Skeletal Muscle Insulin Resistance Is the Primary Defect in Type 2 Diabetes

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Insulin resistance is a characteristic feature of type 2 diabetes and plays a major role in the pathogenesis of the disease (1,2). Although β-cell failure is the sine qua non for development of type 2 diabetes, skeletal muscle insulin resistance is considered to be the initiating or primary defect that is evident decades before β-cell failure and overt hyperglycemia develops (3,4). Insulin resistance is defined as a reduced response of target tissues (compared with subjects with normal glucose tolerance [NGT] without a family history of diabetes), such as the skeletal muscle, liver, and adipocytes, to insulin. Because skeletal muscle is the predominant site of insulin-mediated glucose uptake in the postprandial state, here we will focus on recent advances about the time of onset, as well as the mechanism, of the skeletal muscle insulin resistance.

RESEARCH DESIGN AND METHODS

— The euglycemic insulin clamp technique (5) is considered to be the gold standard for measuring insulin action in vivo. With this technique, whole-body insulin action is quantified as the rate of exogenous glucose infusion (plus any residual hepatic glucose production) required to maintain the plasma glucose concentration at euglycemic levels in response to a fixed increment in the plasma insulin concentration. Because 80–90% of the infused glucose is taken up by skeletal muscle under conditions of euglycemic hyperinsulinemia, insulin sensitivity measured with the insulin clamp technique primarily reflects skeletal muscle (6). Another advantage of this technique is that it can be combined with indirect calorimetry to measure different substrate oxidation rates and with muscle biopsy to examine the biochemical/molecular etiology of the insulin resistance. Measurement of insulin sensitivity by the frequently sampled intravenous glucose tolerance test reflects both hepatic and peripheral insulin resistance and correlates well with the insulin clamp technique (7).

Because insulin clamp studies are not feasible in large epidemiological studies, other surrogate markers of insulin sensitivity from glucose and insulin values in the fasting state or after an oral glucose tolerance test (OGTT) have been developed (8–10). The homeostatic model assessment correlates reasonably well with the insulin clamp (10), but it primarily reflects hepatic insulin sensitivity, since the fasting plasma glucose is determined mainly by the rate of hepatic glucose production (HGP) and insulin is the primary regulator of HGP. The correlation between homeostatic model assessment and the insulin clamp also is less robust when analyzed in subgroups of glucose tolerance (11). During an OGTT, significant (~30–40%) amounts of glucose are taken up by the splanchnic bed, and HGP is less completely suppressed than during the insulin clamp technique (12). As a result, the plasma glucose concentration during OGTT is affected by both hepatic and peripheral (primarily muscle) insulin resistance. Therefore, indexes of insulin resistance from the OGTT, e.g., the Matsuda index, reflect both hepatic and peripheral insulin resistance and correlate well (*R* value ~0.70) with insulin sensitivity measured with the euglycemic insulin clamp (9).

Normal glucose homeostasis

Skeletal muscle is the major site of glucose uptake in the postprandial state in humans. Under euglycemic hyperinsulinemic conditions, ~80% of glucose uptake occurs in skeletal muscle (13). Studies using the euglycemic hyperinsulinemic clamp and femoral artery/vein catheterization to quantitate glucose uptake have allowed investigators to quantify leg muscle glucose uptake. Because adipose tissue uses <5% of an infused glucose load and bone is metabolically inert, the great majority of leg glucose uptake can be accounted for by skeletal muscle. During physiological hyperinsulinemia (80–100 μU/ml), leg muscle glucose uptake increases linearly with time, reaching a plateau value of ~10 mg/kg leg weight per minute after 60 min (13,14). In contrast, in lean type 2 diabetic subjects, the onset of insulin action is delayed and the ability of insulin to maximally stimulate glucose uptake is markedly blunted. During the last hour of the insulin clamp, insulin-stimulated leg muscle glucose uptake is reduced by ~50% in type 2 diabetes (14). These studies support the notion that the primary defect in insulin action in patients with type 2 diabetes resides in the skeletal muscle. Similarly, using the forearm catheterization technique, a number of investigators have demonstrated reduced insulin-mediated glucose uptake by the peripheral tissues, primarily muscle (15). Quantitation of leg muscle glucose uptake in type 2 diabetes with positron emission tomography has provided additional evidence for the presence of severe muscle insulin resistance in type 2 diabetes (16). In the postabsorptive state, the majority (~70–75%) of glucose uptake (~2 mg/kg per min) occurs in insulin-insensitive tissues (brain, erythrocytes, and splanchnic tissues) (17,18), with only ~25% of glucose uptake occurring in insulin-sensitive tissues. In the postabsorptive state, total body glucose uptake is precisely matched by the rate of endogenous glucose production, primarily by the liver and to a smaller extent by the kidney (19). Thus, hepatic glucose production is the main determinant of the fasting plasma glucose concentration and is regulated primarily by the plasma insulin and, to a lesser extent, glucagon concentrations (20).

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Glucose disposal during OGTT

After a mixed-meal or oral glucose load, the ensuing hyperglycemia and hyperinsulinemia work in concert to suppress HGP and stimulate glucose uptake by the splanchnic (liver) and peripheral (muscle) tissues (12,21). After glucose is transported into the cell, it is phosphorylated and subsequently oxidized to carbon dioxide and water or converted to glycogen, which can be stored in the liver or skeletal muscle (22). Glycogen synthesis is regulated by the enzyme glycogen synthase, and glycolysis primarily is controlled by the enzyme complex of pyruvate dehydrogenase. In humans, the rate of glucose oxidation and the nonoxidative glucose metabolism (primarily reflects glycogen synthesis) in the insulin-stimulated state can be estimated by indirect calorimetry or magnetic response spectroscopy (23,24). Approximately 75% of glucose is metabolized nonoxidatively, and impaired glycogen synthesis is one of the earliest metabolic defects seen in the pathogenesis of type 2 diabetes (1,2).

Intracellular pathways of glucose disposal

Under physiologic conditions, approximately two-thirds of all glucose-6-phosphate is converted to glycogen, and one-third enters glycolysis. Of the glucose that enters the glycolytic pathway, the majority (80–90%) is converted to carbon dioxide and water, whereas the remaining 10–20% is converted to lactate. Studies using indirect calorimetry and euglycemic clamp technique have shown that the glucose oxidation is more sensitive (lower half-maximum) but saturates earlier (lower maximum) than glycogen synthesis, which has low sensitivity but high capacity. Skeletal muscle is the predominant site of glycogen synthesis.

Molecular basis of insulin action

In the early stages of development of type 2 diabetes, impaired glycogen synthesis in muscle is the primary defect responsible for the insulin resistance. The initial step in muscle glucose metabolism involves activation of the glucose transport system, leading to influx of glucose into insulin target tissues. The free glucose that has entered the cell is then metabolized by a series of enzymatic steps that are under the control of insulin. In skeletal muscle and adipose tissue, insulin promotes glucose uptake into the cells by activating a complex cascade of phosphorylation-dephosphorylation reactions. In skeletal muscle, insulin binds to the insulin receptor leading to phosphorylation of three key tyrosine molecules on the insulin receptor. Once the insulin receptor has been phosphorylated, insulin receptor substrate (IRS)-1 moves to the cell membrane and becomes phosphorylated on contiguous tyrosine molecules. Tyrosine phosphorylation of IRS-1 results in activation of the p85 regulatory subunit of phosphatidylinositol (PI)-3 kinase and activates the p110 catalytic subunit, leading to an increase in phosphatidylinositol-3,4,5 triphosphate. This results in activation of downstream protein kinase B (also called Akt) and phosphorylation of Akt substrate 160 (AS160), which facilitates the translocation of GLUT4 to the sarcolemma and subsequent entry of glucose into the cell (25). Intracellular glucose is rapidly phosphorylated by hexokinase II and directed to oxidative or nonoxidative pathways. Maintaining the integrity of the IRS-1/PI-3 kinase/Akt pathway is essential for normal insulin-mediated glucose uptake in skeletal muscle (26).

What is the initial metabolic defect in the pathogenesis of type 2 diabetes?

By the time that hyperglycemia is manifest, multiple metabolic abnormalities are present in individuals with type 2 diabetes. Because the majority of type 2 diabetic subjects are obese, they also have daylong elevation of the plasma free fatty acid (FFA) concentration and increased circulating levels of inflammatory cytokines (1,2). Because elevated plasma glucose, FFA, and cytokine concentrations all can induce insulin resistance, it is extremely difficult to separate the contribution of each of these metabolic defects in the pathogenesis of type 2 diabetes. To examine what is the earliest defect(s) in the development of type 2 diabetes, investigators have used two approaches. First, one can study the lean, normal glucose tolerant, first-degree relatives of two parents with type 2 diabetes. These individuals have a very high lifetime risk (~40%) of developing type 2 diabetes (4). In certain high-risk populations, such as Mexican Americans, the prevalence of diabetes in the offspring of two type 2 diabetic parents can reach 70–80%. The advantage of studying this genetically predisposed group is that they do not have other confounding factors that contribute to insulin resistance, such as obesity and hyperglycemia. Thus, they represent an ideal model to study the early metabolic defects in the pathogenesis of type 2 diabetes. A second approach uses the long-term follow-up of normal glucose tolerant subjects as they progress to impaired glucose tolerance and subsequently to type 2 diabetes. This prospective approach has been used in Pima Indians (27).

What is the evidence that muscle insulin resistance is the initial metabolic defect in type 2 diabetes?

Multiple investigators unequivocally have demonstrated that lean NGT offspring of two parents with type 2 diabetes exhibit moderate to severe skeletal muscle insulin resistance (28–33). The natural history of type 2 diabetes is depicted in Fig. A1 (all figures can be found in an online appendix available at http://care.diabetesjournals.org/cgi/content/full/dc09-S302/DC1) (1,34). As Europoid individuals progress from NGT to IGT, insulin sensitivity declines markedly but glucose tolerance deteriorates minimally because of a marked increase in insulin secretion. Similar observations have been made in Pima Indians (Fig. A2) (35) and Mexican Americans and Caucasians residing in San Antonio (Fig. A3) (30,32,36). These results, spanning a wide range of ethnic groups, clearly demonstrate that insulin resistance, and not insulin deficiency, initiates the sequence of events leading to the development of type 2 diabetes. However, progressive β-cell failure is required and ultimately responsible for type 2 diabetes to become fully manifest (1,34,35,37,38).

In humans, ~75–80% of insulin-stimulated muscle glucose disposal during a euglycemic insulin clamp is converted to glycogen, whereas the remaining 20–25% is oxidized to CO_2 and H_2O (39). In type 2 diabetes, impaired glycogen synthesis secondary to reduced glycogen synthase activity is the earliest detectable metabolic defect (39–41). Gulli et al. (32) studied the lean NGT offspring of two diabetic Mexican American parents using a two-step euglycemic insulin clamp (20 and 40 mU/m^2 per min) that produced steady-state elevations in the plasma insulin concentration of ~40 and ~80 μU/ml, respectively, which are close to the half-maximal suppression of HGP and stimulation of muscle glucose uptake and glycogen synthesis. At both plasma insulin concentrations, glucose uptake was decreased by 33 and 43%, respectively (32) (Fig. A4). The impairment in glucose uptake was accounted for en-

tirely by reduced nonoxidative glucose metabolism (Fig. A4), which represents glycogen synthesis. No defect was noted in the suppression of hepatic glucose production by insulin (Fig. A5). These results indicate that the defect in insulin action primarily is localized to skeletal muscle and involves the glycogen synthetic pathway. During both the OGTT and hyperglycemic clamp (Fig. A6), insulin secretion (total, early, and late responses) was significantly increased, excluding a primary defect in β-cell function in the pathogenesis of type 2 diabetes in this ethnic population.

A similar defect in insulin-stimulated glycogen synthesis has been reported by Groop et al. in the Botnia study (42,43). Using nuclear magnetic resonance (NMR) spectroscopy, Perseghin et al. (44) directly quantified the defect in muscle glycogen synthesis in NGT offspring of two diabetic parents. This technique allows one to monitor glycogen synthesis noninvasively over real time. These investigators demonstrated that reduced glycogen synthesis could account for almost all of the decrease in insulin-stimulated glucose disposal in skeletal muscle. Of note, the severity of skeletal muscle insulin resistance in the offspring of two diabetic parents is of similar magnitude to that seen in type 2 diabetic individuals.

Before the incorporation of glucose into glycogen, it first must be transported into the cell and phosphorylated by hexokinase II to glucose-6-phosphate. Using a novel triple isotope (^{12}C-mannitol, ^{13}C-0-methyglucose, 3-^{3}H-glucose) technique in combination with brachial arterial/deep vein forearm catheterization and the euglycemic clamp, Pendergrass et al. (45) quantitated muscle glucose uptake and phosphorylation in the insulin-resistant NGT offspring of two type 2 diabetic parents (Fig. A7). The NGT offspring demonstrated a severity of whole-body and forearm muscle insulin resistance similar to that observed in lean and obese type 2 diabetic subjects and in NGT obese insulin-resistant individuals. Similarly, the NGT offspring manifested defects in muscle glucose transport and phosphorylation that were similar to those in lean and obese type 2 diabetic subjects (Fig. A7). Using ^{14}C-NMR to measure muscle glucose-6-phosphate levels, Rothman et al. (46) demonstrated a similar defect in combined glucose transport/phosphorylation in the NGT offspring of two type 2 diabetic parents.

Another strategy to examine what is the earliest defect responsible for the development of type 2 diabetes is to prospectively follow individuals who are at high risk for the development of type 2 diabetes. This has been done by Weyer et al. (47) in Pima Indians. At-risk individuals received a euglycemic insulin clamp to measure insulin sensitivity (primarily reflects muscle) and an intravenous glucose tolerance test to quantitate insulin secretion and were followed sequentially until they developed diabetes. At-risk individuals were markedly resistant to insulin but, at the stage of NGT, their β-cells were able to secrete sufficient amounts of insulin to offset the insulin resistance (Fig. A8). With time, both progressors (to type 2 diabetes) and nonprogressors (remained as NGT) experienced a further modest reduction (11–14%) in insulin sensitivity. However, nonprogressors were able to offset the worsening insulin resistance in muscle by augmenting insulin secretion (30%), whereas progression to type 2 diabetes was associated with a 78% decline in the acute insulin response to an intravenous glucose challenge (Fig. A8). Using a similar approach, Warram et al. (4) also demonstrated that insulin resistance was a strong predictor for the future diabetes. Because the great majority of glucose disposal after intravenous glucose administration occurs in muscle, these results provide strong evidence that insulin resistance in muscle is the earliest demonstrable defect in the natural history of type 2 diabetes, but that the development of overt type 2 diabetes occurs only in those individuals whose β-cells are unable to compensate for the defect in insulin action (37,38,48,49).

Insulin resistance begets insulin resistance

The normal β-cell response to insulin resistance, irrespective of the etiology of the insulin resistance, is to increase its secretion of insulin (1,2,39). However, a chronic physiologic increase in the plasma insulin concentration has a detrimental effect on skeletal muscle insulin sensitivity. Del Prato et al. (50) demonstrated that a 72 pmol/l (11 μU/ml) increase in the plasma insulin concentration in healthy NGT insulin-sensitive individuals for as little as 72–96 h reduced insulin-stimulated glucose disposal (insulin clamp technique) by 30–40%. The defect in insulin action was accounted for entirely by impaired nonoxidative glucose disposal (Fig. A9). On the other hand, chronic euglycemic hyperinsulinemia did not alter insulin-mediated suppression of hepatic glucose production (50). Koopmans et al. (51,52) showed that chronic hyperinsulinemia (threefold increase above baseline) in conscious rats for 7 days resulted in a reduction in insulin-mediated total-body glucose uptake, glucose storage, and glycolysis by 39, 62, and 26%, respectively. Hepatic glucose production was normally suppressed after 7 days of hyperinsulinemia. Because the majority (>80–90%) of glucose disposal during the euglycemic insulin clamp occurs in muscle, these results demonstrate that a physiologic elevation in the plasma insulin concentration will exacerbate the underlying muscle insulin resistance. Iozzo et al. (53) performed a 240-min euglycemic insulin clamp study with muscle biopsies in healthy volunteers. Subjects then received a low-dose insulin infusion for 72 h (plasma insulin concentration 143 ± 25 pmol/l [21 ± 2 μU/ml]), followed by a repeat insulin clamp with muscle biopsies. After 72 h of sustained physiologic hyperinsulinemia, insulin-stimulated muscle glycogen synthase activity, total body glucose uptake, and nonoxidative glucose disposal (primarily reflects glycogen synthesis in muscle) were significantly reduced. Taken together, these findings indicate that hyperinsulinemia is not only a compensatory response to insulin resistance, but also a self-perpetuating cause of the defect in muscle insulin action.

Molecular etiology of the skeletal muscle insulin resistance in genetically predisposed individuals

Using the euglycemic insulin clamp with skeletal muscle biopsy, a number of investigators have examined the insulin signal transduction system in human skeletal muscle of type 2 diabetic subjects and consistently demonstrated defects in IRS-1 tyrosine phosphorylation and PI-3 kinase and Akt activation (26,54,55). To examine whether similar defects are present in genetically predisposed individuals, Pratipanawatr et al. (36) examined insulin signaling in NGT subjects with a strong family history of type 2 diabetes and demonstrated that both the basal and insulin-stimulated IRS-1 tyrosine phosphorylation and PI 3-kinase activity associated with IRS-1 were significantly decreased (Fig. A10). Insulin stimulation of PI 3-kinase activity is a requisite for activation of glucose transport and glycogen synthesis. Increased serine phosphorylation of IRS-1 has been shown

to impair insulin signaling (tyrosine phosphorylation of both insulin resistance and IRS-1) in type 2 diabetes (56). In lean insulin-resistant NGT offspring of type 2 diabetic parents, increased serine phosphorylation of IRS-1 in skeletal muscle has been documented in association with impaired activation of Akt (57) (Fig. A11). Thus, at the earliest stage in the natural history of type 2 diabetes, i.e., the NGT insulin-resistant offspring of two type 2 diabetic parents, the molecular etiology of the muscle insulin resistance already is well established and is virtually identical to that in their diabetic parents.

Relationship between muscle insulin resistance and altered FFA/muscle lipid metabolism

Gulli et al. (32) were the first to demonstrate that the NGT offspring of two type 2 diabetic parents demonstrated marked muscle insulin resistance but normal sensitivity to the suppressive effect of insulin on hepatic glucose production. However, a normal basal rate of HGP in the face of fasting hyperinsulinemia could be construed to indicate the presence of hepatic insulin resistance. More impressive was the elevated fasting plasma FFA concentration in the presence of fasting hyperinsulinemia and the impaired suppression of plasma FFA during the euglycemic insulin clamp (Fig. A12). These findings indicate the presence of marked adipocyte resistance to the antilipolytic effect of insulin. Impaired insulin-mediated suppression of whole-body lipid oxidation also was present in the NGT offspring (Fig. A12). Petersen et al. (58) documented an increase in intramyocellular lipid content in the offspring of two type 2 diabetic parents. This observation is of important clinical significance, since diacylglycerol, long-chain fatty acyl CoAs, and ceramides all have been shown to cause serine phosphorylation of insulin resistance and IRS-1 and lead to the development of insulin resistance in skeletal muscle (59,60). Collectively, these results suggest that intramyocellular accumulation of toxic lipid metabolites plays an important role in the pathogenesis of muscle insulin resistance.

To further address this question, Kashyap et al. (30) infused a lipid emulsion for 4 days to cause a physiologic elevation in the plasma FFA concentration in NGT insulin-resistant offspring of two type 2 diabetes parents and in NGT insulin-sensitive subjects without any family history of diabetes. Four days of physiological elevation in the plasma FFA concentration in the offspring did not cause any further worsening of insulin-stimulated whole-body glucose disposal, nonoxidative glucose disposal, glucose oxidation, or preexisting defects in insulin-stimulated insulin receptor tyrosine phosphorylation (30). In contrast, in healthy control subjects, chronic lipid infusion was associated with a marked decline in insulin-stimulated glucose uptake and insulin receptor tyrosine phosphorylation (30). When the insulin-resistant offspring were treated with acipimox for 7 days to reduce the plasma FFA concentration and intramyocellular FACoA concentration, a marked improvement in insulin sensitivity was observed (61). These data lend further support to the observation that insulin resistance in skeletal muscle is an early metabolic defect in the pathogenesis of type 2 diabetes and that muscle lipid accumulation plays a central role in the etiology of the muscle insulin resistance.

Mitochondria are the main organelles where fatty acids are oxidized and investigators have focused on their structure and function in patients with type 2 diabetes. Studies using the leg balance technique have documented that fat oxidation is reduced in both type 2 diabetic and obese insulin-resistant nondiabetic individuals (62), suggesting that muscle mitochondrial oxidative capacity is impaired. Recently, two groups independently showed that NGT offspring of two type 2 diabetic parents had a reduced expression of key mitochondrial genes involved in the regulation of oxidative metabolism in skeletal muscle (63,64). The most commonly underexpressed functional genes were those coding for energy generation, including multiple glycolytic, tricarboxylic acid cycle, and oxidative phosphorylation genes. Evidence in support of a role for mitochondrial dysfunction as a cause of muscle insulin resistance in the NGT offspring of two type 2 diabetic parents has been provided by Shulman and colleagues. Using ^{31}P-NMR, these investigators demonstrated impaired mitochondrial activity in NGT insulin-resistant offspring of type 2 diabetic parents (57,58,65). Whereas mitochondria from NGT subjects without any family history of diabetes responded to insulin by increasing ATP production by 90%, mitochondria from insulin-resistant offspring increased ATP production by only 5% (Fig. A13). The authors postulated that muscle mitochondrial dysfunction was the primary defect, leading to elevated intramyocellular fatty acid metabolites (as a consequence of reduced fat oxidation) and subsequent insulin resistance (58,66). However, recent studies by Abdul-Ghani et al. (67) have shown that even small increases in palmitoyl carnitine (5–10 μmol/l) can markedly impair ATP synthesis in mitochondria isolated from human muscle. Thus, it is unclear which is the cart and which is the horse: mitochondrial dysfunction leading to increased intramyocellular lipid content and insulin resistance or increased muscle lipid content (i.e., secondary to elevated plasma FFA levels and/or excessive lipid ingestion) leading to mitochondrial dysfunction and insulin resistance.

SUMMARY — The maintenance of normal glucose homeostasis depends on a finely balanced dynamic interaction between tissue (muscle, liver, and fat) sensitivity to insulin and insulin secretion. Even in the presence of severe insulin resistance, a perfectly normal β-cell is capable of secreting sufficient amounts of insulin to offset the defect in insulin action. Thus, the evolution of type 2 diabetes requires the presence of defects in both insulin secretion and insulin action, and both of these defects can have a genetic as well as an acquired component. When type 2 diabetic patients initially present to the physician, they will have had their diabetes for many years, and defects in insulin action (in muscle, liver, and adipocytes) and insulin secretion will be well established (1,2,39). At this stage, it is not possible to define which defect came first in the natural history of the disease and which tissue is the primary defect responsible for the insulin resistance. Although insulin resistance represents the earliest detectable abnormality in the great majority of type 2 diabetic people, in a minority of individuals (i.e., glucokinase deficiency), it is clear that a β-cell defect initiates the disturbance in glucose homeostasis. Nevertheless, it is now clear that in any given diabetic patient, whatever defect (insulin resistance or impaired insulin secretion) initiates the disturbance in glucose metabolism, it will eventually be followed by the emergence of its counterpart (Fig. A14).

Insulin resistance is a nearly universal finding in patients with established type 2 diabetes. In normal-weight and obese individuals with IGT and in type 2 diabetic subjects with mild fasting hyperglycemia (110–140 mg/dl, 6.1–7.8 mmol/l), both

the basal and glucose-stimulated plasma insulin levels are increased. Although the first-phase insulin response may be decreased in some, but not all, of these subjects, the first phase consistently is increased in the NGT offspring of two type 2 diabetic parents and the total insulin response is increased in NGT offspring and in IGT subjects. In each of these groups, tissue sensitivity to insulin, measured with the insulin clamp technique, has been shown to be diminished. Prospective studies conclusively have demonstrated that hyperinsulinemia and insulin resistance precede the development of IGT and that IGT represents the forerunner of type 2 diabetes. This scenario has been well documented in Pima Indians, Mexican Americans, and Pacific Islanders. It is noteworthy that all of these populations are characterized by obesity and a younger age at onset of diabetes. Such results provide conclusive evidence that insulin resistance is the inherited defect that initiates the diabetic condition in the majority of type 2 diabetic patients. Studies in NGT first-degree relatives of diabetic individuals and in the offspring of two diabetic parents indicate that the inherited defect in insulin action results from an abnormality in the glycogen synthetic pathway in muscle and more proximal defects in glucose transport/phosphorylation and insulin signal transduction. As the insulin resistance progresses and muscle glucose uptake becomes further impaired, the postprandial rise in plasma glucose concentration becomes excessive, but the increase in basal hyperinsulinemia is sufficient to maintain the fasting plasma glucose concentration and HGP within the normal range. Nonetheless, there is an excessive postprandial rise in plasma glucose concentration, and a longer time is required to restore normoglycemia after each meal. Eventually, however, the insulin resistance becomes so severe that the compensatory hyperinsulinemia is no longer sufficient to maintain the fasting glucose concentration at the basal level. The development of hyperglycemia further stimulates β-cell secretion of insulin, and the resultant hyperinsulinemia causes a downregulation of insulin receptor number and of the intracellular events involved in insulin action, thus exacerbating the insulin resistance. Initially, the hyperglycemia-induced increase in insulin secretion serves a compensatory function to maintain near-NGT. In some individuals, the persistent stimulus to the β-cell to oversecrete insulin leads to a progressive loss of β-cell function. Chronic hyperglycemia (glucose toxicity) and/or disturbances in lipid metabolism (lipotoxicity) may contribute to the defect in insulin secretion. The resultant insulinopenia leads to the emergence/exacerbation of postreceptor defects in insulin action. Many of the intracellular events involved in glucose metabolism depend on the surge of insulin that occurs three to four times per day in response to nutrient ingestion. When the insulin response becomes deficient, the activity of the glucose transport system becomes severely impaired and a number of key intracellular enzymatic steps involved in glucose metabolism become depressed. Additionally, when severe insulinopenia ensues, plasma FFA levels rise, further contributing to the defects in intracellular glucose disposal. There is also compelling evidence that hyperglycemia per se can downregulate the glucose transport system, as well as a number of other intracellular events involved in insulin action (glucose toxicity), and a similar argument can be made concerning the intracellular derangement in lipid metabolism. This pathogenetic sequence can explain all of the clinical and laboratory features observed in type 2 diabetic patients. Insofar as the cellular defect is generalized, both hepatic and peripheral tissues (skeletal muscle and adipocytes), and possibly the β-cells themselves, would manifest insulin resistance, and the numerous metabolic alterations characteristic of the diabetic state could be related to one and the same primary defect.

The NGT offspring of two type 2 diabetic parents also manifest marked adipocyte resistance to the suppressive effects of insulin on lipolysis. One could argue, therefore, that the adipocyte represents the primary tissue responsible for the insulin resistance. According to this scenario, the elevated plasma FFA levels produce insulin resistance in muscle and liver and impair β-cell function. Adipocytes in the NGT offspring of two type 2 diabetic parents also secrete excessive amounts of inflammatory and insulin resistance producing adipocytokines that could initiate/exacerbate the insulin resistance in skeletal muscle. As reviewed by Iozzo in this symposium, the adipocyte insulin resistance could be genetic in origin or induced in utero during the third trimester by nutritional deprivation or overfeeding.

There is less evidence to support a role for the liver as the organ responsible for the insulin resistance. However, the NGT offspring of two type 2 diabetic parents have a normal rate of HGP in the presence of fasting hyperinsulinemia, suggesting the presence of hepatic resistance to the suppressive effect of insulin on glucose production. Therefore, one could argue that the resultant fasting hyperinsulinemia leads to the development of insulin resistance in skeletal muscle.

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