Unraveling the Cellular Mechanism of Insulin Resistance in Humans: New Insights from Magnetic Resonance Spectroscopy

Insulin resistance plays a major role in the pathogenesis of type 2 diabetes, yet despite much research the underlying mechanism responsible for it is poorly understood. In this review, some recent advances in the understanding of insulin resistance in humans that have been made by using magnetic resonance spectroscopy are discussed.

Type 2 diabetes is rapidly becoming a worldwide epidemic (50). Although the primary cause of this disease is unknown, it is clear that insulin resistance plays a major role in its development. Evidence for this comes from cross-sectional studies demonstrating the presence of insulin resistance in virtually all patients with type 2 diabetes as well as from prospective studies demonstrating the presence of insulin resistance one to two decades before the onset of the disease (4, 19, 20). In addition, insulin resistance in offspring of parents with type 2 diabetes has been shown to be the best predictor for the later development of the disease (43), and finally, perturbations that reduce insulin resistance prevent the development of diabetes (1). It is therefore important to understand the cellular mechanisms responsible for insulin resistance to identify potential targets for primary and secondary prevention. In this brief review, some recent advances in our understanding of insulin resistance in humans that were made by using magnetic resonance spectroscopy (MRS) will be discussed, and a unifying hypothesis will be proposed that may explain its pathogenesis under different pathological conditions.

Insulin Resistance and Muscle Glucose Metabolism

Before the advent of MRS, it was virtually impossible to measure rates of muscle glycogen synthesis in humans under physiological conditions by using traditional biopsy techniques. Using 13C-MRS, My colleagues and I found that we could noninvasively monitor the rate of [1-13C]glucose incorporation into muscle glycogen. Using this approach, we found that, under steady-state plasma concentrations of insulin and glucose that mimic postprandial conditions, muscle glycogen synthesis was ~50% lower in diabetic subjects than in normal volunteers. When the mean rate of muscle glycogen synthesis was extrapolated to the whole body, the synthesis of muscle glycogen accounted for most of the whole body glucose uptake and virtually all of the nonoxidative glucose metabolism in both normal and diabetic subjects (40). These studies demonstrate that under hyperglycemic, hyperinsulinemic conditions, muscle glycogen synthesis is the major pathway for glucose metabolism in both normal and diabetic individuals and that defective muscle glycogen synthesis plays a major role in causing insulin resistance in patients with type 2 diabetes.

In a subsequent study (38), we performed 31P-MRS to measure intramuscular synthetic rates and concentrations of glucose-6-phosphate (G6P) in muscle of patients with type 2 diabetes and muscle of age- and weight-matched control subjects. Intracellular G6P is an intermediary metabolite between glucose transport/hexokinase and glycogen synthesis, so its intracellular concentration will respond to the relative activities of these two steps (FIGURE 1). In the event of decreased activity of glycogen synthase in diabetes, G6P concentrations in diabetic patients would be expected to increase relative to those of normal individuals. Using 31P-MRS to noninvasively assess intracellular G6P concentrations, we found that incremental changes in G6P in the type 2 diabetic patients in response to insulin stimulation were significantly blunted, suggesting either decreased glucose transport activity or decreased hexokinase II activity as the cause of muscle insulin resistance in these subjects.

To examine whether this defect was a primary defect or an acquired defect secondary to other factors, we also studied lean, normoglycemic, insulin-resistant offspring of parents with type 2 diabetes (IR offspring), who have a high likelihood of developing diabetes later in life, by using a similar protocol. We found that these IR offspring had a 50% reduction in the rate of insulin-stimulated whole body glucose metabolism, which could be attributed to a decrease in the rate of muscle glycogen synthesis (37). This reduction in insulin-stimulated muscle glycogen synthesis was associated with a blunted increase in the intramuscular G6P concentration. These data suggest that defects in insulin-stimulated muscle
glucose transport/phosphorylation activity are a very early event in the pathogenesis of type 2 diabetes.

We next examined whether we could reverse this defect in glucose transport/phosphorylation activity with chronic exercise training (29). A similar cohort of IR offspring was recruited to exercise four times a week at 65% VO$_{2_{max}}$ for 40 min on a StairMaster for 6 wk. We found that by following this exercise regimen the IR offspring normalized their rates of insulin-stimulated muscle glycogen synthesis, which could be attributed to correction of their defect in glucose transport/phosphorylation activity. These data suggest that aerobic exercise might be useful in reversing the insulin resistance in these prediabetic individuals and thus prevent the development of type 2 diabetes. This hypothesis has gained support from the results of the recent Diabetes Prevention Program study, which demonstrated that the combination of diet and exercise was effective in decreasing the incidence of type 2 diabetes in patients with impaired glucose tolerance (18).

Finally, to delineate whether glucose transport or hexokinase II activity was rate controlling for insulin-stimulated muscle glycogen synthesis in patients with type 2 diabetes, we developed a novel $^{13}$C-NMR method to noninvasively assess intracellular free glucose concentrations in muscle (3). Intracellular glucose is an intermediary metabolite between glucose transport and glucose phosphorylation, and its concentration reflects the relative activities of glucose transporters (particularly GLUT4) and of hexokinase II (FIGURE 1). If hexokinase II activity is reduced relative to glucose transport activity in type 2 diabetes, one would predict a substantial increase in intracellular glucose concentration (>2 mM), whereas if glucose transport is primarily responsible for maintaining intracellular glucose metabolism, intracellular glucose and G6P should change proportionately. We found that the intracellular glucose concentration was far lower in the diabetic subjects than the concentration expected if hexokinase II was the primary rate-controlling enzyme for glycogen synthesis. These data suggested a predominant role for glucose transport control of insulin-stimulated muscle glycogen synthesis in patients with type 2 diabetes.

**Fatty Acid-Induced Muscle Insulin Resistance**

Increased plasma free fatty acid concentrations are typically associated with many insulin-resistant states, including obesity and type 2 diabetes mellitus (2). In a cross-sectional study of young, normal-weight offspring of type 2 diabetic patients, we found an inverse relationship between fasting plasma fatty acid concentrations and insulin sensitivity, consistent with the hypothesis that altered fatty acid metabolism might contribute to insulin resistance in patients with type 2 diabetes (41). Furthermore, recent studies measuring intramyocellular triglyceride content by $^{1}$H-NMR have shown an even stronger relationship between accumulation of intramyocellular triglyceride and insulin resistance (41).

Previous studies by Randle and colleagues (34) demonstrated that fatty acids compete with glucose for substrate oxidation in isolated rat heart and diaphragm muscle preparations. They speculated that increased fat oxidation was responsible for the insulin resistance associated with obesity. The mechanism they proposed to explain the insulin resistance was that an increase in fatty acids caused an increase in the intramitochondrial acetyl-CoA/CoA and NADH/NAD$^+$ ratios, with subsequent inactivation of pyruvate dehydrogenase. This in turn would cause intracellular citrate concentrations to increase, leading to inhibition of phosphofructokinase, a key rate-controlling enzyme in glycolysis. Subsequent accumulation of G6P would inhibit hexokinase II activity, resulting in an increase in intracellular glucose concentrations and decreased glucose uptake.

However, a recent series of MRS studies by our group has challenged this hypothesis (36). We applied $^{13}$C- and $^{31}$P-MRS to measure skeletal muscle glycogen and G6P concentrations, respectively, in healthy volunteers. The subjects were maintained under euglycemic, hyperinsulinemic conditions with either low or high levels of plasma fatty acids. The increment of the plasma fatty acid concentration for 5 h caused a reduction of ~50% in insulin-stimulated rates of muscle glycogen synthesis and whole body glucose oxidation compared...
with controls. In contrast to the results from the model of Randle and co-workers (34), which predicted that fat-induced insulin resistance would result in an increase in intramuscular G6P concentrations, we found that the drop in muscle glycogen synthesis was preceded by a fall in intramuscular G6P, suggesting that increases in plasma fatty acid concentrations initially induce insulin resistance by inhibiting glucose transport or phosphorylation activity and that the reduction in muscle glycogen synthesis and glucose oxidation follows. The reduction in insulin-activated glucose transport/phosphorylation activity in normal subjects maintained at high plasma fatty acid levels is similar to that seen in obese individuals (32), patients with type 2 diabetes (38), and lean, normoglycemic insulin-resistant offspring of type 2 diabetic individuals (37). Hence, accumulation of intramuscular fatty acid metabolites appears to play an important role in the pathogenesis of insulin resistance seen in obese patients and patients with type 2 diabetes.

To distinguish between possible effects of fatty acids on glucose transport activity and on hexokinase II activity, we measured intracellular concentrations of glucose in muscle using 13C-MRS (5). The logic of this experiment was similar to that described above, in which we followed intramyocellular concentrations of G6P to determine the relative activity of glucose transport and glycogen synthesis. Because intracellular glucose is an intermediary metabolite between glucose transport and hexokinase II, its concentration reflects the relative activities of these two steps. If a decrease in hexokinase II activity were responsible for the lower rate of insulin-stimulated muscle glycogen synthesis, intracellular glucose concentrations would increase. However, if the impairment were at the level of intracellular glucose concentrations, we found that the drop in muscle glycogen synthesis was preceded by a fall in intramuscular G6P and glucose concentrations.

This reduced glucose-transport activity could be the result of fatty acid effects on the GLUT4 transporter directly (alterations in the trafficking, budding, fusion, or activity of GLUT4), or it could result from fatty acid-induced alterations in upstream insulin-signaling events, resulting in decreased GLUT4 translocation to the plasma membrane. To explore the latter possibility, we examined insulin receptor substrate-1 (IRS-1)-associated phosphatidylinositol 3-kinase (PI3K) activity in muscle biopsy samples, using the identical lipid-infusion protocol described above for study of fatty acid effects. We found that elevations in plasma fatty acid concentrations similar to those in previous MRS studies abolished insulin-stimulated, IRS-1-associated PI3K activity compared with a fourfold insulin stimulation observed in the glycerol-control infusion studies (5). The reduced insulin-stimulated PI3K activity may be due to a direct effect of intracellular free fatty acids (or some fatty acid metabolite) on PI3K or may be secondary to alterations in upstream insulin-signaling events.

Consistent with an indirect effect, we found that a similar lipid-infusion protocol in rats resulted in a reduction of insulin-stimulated IRS-1 tyrosine phosphorylation, which was associated with activation of protein kinase C-θ (9), a known serine kinase that has been shown to be activated by diacylglycerol. An attractive hypothesis to account for the effects of fatty acids in muscle cells may be that increasing intracellular fatty acid metabolites, such as diacylglycerol or fatty acyl-CoA, activates a serine/threonine kinase cascade involving protein kinase C, leading to phosphorylation of serine/threonine sites on IRS-1 (9). Serine-phosphorylated forms of these proteins fail to associate with and activate PI3K, resulting in decreased activation of glucose transport and other downstream associated events. If this hypothesis is correct, any perturbation that results in accumulation of intracellular fatty acyl-CoA or other fatty acid metabolites in muscle and liver, either through increased delivery and/or decreased metabolism, might be expected to induce insulin resistance.

**Potential Role of the Inflammatory Pathway in Insulin Resistance**

Over 100 years ago, Ebstein (6) and later Williamson (44) found that high doses of sodium salicylate dramatically reduced glucosuria in diabetic patients. In the 1950s, more detailed prospective analyses suggested that glucose homeostasis might be improved by aspirin therapy in diabetic subjects; in the 1980s, conflicting results on the effects of aspirin in normal and diabetic subjects were subsequently reported. The mechanism by which salicylate may affect whole body glucose metabolism remained unknown until Yin et al. (47) discovered that salicylate inhibits the activity of a known serine kinase called IκB kinase-β (IKK-β). Shoelson and co-workers (49) hypothesized that IKK-β might be involved in causing insulin resistance and speculated that salicylate might prevent insulin resistance by inhibiting the activity of IKK-β. This hypothesis has been supported by...
recent rodent studies demonstrating that high-dose salicylate treatment and IKK-β inactivation prevented lipid-induced insulin resistance in salicylate-treated rats and IKK-β−/− heterozygous mice (17). Furthermore, these observations appear to translate to type 2 diabetic patients in that high-dose aspirin treatment for 2 wk reduced fasting hyperglycemia, reduced basal hepatic glucose production, and improved insulin-stimulated muscle glucose uptake (12). Together, these data support a potential role of IKK-β in mediating fatty acid-induced insulin resistance in humans as part of a serine kinase cascade that is triggered by accumulation of intracellular fatty acid metabolites, possibly downstream of PKC. It is also possible that IKK-β activation may cause insulin resistance by transcriptional activation of several inflammatory genes. In this regard, several studies have shown that the expression of inducible nitric oxide synthase (iNOS) (28) and the suppressors of cytokine signaling (SOCS) (7) are increased in obesity. Furthermore, targeted disruption of iNOS has been shown to protect mice from high-fat-induced insulin resistance in muscle (28).

**A Unifying Hypothesis for Insulin Resistance in Skeletal Muscle**

A unifying hypothesis to explain the cause of several forms of insulin resistance in humans is shown in [Figure 2](#). This model holds that increasing intracellular fatty acid metabolites activates a serine/threonine kinase cascade [possibly initiated by PKC-β in rodents (48) or by PKC-β and -δ in humans (13)] and subsequent activation of other serine kinases such as IKK-β (13, 49) and JNK-1 (11), leading to phosphorylation of serine sites on IRS-1 (39). Serine-phosphorylated forms of IRS-1 fail to bind and activate phosphoinositide 3-kinase (PI3K), resulting in reduced insulin-stimulated glucose transport activity and other downstream events downstream of PI3K, LPL, lipoprotein lipase; FATP1, fatty acid transport protein 1; UCP3, uncoupling protein 3.

**Increased Energy Intake Leading to Obesity and Insulin Resistance**

The most common cause of insulin resistance occurs when energy intake exceeds the metabolic rate, leading to obesity ([Figure 3](#)). Under these conditions, increased energy intake leads to increased fat delivery from either exogenous fat in the diet or endogenous fat from hepatic lipogenesis to muscle and liver, resulting in increased fat storage in these tissues and insulin resistance through the mechanisms described earlier in this review. However, it is well established that not all obese subjects are insulin resistant. As first described by Vague (42), those individuals who have a tendency to store fat centrally (android or apple-shaped individuals) are typically insulin resistance.
resistant, whereas those who store fat around the hips (gynoid or pear-shaped individuals) are typically not insulin resistant. One potential explanation for these differences in fat distribution leading to differences in insulin sensitivity is that those individuals with central obesity cannot store fat as effectively in the visceral fat cell and that excess fat is then displaced to liver and muscle cells, where it causes insulin resistance in these tissues. In contrast, those individuals who have a gynoid distribution of fat (sometimes referred to as the “fit and fat” individual) have adipocytes in these areas that store fat more effectively, which keeps fat distributed away from muscle and liver.

**Defects in Adipocyte Fatty Acid Metabolism Leading to Insulin Resistance**

Evidence for defects in adipocyte metabolism causing insulin resistance comes from recent studies in both transgenic mouse models of lipodystrophy and patients with severe lipodystrophy. A-ZIP/F-1 transgenic mice are almost totally devoid of fat because their adipocytes express the A-ZIP/F-1 protein, which blocks the function of several classes of transcription factor (23). Interestingly, these fatless mice also manifest severe liver and muscle insulin resistance and develop diabetes (8, 16). These abnormalities were associated with an approximately twofold increase in fatty acyl-CoA content in muscle and liver and defects in insulin activation of IRS-1- and IRS-2-associated PI3K in muscle and liver (16).

Furthermore, transplantation of fat tissue obtained from normal littermates into these fatless mice normalized fatty acyl-CoA content in muscle and liver as well as sensitivity in muscle and liver (16).

Similar results have been seen in patients with severe lipodystrophy following chronic leptin-replacement therapy (33). Before leptin treatment, these lipodystrophic patients were found to have severe insulin resistance in both liver and muscle, similar to the lipodystrophic mice. These changes were associated with severe hepatic fatty liver but surprisingly normal intramyocellular lipid content despite severe muscle insulin resistance (33). These data are consistent with recent studies that have demonstrated that intramyocellular triglyceride is not the trigger in mediating insulin resistance but more likely a marker for some other intracellular fatty acid metabolite that acts as the trigger for fatty acid-induced insulin resistance (48). Replacement leptin therapy for 3–6 months reversed both hepatic and muscle insulin resistance, and these changes were associated with a reduction in both intrahepatic triglyceride and intramyocellular lipid content (33). These findings offer further evidence in support of the hypothesis that insulin resistance develops in obesity, type 2 diabetes, and lipodystrophy because of alterations in the partitioning of fat between the adipocyte and muscle and liver. This in turn leads to the accumulation of intracellular fatty acid metabolites in muscle and liver, which then leads to activation of a serine kinase cascade, leading in turn to defects in insulin signaling and insulin action in these tissues (FIGURE 3).

This hypothesis might also explain how thiazolidinediones improve insulin sensitivity in muscle and liver tissue. By activating PPAR-γ receptors in the adipocyte and promoting adipocyte differentiation, these agents promote a redistribution of fat from liver and muscle into the adipocyte, much as fat transplantation does in fat-deficient lipodystrophic mice (8, 16). This hypothesis is supported by a recent thiazolidinedione study in patients with type 2 diabetes. Three months of rosiglitazone therapy improved muscle insulin responsiveness, and these changes were associated with a marked reduction in intrahepatic fat content, a decrease in the intramyocellular/extracellular lipid content in muscle, and increased peripheral adipocyte insulin responsiveness as assessed by microdialysis (21). Interestingly, rosiglitazone has also been shown to be effective in reversing skeletal muscle insulin resistance in lipodystrophic A-ZIP/F fatless mice (15). In this case the liver appears to take over the role of the absent adipocytes in that rosiglitazone treatment results in a redistribution of fat (and intra-

[FIGURE 3. Mechanisms for increased intracellular lipid accumulation in muscle and liver]

1. Increased delivery of fat to muscle and/or liver due to overnutrition; 2. alterations in adipocyte metabolism leading to increased adipocyte lipolysis [e.g., lipodystrophy, peroxisome proliferator-activated receptor-γ (PPAR-γ) mutations, perlipin abnormalities, etc.]; and 3. decreases in intracellular fatty acid oxidation due to inherited [insulin-resistant (IR) offspring] or acquired reduction (aging) in mitochondrial content and/or function.

In contrast to humans, A-ZIP/F fatless mice have significant expression of PPAR-γ in liver.
Defects in Mitochondrial Function Leading to Insulin Resistance

As hypothesized earlier (39), it might also be expected that any alteration in the ability of muscle and liver to metabolize fatty acids, such as inherited or acquired defects in mitochondrial function, would also lead to intracellular accumulation of fatty acid metabolites and subsequent defects in insulin signaling and action. Indeed, a recent multinuclear MRS study by our group (30) has demonstrated that insulin resistance in the elderly could be attributed to increased intramyocellular and intrahepatic lipid content, which in turn was linked to a reduction in mitochondrial oxidative phosphorylation activity assessed by $^{13}$C/$^{31}$P-MRS (30). It is likely that these changes can be ascribed to an age-associated reduction in mitochondrial content due to accumulated mutations in mtDNA that have been described to occur with aging (22).

In more recent studies, using the same $^{31}$P-MRS techniques to assess rates of ATP synthesis in skeletal muscle, we have found similar reductions in mitochondrial activity associated with an increase in intramyocellular lipid content in young, lean, insulin-resistant offspring of parents with type 2 diabetes, a group that has a strong tendency to develop diabetes latter in life (31). In addition, these insulin-resistant subjects were found to have a reduction in the ratio of type I fibers (mostly oxidative) to type II fibers (mostly glycolytic) compared with insulin-sensitive control subjects. These alterations in mitochondrial function are consistent with studies that have demonstrated reductions in the activity of rotenone-sensitive NADH:O$_2$ oxidoreductase in isolated muscle mitochondria obtained from type 2 diabetic subjects (14). Together, these data suggest that alterations in nuclear-encoded genes that regulate mitochondrial biogenesis such as PGC-1α (46), AMP kinase (51), and CaMK IV (45) may form the genetic basis for inheritance of type 2 diabetes. This hypothesis is supported by recent microarray data demonstrating downregulation of PGC-1α-responsive genes in patients with type 2 diabetes (24, 27) and their first-degree relatives (27).

Emerging Frontiers: Mitochondrial Dysfunction—Thrifty Genes and a Potential Genetic Cause of Obesity

Why would nature preserve genes that lead to a reduction in mitochondrial content and the potential to develop insulin resistance? One intriguing possibility is that the genetic alterations responsible for reduced mitochondrial biogenesis represent “thrifty genes” (25). By slightly (~30%) decreasing mitochondrial content in muscle and other tissues, energy requirements would be slightly lower, allowing these individuals to better survive famine, which was a regular occurrence for our ancestors. Indeed, lean insulin-resistant offspring have a strong tendency toward lower resting energy expenditure, as assessed by indirect calorimetry, when compared with their age-, weight-, height-, and activity-matched insulin-sensitive counterparts (31). In addition, having a reduced ratio of type I fibers (oxidative slow twitch) to type II fibers (glycolytic fast twitch) would have an added survival advantage by possibly making these individuals better sprinters.

Insulin resistance might also have evolved as an important survival mechanism to preserve protein stores in times of famine (35). During prolonged fasting, it is well known that fatty acids increase due to increased lipolysis. Although this increase in plasma fatty acids will result in reduced insulin-stimulated glucose uptake in muscle, other insulin signaling pathways that regulate protein metabolism and other insulin-regulated processes that are PI3K independent might remain unaffected. In this way, the body preserves circulating glucose for the central nervous system and other obligate glucose-requiring organs while preserving protein stores, which are both essential for survival. Although this protective mechanism works well in times of famine, in our present-day society of caloric excess and reduced physical activity it leads to insulin resistance associated with obesity, hyperlipidemia, hypertension, and cardiovascular disease (i.e., metabolic syndrome).

Finally, reduced mitochondrial content/activity, be it acquired or inherited, may be an important factor that promotes obesity by two mechanisms (FIGURE 4). First, by decreasing daily energy expenditure, even by a small amount, it can lead to progressive weight gain. For example, a 50 Cal/day reduction in energy expenditure in a typical adult can lead to an ~5 lb. weight gain every year. Second, a reduction in skeletal muscle mitochondrial activity will predispose a person to accumulate intramyocellar lipid content in young, lean, insulin-resistant offspring of parents with type 2 diabetes (31). In addition, these insulin-resistant subjects were found to have a reduction in the ratio of type I fibers (mostly oxidative) to type II fibers (mostly glycolytic) compared with insulin-sensitive control subjects. These alterations in mitochondrial function are consistent with studies that have demonstrated reductions in the activity of rotenone-sensitive NADH:O$_2$ oxidoreductase in isolated muscle mitochondria obtained from type 2 diabetic subjects (14). Together, these data suggest that alterations in nuclear-encoded genes that regulate mitochondrial biogenesis such as PGC-1α (46), AMP kinase (51), and CaMK IV (45) may form the genetic basis for inheritance of type 2 diabetes. This hypothesis is supported by recent microarray data demonstrating downregulation of PGC-1α-responsive genes in patients with type 2 diabetes (24, 27) and their first-degree relatives (27).

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ocellular lipid, which in turn will result in chronic hyperinsulinemia (30, 31). This small increase in intramyocellular lipid mass, which may represent only a few pounds of body weight, results in a "metabolically obese" phenotype and chronic hyperinsulinemia, which in turn will promote obesity by increasing lipogenesis, inhibiting lipolysis, and promoting increased caloric intake.

**Summary**

Insulin resistance plays a major role in the pathogenesis of type 2 diabetes. In this short review, we have discussed some recent MRS studies that potentially shed new light on the pathogenesis of insulin resistance in humans. Specifically, we have discussed the following:

1. Insulin resistance in skeletal muscle can mostly be attributed to defects in insulin-stimulated glucose transport activity.

2. In contrast to the original mechanism proposed by Randle et al. (34), in which fatty acids cause insulin resistance by inhibiting pyruvate dehydrogenase activity, we found that fatty acids cause insulin resistance in human skeletal muscle by directly interfering with insulin-stimulated glucose transport activity.

3. Reduced insulin activation of glucose transport activity can be attributed to an acquired defect in insulin-stimulated, IRS-1-associated PI3K activity at the level of IRS-1 tyrosine phosphorylation. This in turn can be ascribed to fatty acid activation of a serine kinase cascade, which causes increased serine phospho-rylation of IRS-1 at critical sites that interfere and block tyrosine phos-phorylation of IRS-1 tyrosine sites that are required to bind and activate PI3K. (A similar mechanism involving IRS-2 appears to occur in the liver.)

4. Any perturbation that leads to an increase in intramyocellular fatty acid metabolite (e.g., fatty acyl-CoA, diacylglycerol, etc.) content, such as acquired (e.g., aging) or inherited (e.g., potential type 2 diabetes genes) defects in mitochondrial fatty acid oxidation, defects in adipocyte fat metabolism (e.g., lipodystrophy) leading to increased fat delivery to liver and muscle, or, most commonly, increased fat delivery due to increased caloric intake, will lead to insulin resistance through this final common pathway.

5. Mitochondrial dysfunction, be it acquired or inherited, may be an important contributing factor to the development of obesity.

Understanding these key cellular mechanisms of insulin resistance should help elucidate new targets for treating or preventing type 2 diabetes. ■

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**References**


