NIDDM. NIDDM is associated with resistance to the ability of insulin to inhibit hepatic glucose output and stimulate the uptake and use of glucose by fat and muscle.^{86,87} As compared with the insulin resistance of obesity, in which the dose-response relation for the use of glucose by peripheral tissues is consistent with a simple loss of insulin sensitivity, there is greater peripheral insulin resistance in patients with NIDDM, generally characterized by a further loss of insulin sensitivity and a reduction in the maximal insulin response.⁸⁶

The number of insulin receptors is somewhat decreased in several tissues of nondiabetic obese persons and lean or obese patients with NIDDM, possibly as a result of receptor down-regulation due to basal hyperinsulinemia.^{34,86} This moderate decrease in the number of receptors cannot account for the degree of insulin resistance in most patients, suggesting that the function of receptors in such patients may be affected. The ability of insulin to stimulate autophosphorylation and tyrosine kinase activity is impaired in insulin receptors derived from fat, skeletal muscle, liver, and circulating monocytes of patients with NIDDM.⁸⁸ Obese patients without overt hyperglycemia may have similar defects in receptor function in skeletal muscle.⁸⁹ Importantly, in obese patients with NIDDM weight loss substantially improves both hyperglycemia and the defect in kinase activity of insulin receptors.⁹⁰ This defect in receptor function thus appears to

be a consequence of the abnormal metabolic milieu rather than a primary cause of insulin resistance. Whether inherited defects in one or more proteins render some people more susceptible to acquired receptor dysfunction is an important subject for future research.

The ability of insulin to increase the rate of glucose uptake in muscle and fat is a key step in the action of insulin to promote glucose disposal. Indeed, impairment of insulin-stimulated glucose transport has been demonstrated in muscle and adipocytes of patients with NIDDM.^{91,92} Obesity alone may be associated with a similar but less severe defect.⁹¹ Defective glucose transport could result from a decrease in the number of specific transporters or from an impaired ability of insulin to signal the recruitment and activation of existing transporters.² Studies in patients with NIDDM suggest that the number of glucose transporters in adipocytes is reduced.⁹¹ Muscle, however, is the predominant site of insulin-stimulated glucose disposal *in vivo*,⁸⁷ and a recent study suggested that the total number of insulin-responsive glucose transporters (GLUT-4) in the skeletal muscle of patients with NIDDM is unaltered.⁹³ The mechanism of defective glucose transport in NIDDM is probably at least in part a consequence of hyperglycemia itself, since the insulin-stimulated transport of glucose is also impaired in IDDM and in animal models of insulin-deficient diabetes, in which the restoration of euglycemia alone is associated with the normalization of glucose transport.⁶⁰

Patients with NIDDM have additional defects in the pathways through which insulin stimulates the disposal of glucose, apart from activation of the insulin receptor and transport of glucose into cells. Direct measurements of enzyme activity in tissue suggest that the ability of insulin to activate pyruvate dehydrogenase,⁹⁴ muscle glycogen synthase,⁹⁵ and muscle glycogen synthase phosphatase (protein phosphatase 1)⁹⁶ (Fig. 2) is impaired in NIDDM. Studies using indirect calorimetry^{87,97} and nuclear magnetic resonance spectroscopy⁹⁸ have been interpreted as showing that the peripheral insulin resistance of NIDDM may preferentially affect nonoxidative glucose metabolism (storage as glycogen) rather than oxidative glucose metabolism. More recent studies, however, have suggested that the transport of glucose (or the initial phosphorylation of glucose to glucose-6-phosphate) is rate-limiting for the impaired uptake and storage of glucose in muscle in NIDDM.^{99,100}

Whatever the disease's molecular basis, family studies in homogeneous populations with a high frequency of NIDDM (such as the Pima Indians)¹⁰¹ and in the more heterogeneous offspring of parents with NIDDM¹⁰² clearly show that a component of insulin resistance is inherited and may predispose family members to the development of diabetes. A critical goal of current research is to identify the specific gene defects that are responsible for the inherited aspects of insulin resistance of NIDDM. Although some hetero-

zygous relatives of patients with severe insulin resistance due to insulin-receptor mutations involving both receptor alleles have impaired glucose tolerance and insulin resistance like that in NIDDM,^{14,16,17} defects in the coding region of the insulin-receptor gene have not been detected in Pima Indians^{103,104} and are apparently uncommon in other groups of patients with NIDDM.²² Future studies will focus on potential alterations in other candidate genes, such as GLUT-4, in which one uncommon mutation of as yet unknown functional importance has recently been detected.^{105,106} In one large kindred with maturity-onset diabetes of the young — a rare subtype of NIDDM — diabetes was linked to a DNA polymorphism on the long arm of chromosome 20; impaired insulin secretion was the predominant physiologic defect in the family, however.¹⁰⁷ NIDDM is clearly a clinically heterogeneous syndrome with respect to factors such as body weight, age at onset, and pattern of inheritance. Whether and by what mechanisms different “diabetogenes” that confer susceptibility to NIDDM relate to this physiologic and phenotypic diversity remain to be determined.

Other Disorders Associated with Insulin Resistance

Insulin Resistance and Ovarian Dysfunction

Apart from the previously discussed association of severe insulin resistance with ovarian thecal hyperplasia and hyperandrogenism,⁵ obesity and insulin resistance (hyperinsulinemia) are common among women with the typical polycystic ovary syndrome. Hyperandrogenism and hyperinsulinemia are correlated positively in such patients, independently of obesity.^{44,45} Furthermore, 5 percent of women with this syndrome have acanthosis nigricans, and they are the most insulin-resistant.⁷² Treatment of hyperandrogenism in insulin-resistant patients with the polycystic ovary syndrome fails to improve insulin resistance^{44,108}; hyperandrogenism thus does not cause or contribute to insulin resistance to an important degree. In contrast, attempts to raise insulin levels abruptly in patients with the polycystic ovary syndrome have produced variable increases in androgen levels.⁴⁴ On balance, hyperinsulinemia that results from insulin resistance of unknown causes may contribute to the pathogenesis of the polycystic ovary syndrome.

Insulin Resistance, Hypertension, Hyperlipidemia, and Atherosclerosis

In addition to the well-appreciated association of IDDM and NIDDM with ischemic heart disease, recent epidemiologic data suggest that hyperinsulinemia is itself an independent risk factor for cardiovascular disease.¹⁰⁹ After other known risk factors have been considered, NIDDM and impaired glucose tolerance without overt diabetes are associated with a similar risk of cardiovascular disease; the additional effect of hyperglycemia in these common syndromes is therefore likely to be small relative to the risk of insulin

resistance.¹⁰⁹ Limited evidence suggests that insulin may promote the growth of vascular cells and atherosclerosis directly.¹⁰⁹ Insulin resistance has also been implicated in the pathogenesis of essential hypertension and hypertriglyceridemia.¹¹⁰ The term "syndrome X" was recently applied to the clinical association of insulin resistance, hypertension, and increased very-low-density lipoprotein (VLDL) and decreased high-density lipoprotein (HDL) cholesterol concentrations in plasma.¹¹⁰ How hyperinsulinemia contributes to the pathogenesis of hypertension is poorly understood; however, insulin can increase the activity of the sympathetic nervous system¹¹¹ or independently promote the renal reabsorption of sodium.¹¹⁰ Insulin resistance is strongly correlated with elevations in VLDL and reductions in HDL cholesterol concentrations, and hyperinsulinemia may directly promote hepatic VLDL production even when there is resistance to the glucose-lowering effect of insulin.¹¹⁰

CONCLUSIONS

In this review we have discussed recent progress in our understanding of the mechanisms of insulin action and the basis for disorders characterized by insulin resistance. Progress in understanding the syndromes of severe insulin resistance has been marked. Given the current evidence that hyperinsulinemia and insulin resistance have an important role not only in diabetes but also in hypertension, dyslipidemia, and cardiovascular disease, the molecular basis for mild insulin resistance in these disorders will merit intensive investigation in the years to come.

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