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INSULIN RECEPTORS AND INSULIN RESISTANCE

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ABSTRACT

Resistance to the action of insulin plays a central role in many important disease states, including diabetes and obesity. Many insights into the mechanism and significance of insulin resistance in these and other disorders have followed upon our expanding knowledge regarding insulin receptors. In this article, we review our current understanding of insulin receptors and their regulation, and we assess the role of insulin receptor pathology in the various syndromes characterized by insulin resistance.

INTRODUCTION

Insulin is a 6000 MW peptide secreted by the beta cell of the pancreas; it plays a central role both in the regulation of metabolism and in the pathophysiology and treatment of the diabetic syndromes. Since its discovery, considerable efforts have been directed toward determining the mechanism of action of this hormone. Although much remains unknown, a great deal has been learned about the first step in insulin action—the binding to specific receptors in the plasma membrane of the cell (1, 2). The rapid accumulation of information regarding insulin receptors has furthered our understanding of disease mechanisms. This is especially true for diseases characterized by insulin resistance.

Insulin resistance is a state in which a given concentration of insulin produces a subnormal biologic response. Over the past 10 years, studies of insulin receptors and of insulin-resistant disease states have advanced in parallel. Thus, the direct measurement of insulin receptors on target tissues

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has improved our understanding of the mechanism responsible for insulin resistance in a variety of diseases (2, 3). In a complementary fashion, studies of the manner in which insulin receptors may be altered in disease have led to many insights into the molecular mechanism of insulin action (4). In this review, I discuss the mechanisms of insulin resistance in the light of current knowledge of insulin action, and assess the clinical states of insulin resistance from the perspective of insulin receptor biology.

INSULIN ACTION—GENERAL CONSIDERATIONS

A complete understanding of the mechanism of insulin action at the cellular level has been difficult to obtain, for several reasons. Although insulin is best known for its promotion of glucose metabolism, it exerts a wide variety of effects at the cellular level (5). Thus, in addition to stimulating glucose and amino acid transport, insulin can also activate or inactivate cytoplasmic and membrane enzymes, alter the rate of synthesis of protein and DNA, and influence the processes of cell growth and differentiation. These multiple effects vary widely with respect to dose response and time course. Some effects, such as stimulation of glucose transport, occur within seconds at very low insulin concentrations (10^{-11}M). At the other extreme, actions on DNA synthesis and cell growth require hours and generally involve higher concentrations of the hormone (10^{-7}M). A recently recognized factor that further complicates the study of insulin action is the relationship between insulin and another family of peptides possessing a similar range of activities, the so-called insulin-like growth factors (IGFs) (6). These peptides (IGF I and II) have major structural homologies with insulin, but have little or no immunologic cross reactivity with the hormone (7). In general, they have more potent growth-promoting effects, but less potent metabolic actions when compared to insulin. Both IGF I and II have distinct receptors to which insulin is capable of binding with reduced affinity (8). Any discussion of insulin action must take account of these complexities.

Insulin Receptors

In order for insulin to act, it must first bind to specific receptors located on the plasma membranes of cells (1, 2). These receptors were first defined by virtue of their insulin-binding characteristics, which typically included high affinity for insulin, rapid and saturable binding, and specificity for insulin and related molecules in proportion to their biological activity (1, 2). These functional characteristics of the binding of insulin to its receptor have been highly conserved through evolution (9). In recent years, much has also been learned about the structure of the receptor molecule (4, 5, 10). The insulin receptor is now known to be a glycoprotein, composed of at least two

distinct subunits referred to as α and β with MW of 135,000 and 95,000. Interchain disulfide bonds are present and the stoichiometry, although not known with certainty, may be $\alpha_2\beta_2$. A similar subunit composition has been found in receptors purified from a number of species and from a variety of target tissues. Subtle structural or organizational heterogeneity of insulin receptors from different tissues, or within a single tissue, may yet be found. The number of receptors expressed per cell varies considerably, from several hundred per mature erythrocyte, to several hundred thousand per adipocyte.

RECEPTOR REGULATION A central feature of insulin receptor physiology is the fact that insulin receptors are not a static component of the cellular machinery; rather, they have a half-life measured in hours. In addition to this rapid turnover under basal conditions, the affinity and number of insulin receptors are subject to dynamic regulation by many signals emanating from inside and outside the cell (2, 11). A major factor now known to regulate the concentration of insulin receptors is insulin itself (12). Thus, when cells (including lymphocytes, hepatocytes, fibroblasts, and adipocytes) are cultured in media containing insulin, they exhibit a time- and temperature-dependent decrease in the concentration of insulin receptors, a phenomenon termed down regulation (12, 13). The mechanism for this phenomenon may be complex, but accelerated receptor degradation after exposure to insulin appears to be involved (14). In addition to this in vitro phenomenon of down regulation, the number of insulin receptors on cells acutely removed from patients with a variety of diseases correlated inversely with the concentration of insulin to which the cells are tonically exposed in vivo (11). This phenomenon, whereby the concentration of insulin receptors is regulated by ambient insulin levels, is believed to play a major role in the pathogenesis of insulin resistance in a variety of disease states. Many other modulators of receptor concentration or affinity have been described through in vivo or in vitro studies. These include dietary maneuvers such as fasting or high carbohydrate feeding; exercise; and the levels of specific molecules that can influence receptor expression such as hormones (cortisol, growth hormone), ions, nucleotides, ketones, and autoantibodies against the receptor (15–17). In many diseases, one or more of these receptor modulators may be responsible for insulin receptor alterations and clinical resistance to insulin.

POSTRECEPTOR MECHANISMS OF INSULIN ACTION The mechanism (or mechanisms) by which the insulin-receptor complex generates a signal (or signals) to activate (or inactivate) cellular processes is largely unknown at this time. Potential mediators such as cyclic nucleotides and ions have

been studied, but as yet none of the actions of insulin can be attributed to such known biochemical mediators (5). Several recent studies suggest that unique early events may be involved in insulin's signal to the cell. Several laboratories report the existence of an as yet poorly characterized small peptide that may be generated in plasma membranes subsequent to insulin binding (5, 18). This molecule has been claimed to act upon a variety of insulin-responsive enzymes, and to modify their activity by changing their state of phosphorylation. In this regard, it was also recently demonstrated that insulin receptors may themselves be rapidly phosphorylated after interaction with insulin (19). Given the diverse nature of insulin's effects on cellular function, it may be that no single early biochemical event will emerge as central to all of the actions of insulin. The limited state of our knowledge in this area increases the difficulty of defining molecular defects responsible for insulin resistance in disease.

INSULIN RESISTANCE—GENERAL CONSIDERATIONS

Insulin resistance may be defined as a state in which a given concentration of insulin produces less than the expected biologic effect. Clinically, this brings to mind the image of an insulin-treated patient who remains hyperglycemic while on large doses of exogenous insulin. Although such a patient certainly qualifies as being insulin resistant, the example ignores the many subtleties inherent in the concept of insulin resistance. To avoid confusion, a number of points should be clarified in any case of presumed insulin resistance. As discussed above, insulin has diverse cellular actions that may result from more than one biochemical mediator and that may even involve more than one receptor type (e.g. insulin action via IGF receptors). As a consequence, resistance to one action of insulin (e.g. its glucose-lowering effect) need not necessarily be associated with resistance to other important actions (i.e. antilipolysis, amino acid uptake, or growth stimulation). Discordance in the degree of resistance in various pathways may have great clinical importance. A second caveat relates to the level of organization at which the insulin resistance is being analyzed. Studies at the level of isolated cells may be expected to produce different data from that obtained with isolated organs or with the intact organism. Extrapolation of data from one level to another may not always be appropriate.

States of insulin resistance span a broad spectrum with respect to glucose homeostasis and, as a consequence, insulin resistance may be discovered by a variety of means. Thus, at one end of the spectrum patients with insulin resistance may be grossly diabetic despite large doses of insulin. At the other end of the clinical spectrum, patients may be normoglycemic through the

effect of compensatory secretion of endogenous insulin. In the latter, very common situation (e.g. most patients with obesity), resistance to insulin is not clinically evident, but can be demonstrated by a variety of methods. A commonly employed indirect approach infers the degree of insulin resistance from the level of insulin in blood, most often the level of insulin after an overnight fast. In many situations the fasting insulin level was inversely related to the directly measured insulin sensitivity, but the approach is subject to error if the insulin measured by radioimmunoassay is not fully potent in a bioassay, as is the case in a syndrome involving a point mutation in the structure of the insulin molecule (20). Insulin sensitivity can also be assessed by measuring the response to direct infusion of insulin, usually by the intravenous route. Although useful information can be obtained by measuring the response to a bolus injection of insulin, the variable secretion of counter-insulin hormones in response to hypoglycemia makes mechanistic interpretation of data obtained with such a method difficult. To circumvent this problem, many investigators employ the euglycemic insulin clamp technique first used by Andres et al (21). With this technique, the response (i.e. glucose disposal, antilipolysis, etc) can be assessed at different steady-state insulin levels while plasma glucose levels are being held constant with a computer-assisted variable glucose infusion.

A quantitative analysis of insulin action also requires an assessment of dose response data, i.e. measurement of hormone action over a wide range of hormone concentrations. Two useful parameters that are easily measured with such an approach are (*a*) the hormone concentration that produces a half-maximal biological response and (*b*) the maximal biological response that the hormone is capable of producing. Kahn (22) proposed that an altered dose response curve due to a change in the concentration of hormone producing half-maximal activation be referred to as a change in hormone sensitivity, and that an altered dose response curve characterized by a change in the maximal response to the highest concentration of hormone be called a change in hormone responsiveness (22). Uniform use of this terminology may be expected to dispel controversies based solely on imperfect communication between investigators.

A key question to be addressed at this point is: How would we expect the insulin dose response curve to change with a change in the number of insulin receptors, or with changes in intracellular, postreceptor pathways in insulin action? This question cannot be answered without brief consideration of the subject of spare receptors (23). Most insulin-sensitive pathways are maximally activated at hormone concentrations that occupy less than the total number of available receptors. The receptors available for binding after the maximal bioeffect has been reached may be considered "spare." (Many lines of evidence show that all available receptors are potentially coupled to a

biological response, and that which receptors become occupied and which are spare is simply a statistical matter.) After a certain number of receptors become occupied, subsequent steps in the biochemical sequence being measured may become rate limiting, and thus no further response is observed. In this context, a sequential reduction in the overall number of receptors would, by the law of mass action, be expected to progressively shift the biological dose response curve to the right, with decreased response at low hormone concentrations and normal insulin action at maximally effective concentrations. If receptor loss becomes so severe that "spare receptors" are no longer present and inadequate receptors are present to generate a maximal insulin response, then the dose response curve, in addition to being shifted to the right, becomes flattened as well. The effect of postreceptor alterations on insulin dose response curves is more ambiguous. Depending upon whether or not the defective step is rate limiting for a particular insulin action, a post-receptor abnormality could cause either pattern of dose response alteration (i.e. decreased sensitivity or responsiveness). Mechanistic interpretation of insulin dose response data is further complicated by the fact that the proportion of "spare receptors" varies with different cell types and is also a function of which particular bioeffect is being measured. Attempts to analyze in vivo dose response data according to this scheme are useful, but, because of the existence of many intervening variables, overinterpretation from a mechanistic point of view should be avoided.

CLINICAL STATES OF INSULIN RESISTANCE: ROLE OF THE INSULIN RECEPTOR

It is helpful to classify the clinical states of insulin resistance according to a pathophysiological scheme. One such scheme considers three general causes of insulin resistance: (*a*) certain abnormalities of the insulin molecule; (*b*) circulating antagonists of insulin action; and (*c*) target cell defects in the pathways for insulin action. I discuss the insulin-resistant states according to this scheme, bearing in mind the fact that overlap between these categories exists. Greatest attention is paid to those conditions in which receptor defects are important components of the insulin-resistant state.

Abnormal Insulin

According to receptor theory, an abnormal insulin molecule that had reduced intrinsic activity compared to receptor-binding ability would be expected to produce a state of hormone resistance, analogous to that produced by pharmacologic receptor antagonists, such as those that inhibit angiotensin action. Although suspected for years, it was recently demonstrated for

the first time that a structurally abnormal insulin does exist, although at this point only in a single patient (20). The patient was a Type II diabetic with fasting hyperglycemia and hyperinsulinemia, but with surprisingly normal sensitivity to exogenous insulin. Insulin purified from this patient had a single leucine-phenylalanine substitution in the bioactive site of the insulin molecule, associated with a 60% reduction in binding affinity and an 85% reduction in bioactivity in isolated adipocytes. The prevalence of this disorder is probably low. Abnormalities at the level of the insulin receptor would not be expected in this disorder, and in limited studies receptor binding has been normal.

Circulating or Prereceptor Antagonists of Insulin Action

ANTIBODIES TO INSULIN Virtually all patients treated with exogenous insulin (beef, pork, or even human) develop insulin-binding IgG antibodies within a few months. These antibodies have not proven significant in most patients; in a small minority (0.1%) antibody titers rise and clinically important insulin resistance ensues (24). This resistance is usually self-limited, but may be treated by substitution of less immunogenic forms of insulin (pork vs beef; sulfated) or by therapy aimed at the immune response itself (i.e. prednisone). These antibodies appear to limit the access of insulin to its receptors, and no receptor abnormalities have been described in this setting.

AUTOANTIBODIES TO THE INSULIN RECEPTOR Although these antibodies are present in the circulation, the insulin resistance that they produce is more reasonably considered together with the target tissue defects in insulin action (see below).

HORMONAL ANTAGONISTS Cortisol, growth hormone, glucagon, and catecholamines are each capable of producing states of insulin resistance (25). The phenomenon is relevant to the insulin resistance seen in clinical syndromes due to hypersecretion of these hormones (e.g. Cushings), as well as to the insulin resistance of stress, in which the hormones synergize to amplify their insulin antagonism (26). These hormones may produce insulin antagonism by a variety of mechanisms, including (*a*) actions on peripheral tissues to influence the levels of important substrates such as fatty acids, which may antagonize insulin action; (*b*) actions to stimulate hepatic enzymes that counter the action of insulin, such as those that mediate gluconeogenesis and glycogenolysis; (*c*) actions to influence insulin secretion by the beta cell; and (*d*) actions to directly impair insulin-sensitive processes in target tissues, including effects on the glucose transport system and on the expression of insulin receptors (25).

Because of the complexity of these mechanisms and the capacity for interaction between them, it is difficult to assess the role of insulin receptor changes in the insulin resistance due to an excess of these hormones. Two examples will suffice. Many studies of insulin binding and insulin action in response to glucocorticoid excess have now been carried out. In early studies, in vivo glucocorticoid excess reduced insulin binding to rat hepatocytes and fat cells, and this was predominantly due to a change in receptor affinity (27, 28). A major role for receptor alterations in the production of steroid-induced insulin resistance has been questioned, however. First, when cells are exposed to glucocorticoids in vitro, insulin receptor changes are found in some, but not all studies (29, 30). Second, in a large number of in vivo studies of insulin receptors on circulating monocytes or red cells, diverse and conflicting observations were made (31–33). Unexpected differences between different steroid preparations were also noted. Although a role for insulin receptor abnormalities in glucocorticoid-induced insulin resistance in man seems likely, more in vivo studies employing relevant target tissues such as liver, fat, and muscle are needed.

The insulin resistance due to growth hormone excess is less well studied, but current evidence does not support a major role for insulin receptor alterations in this situation. Thus, insulin binding over the physiologic range of insulin concentrations is normal in cells removed from man (monocytes) and rats (liver) with growth hormone excess, although subtle alterations of receptor affinity may be seen (27, 34). Exposure of adipocytes to growth hormone in vitro produces insulin resistance, but insulin receptors are unchanged (35). The nature of the postreceptor defect in insulin action induced by growth hormone has not been defined.

As discussed below, insulin itself may be considered to be a potent hormonal antagonist of insulin action, via the phenomenon of insulin-induced down regulation or desensitization of target cells (12).

Clinical States of Insulin Resistance with Target Cell Defects

INSULIN RESISTANCE AND OBESITY Following the development of the insulin radioimmunoassay, it became evident that nondiabetic obese individuals had high circulating levels of insulin both in the fasting and postprandial states (36, 37). This indirectly suggested that such individuals were resistant to the action of insulin. Subsequent studies in man and experimental animals confirmed these observations, and in vivo infusions of insulin were employed to directly demonstrate that tissues of obese individuals were resistant to the glucose-lowering effect of insulin (38). The clinical significance of insulin resistance in nondiabetic obese individuals has not been defined; however, many studies of this phenomenon were motivated

by the knowledge that obesity is present in 80–90% of adults with Type II diabetes, a disorder characterized by insulin resistance as well (see below). Thus, it is hoped that insight into the mechanisms responsible for insulin resistance in obesity can be applied to our understanding of Type II diabetes.

Animal studies Insulin resistance has been demonstrated in a variety of animal models of obesity, including those that are genetic and acquired, with and without abnormal glucose tolerance (39). The insulin receptor was studied in many of these models, and, with one exception, insulin binding to plasma membrane receptors was reduced in the basal state (39). The reduction of insulin binding in obesity was shown to be due to a decrease in the number of available receptors, with all other binding parameters (e.g. affinity, temperature dependence) being normal (39). In addition, the receptor defect has been seen in all tissues studied, including muscle, liver, fat, and thymic lymphocytes (39). In most of these models, the extent of the decrease in insulin receptor concentration is proportional to the height of the basal insulin level (39). This relationship could be due to a primary receptor defect and compensatory hyperinsulinemia, but little evidence has accrued to support this thesis. Instead, the major factor regulating the concentration of receptors in obesity appears to be the circulating level of insulin. Thus, amelioration of the hyperinsulinemia through diet or streptozotocin treatment corrects the receptor defect (40, 41). It should be stressed that correction of the receptor defect can be seen even while obesity persists, which stresses that obesity per se is not the proximate cause of the observed receptor defect. The suggestion from these animal experiments that insulin regulates the expression of its own cellular receptors is consistent with the pioneering work of Roth and colleagues, who first demonstrated that insulin could directly regulate the concentration of its own receptors in vitro, a phenomenon that they termed down regulation (12). This phenomenon has been observed subsequently with insulin in adipocytes and fibroblasts in vitro, and it appears to be a general mechanism for hormonal regulation of target cell sensitivity (23).

Although the insulin receptor deficiency of obesity is indisputable, and its cellular mechanism is fairly well understood, the relationship between the receptor deficiency and the target cell resistance to insulin is not straightforward, at least in part because of the phenomenon of spare receptors. To probe this question, insulin binding to its receptor has been assessed over a wide range of insulin concentrations, and this has been compared with dose response curves for both early (glucose transport) and late (glucose oxidation) events in insulin action. The results obtained in studies with adipocytes from spontaneously obese rodents and muscles from ob/ob mice

have been quite similar. In each case, the functional consequence of receptor loss was seen as a rightward shift in the insulin dose response curve for stimulation of glucose transport (42, 43). However, the predominant abnormality responsible for the cellular insulin resistance in both cases has proven to be a postreceptor defect in the intracellular pathway of glucose metabolism (42, 43). The precise biochemical locus of this intracellular abnormality is not known, but recent in vitro experiments suggest, at least for adipocytes, that prolonged exposure to high concentrations of insulin may induce resistance to insulin not only by causing loss of insulin receptors, but by impairing postreceptor steps as well (44). Thus, both receptor and postreceptor defects in obesity could be the consequence of hyperinsulinemia.

Human studies Studies of insulin receptors and insulin action in obese humans strongly parallel those just described for obese rodents. Thus, the concentration of insulin receptors on freshly obtained monocytes, red blood cells, and adipocytes was reduced in the basal state in most studies (45, 46). The receptor deficiency is, in general, inversely related to the basal insulin level, and diet as well as diazoxide (a drug that inhibits insulin secretion) can restore insulin binding to or toward normal (45). As with obesity in rodent models, it appears most likely that the receptor impairment is secondary to the hyperinsulinemia, and this is most likely a consequence of hyperphagia.

A causal connection between receptor deficiency and the systemic resistance to insulin has been assessed by considering receptor status in the context of in vivo insulin dose response curves obtained by the euglycemic insulin clamp technique. It is concluded from these studies that the insulin receptor deficiency contributes to insulin resistance in all obese subjects (47). However, in those subjects with the most marked hyperinsulinemia and insulin resistance, a postreceptor abnormality is present as well (47). If the in vitro data discussed above can be extrapolated to these in vivo experiments, it may be postulated that the postreceptor defect is also a consequence of the hyperinsulinemia. Much further work is needed to substantiate this hypothesis.

INSULIN RESISTANCE AND TYPE II DIABETES Insulin secretion and insulin sensitivity have been carefully studied in Type II, non-insulin-dependent diabetes mellitus, in order to determine whether this syndrome is caused by insulin deficiency, insulin resistance, or a combination of the two. Studies of insulin secretion have produced much controversy, owing in part to a failure to distinguish between patients having defects of different severity.

Thus, patients with impaired glucose intolerance, also referred to as having chemical diabetes (i.e. fasting glucose <140 mg/dl with abnormal oral glucose tolerance test) typically have normal or elevated plasma insulin levels after oral glucose administration, even when compared with control groups matched for weight (48). In contrast, patients with significant fasting hyperglycemia (i.e. overt diabetes) typically have insulin levels that are normal or high in the fasting state, but low after oral glucose administration (48). In the glucose intolerant, hyperinsulinemic group, insulin resistance seemed likely. In the overtly diabetic group, the state of insulin sensitivity was less clear. Insulin sensitivity was directly assessed in both groups with the euglycemic insulin clamp technique, and the findings were straightforward. Most patients with glucose intolerance displayed the predicted resistance to insulin (49, 50). Patients with fasting hyperglycemia displayed even greater degrees of insulin resistance (50).

As in obesity, the mechanism responsible for insulin resistance in Type II diabetes was probed by studying insulin receptors, and at the same time, assessing the shape of the in vivo dose response curve for insulin-mediated glucose disposal. Circulating monocytes and erythrocytes, as well as freshly isolated adipocytes, provide convenient tissues for the study of insulin receptors in these patients; and, in general, patients with impaired glucose tolerance and overt diabetes have fewer insulin receptors than controls on a per cell basis (50). Qualitative aspects of these receptors (kinetics of binding, etc) are not well studied, but are assumed to be normal. Despite the greater severity of insulin resistance in patients with overt fasting hyperglycemia vs those with impaired glucose tolerance, the severity of the binding defect is similar in the two groups (50). This was the first hint that defects apart from receptor binding might be important components of the insulin resistance of Type II diabetes. Further data on in vivo dose response curves for insulin-mediated glucose disposal support this notion. Thus, in patients with impaired glucose tolerance and mild insulin resistance, there is diminished insulin sensitivity that can be attributed solely to a decreased number of cellular insulin receptors (51). In patients with Type II diabetes and more severe insulin resistance, a receptor defect does account for reduced insulin sensitivity, but a postreceptor defect is also present and may be the dominant abnormality (51). Neither the biochemical nature of this apparent postreceptor defect nor the causal sequence leading to the abnormality are currently known. Although most patients with Type II diabetes are obese, the fact that obese and nonobese Type II diabetics have similar degrees of insulin resistance suggests that, whatever the additive effect of obesity, insulin resistance is a function of the diabetes itself. Hyperglycemia, elevated free fatty acid levels, or insulin deficiency could each be responsible

for the increasingly severe postreceptor defect in Type II diabetes, as could a currently unknown factor. The fact that insulin binding and action are normal in fibroblasts cultured from these patients makes it more likely that the insulin resistance is caused by some aspect of the in vivo metabolic milieu (52, 53).

SYNDROMES OF EXTREME TISSUE RESISTANCE TO INSULIN In contrast to obesity and diabetes, in which tissue resistance to insulin is typically modest, there is a group of syndromes in which tissue resistance to the actions of insulin is extreme (3). In addition to their clinical interest, these syndromes have led to important insights regarding the mechanism of action of insulin. Although clinically diverse in their manifestations, patients with these syndromes nearly all manifest the skin lesion acanthosis nigricans. This cutaneous disorder is characterized by symmetric, hyperpigmented, verrucous, hyperkeratotic thickening. It most often affects the nape of the neck, axillae, and groins, and it appears to be a cutaneous manifestation of severe target cell insulin resistance, regardless of the specific etiology. It is not known whether acanthosis occurring with malignancy has the same basis. The presence of acanthosis nigricans should raise suspicion of insulin resistance even in nondiabetic patients, since compensatory hyperinsulinemia may prevent the development of diabetes.

The Type B syndrome of insulin resistance with insulin receptor autoantibodies Insulin receptor autoantibodies were first discovered during the evaluation of several patients with extreme insulin resistance in 1975, and since that time approximately 25 patients have been described (54, 55). Clinically, there is female preponderance, and the majority of patients have been Blacks, with several cases in Caucasians and Japanese. The mean age of onset is 43, with a range of 12 to 78 years of age.

The most common clinical presentation is symptomatic diabetes, with polyuria, polydipsia, and weight loss. Ketoacidosis is generally absent or mild. Resistance to exogenous insulin therapy is present from its initial use, and some patients fail to respond to over 100,000 units of insulin per day. A minority of patients have only mild glucose intolerance, or frank hypoglycemia in association with insulin resistance. These phenomena and the pathogenetic antibodies are discussed below.

Most of these patients had symptoms or laboratory tests suggestive of autoimmune disease including alopecia, vitiligo, arthralgias and arthritis, splenomegaly, Raynaud's phenomenon, enlarged salivary glands, elevated ESR, leukopenia, and hypergammaglobulinemia (55). One third of the cases could be classified as having a specific autoimmune syndrome such as Sjögren's syndrome or systemic lupus erythematosus.

Insulin receptors were studied on circulating monocytes and erythrocytes, as well as adipocytes of these patients, and insulin binding was severely depressed (54). Unlike obesity and Type II diabetes, the receptor defect appears to be that of reduced affinity for insulin (56).

The key to understanding this syndrome was the observation that sera from affected patients could inhibit insulin binding to normal insulin receptors in vitro (57). It was subsequently proven that these sera contain antibodies, predominantly IgG, that bind to the insulin receptor molecule and are capable of precipitating it from solution (58, 59). Titers vary over a wide range, and tend to correlate with the clinical severity of the insulin resistance (55).

The ability of these antibodies to bind to the insulin receptor and inhibit binding provided a convenient explanation for the observed insulin resistance. However, subsequent findings proved more complex. Exposure of cells to these antibodies will elicit insulin-like effects acutely (4). This finding raised a potential paradox between in vitro and in vivo observations. The resolution came from in vitro studies in which the insulin-like effects were seen to be transient, followed by insulin resistance due to a postreceptor desensitization (4). Persistent insulin-like action of these antibodies could account for the hypoglycemia occurring during the course of some of these patients.

Over several years of follow-up, patients with this syndrome have had a variety of different outcomes (60). Remission of insulin resistance with disappearance of receptor antibodies has been observed. Patients with refractory severe insulin resistance have been treated with a variety of regimens, including glucocorticoids, antimetabolites, and plasma exchange (61). These have produced only limited success.

The Type A syndrome of insulin resistance The initial description of this syndrome described three young, thin, females with carbohydrate intolerance (in one case manifested as overt diabetes), severe target cell resistance to insulin, hyperandrogenism, and acanthosis nigricans (54). The cellular basis for the insulin resistance has been investigated in detail. Freshly obtained circulating monocytes displayed markedly decreased insulin binding, owing to a reduction in the number of available binding sites (56).

Receptors on monocytes appeared to be qualitatively normal (56). Unlike obesity, insulin binding failed to increase after three days of fasting, which suggests that insulin-induced down regulation might not account for this condition (56). Further studies add support to the notion that these patients might be suffering from a genetically determined disorder of insulin receptors. First, two families were described with severe insulin

resistance and hyperandrogenism in multiple members (62, 63). In one family, a male was also insulin resistant, which demonstrated the nonessentiality of the hyperandrogenism in the genesis of the insulin resistance (62). Second, decreased insulin binding was seen in cells cultured from these patients and grown outside of the in vivo milieu (63, 64).

The mechanism by which insulin resistance due to a genetic defect at the level of insulin receptors causes ovarian hyperandrogenism is unknown, but the gonadal problem is often the most troubling clinical feature (65). Unlike patients with antireceptor antibodies, remissions have not been demonstrated. One patient with a similar clinical and biochemical profile had normal receptors on circulating monocytes, which suggested the presence of a postreceptor defect (66).

Another, presumably distinct, group of patients may be easily mistaken as having Type A syndrome. This is a fairly large group of obese, nondiabetic women with hyperandrogenism and acanthosis nigricans. Insulin resistance is at the severe end of that seen with obesity, but the resistance and the receptor defect are less marked than what is present in the classical Type A syndrome. Insulin binding increases with caloric restriction in these patients, and thus, they more closely resemble those patients with insulin resistance due to obesity (67).

Leprechaunism and lipoatrophic diabetes Two other rare syndromes that involve extreme tissue resistance to insulin are leprechaunism and lipoatrophic diabetes. In addition to insulin resistance, the former syndrome affects infants with hirsutism, low birth weight, characteristic facial features, and failure to thrive (68, 69). Studies of insulin binding to circulating cells have been performed in only one case, and they were normal (70). Despite the syndromes' rarity, studies of fibroblasts from several patients yielded different results. In one study, insulin receptor binding was normal, and impaired insulin-stimulated glucose transport was ascribed to a postreceptor defect (70). In another study, insulin binding was reduced, and several qualitative abnormalities of insulin receptor binding were observed (71).

Lipoatrophic diabetes, although rare, probably represents a number of distinct clinical syndromes (72). Thus, the lipoatrophy can be congenital or acquired, complete or partial. This clinical heterogeneity may in part explain the discordant insulin-binding data, with binding to circulating monocytes or cultured skin fibroblasts reported to be normal, decreased, or even increased (72–74).

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