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MECHANISMS OF ENDOCRINE DISEASE

Role of the Adipocyte, Free Fatty Acids, and Ectopic Fat in Pathogenesis of Type 2 Diabetes Mellitus: Peroxisomal Proliferator-Activated Receptor Agonists Provide a Rational Therapeutic Approach

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Type 2 diabetes mellitus (T2DM) is characterized by insulin resistance in liver and muscle and impaired insulin secretion. Considerable evidence also implicates deranged adipocyte metabolism and altered fat topography in the pathogenesis of glucose intolerance in T2DM. 1) Fat cells are resistant to insulin's antilipolytic effect, leading to day-long elevated plasma FFA levels. Chronically increased plasma FFA stimulates gluconeogenesis, induces hepatic/muscle insulin resistance, and impairs insulin secretion in genetically predisposed individuals. These FFA-induced disturbances are referred to as lipotoxicity. 2) Dysfunctional fat cells produce excessive amounts of insulin resistance-inducing, inflammatory, and atherosclerotic-provoking cytokines and fail to secrete normal amounts of insulin-sensitizing adipocytokines. 3) Enlarged fat cells are insulin resistant and have diminished capacity to store fat. When adipocyte storage capacity is exceeded, lipid "overflows" into muscle, liver, and perhaps β-cells, causing muscle/hepatic insulin resistance and impaired insulin secretion. Thiazolidinediones enhance adipocyte insulin sensitivity, inhibit lipolysis, reduce plasma FFA, and favorably influence the production of adipocytokines. Thiazolidinediones also redistribute fat within the body (decreased visceral and hepatic fat; increased sc fat) and decrease intracellular concentrations of triglyceride metabolites in muscle, liver, and β-cells, contributing to improvements in muscle/hepatic insulin sensitivity and pancreatic function in type 2 diabetics.

I. Pathogenesis of T2DM

The pathophysiology of glucose intolerance in T2DM is complex and involves both genetic and acquired factors (1, 2). Among the acquired factors, weight gain (1–3) and physical inactivity (1, 2, 4) are of paramount importance. In diabetic individuals with overt fasting hyperglycemia, the triumvirate (1, 2) of 1) impaired insulin secretion by the pancreatic β-cells, 2) muscle insulin resistance, and 3) hepatic insulin resistance all play central roles in the development and progression of glucose intolerance.

A. Insulin secretion

Before the onset of postprandial and fasting hyperglycemia, individuals genetically predisposed to develop T2DM are known to be resistant to the action of insulin (5–8). Nonetheless, glucose homeostasis remains normal because of a marked increase in insulin secretion by pancreatic β-cells (1, 2, 5–11). The increase in the fasting plasma insulin concentration is sufficient to offset the hepatic insulin resistance, and the basal rate of hepatic glucose production (HGP) remains normal, whereas the hyperinsulinemic response to carbohydrate ingestion is sufficient to cause normal suppression of basal HGP and to overcome the defect in muscle glucose uptake (1, 2, 5–8, 12, 13). With the onset of impaired glucose tolerance (IGT), there is a worsening of the insulin resistance in muscle and liver (1, 2, 6, 13, 14) and a further increase in the total insulin response to an oral glucose load (1, 2, 9, 12). However, the timing of insulin release in IGT is disrupted, with a decline in early phase insulin secretion, followed by an excessive late phase insulin response (1, 6, 9, 12–17). The progression from IGT to overt T2DM is associated with little or no further deterioration in insulin resistance (1, 2, 11, 18). Rather, the ability of the pancreas to maintain its high insulin secretory rate declines (1, 2, 9, 11, 13, 15, 16, 18, 19), leading to a worsening of glucose intolerance and eventual development of overt T2DM. The inverted U-shaped curve of insulin secretion as individuals progress from normal glucose tolerance to IGT to T2DM has been referred to as Starling's curve of the pancreas (1). Initially, the defect in glucose homeostasis is evident by an excessive rise in the postprandial glucose excursion (IGT and mild diabetes), and this is followed by a rise in the fasting plasma glucose concentration.

Abbreviations: ASP, Acylation-stimulating protein; C/EBP, CCAAT/enhancer-binding protein; CoA, coenzyme A; CRP, C-reactive protein; DAG, diacylglycerol; FA, fatty acyl; FFA, free fatty acid; G-6-P, glucose-6-phosphate; HbA_{1c}, hemoglobin A_{1c}; HGP, hepatic glucose production; IGT, impaired glucose tolerance; IKK-β, IκB kinase; IRS-1, insulin receptor substrate-1; PAI-1, plasminogen activator inhibitor-1; PPAR, peroxisomal proliferator-activated receptor; RSK2, p90 ribosomal S6 kinase; T2DM, type 2 diabetes mellitus.

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B. Muscle glucose uptake

Muscle tissue in T2DM individuals is moderately to severely resistant to the action of insulin (1, 2, 20, 21). When insulin is infused systemically or locally into the leg or forearm, the stimulatory effect of hyperinsulinemia on muscle glucose uptake is markedly reduced (20). This defect in muscle glucose uptake in concert with the impaired ability of insulin to suppress the elevated basal rate of hepatic glucose production (20–22) is responsible for the excessive rise in the plasma glucose concentration after glucose ingestion, *i.e.* postprandial hyperglycemia (23). In nondiabetic individuals, approximately one third of the glucose that is taken up by muscle in response to a physiological insulin stimulus is oxidized, and the other two thirds is converted to glycogen (1, 2, 21, 24). In type 2 diabetics, the ability of physiological and pharmacological increases in the plasma insulin concentration to augment muscle glucose oxidation and glycogen synthesis is severely impaired (1, 2, 21, 24).

C. HGP

In T2DM individuals with established fasting hyperglycemia, the basal rate of hepatic glucose production is increased despite fasting plasma insulin concentrations that are 2- to 4-fold elevated (1, 2, 21, 22), indicating the presence of hepatic resistance to the action of insulin. The hepatic insulin resistance is further evident by the impaired ability of hyperinsulinemia to suppress basal HGP (1, 2, 21). The elevated basal rate of HGP is closely correlated with the increase in fasting plasma glucose concentration in T2DM patients (1, 22) and primarily is accounted for by an increase in gluconeogenesis (25).

II. Role of the Adipocyte and FFA in the Pathogenesis of T2DM: The Dysharmonious Quartet

A. Overview

The majority (>80%) of patients with T2DM in the U.S. are overweight (26), and both lean and especially obese type 2 diabetics are characterized by day-long elevations in the plasma free fatty acid (FFA) concentration which fail to suppress normally following ingestion of a mixed meal or oral glucose load (27) or in response to insulin (21, 28). Similar abnormalities in FFA metabolism have been documented in individuals with IGT and nondiabetic, insulin resistant obese individuals (29, 30). FFA are stored as triglycerides in adipocytes and serve as a source of energy during fasting conditions. Insulin is a potent inhibitor of lipolysis (21) and restrains the release of FFA from the adipocyte by inhibiting the enzyme hormone-sensitive lipase. In type 2 diabetics, the ability of insulin to inhibit lipolysis (as reflected by suppression of radioactive palmitate turnover) and to reduce the plasma FFA concentration is markedly impaired (21). It is now recognized that chronically elevated plasma FFA concentrations cause insulin resistance in muscle and liver (1, 2, 28, 30, 31) and impair insulin secretion (32, 33). Thus, elevated plasma FFA levels can cause/aggravate the three major pathogenic disturbances that are responsible for impaired glucose homeostasis in T2DM individuals, and the time has arrived for the "triumvirate" (muscle, liver, and β-cell) to be joined by the "fourth musketeer" (29) to form the "dysharmonious quartet" (Fig. 1). In addition to FFA that circulate in plasma in increased amounts, T2DM patients have increased stores of triglycerides in muscle (34, 35) and liver (36, 37), which correlate closely with the presence of insulin resistance in these tissues. The triglycerides in liver and muscle are in a state of constant turnover, and the metabolites [*i.e.* fatty acyl coenzymes A (CoAs), ceramides, diacyglycerol, *etc.*] of intracellular triglyceride lipolysis impair insulin action in both liver and muscle (2, 38). This sequence of events has been referred to as lipotoxicity (2, 32, 39). Evidence also has accumulated to implicate lipotoxicity as an important cause of β-cell dysfunction (32, 40).

B. FFA and insulin secretion

After the ingestion of a mixed meal or infusion of lipid, the plasma FFA concentration rises, and FFA are transported into the β-cell via fatty acid-binding protein 2 (32, 40–42). Within the cytosol, fatty acids are converted to their fatty acyl CoA derivative, which, in turn, augments insulin secretion via a variety of mechanisms (32, 40–42): 1) increased formation of phosphatidic acid and diacylglycerol, which directly and indirectly (through activation of protein kinase C) enhance exocytosis of insulin stored within secretory granules; 2) stimulation of endoplasmic reticulum Ca^{2+}-adenosine triphosphatase, leading to an increase in intracellular calcium concentration and augmentation of insulin secretion; and 3) closure of the K^{+}-ATP channel with resultant depolarization of the β-cell membrane, which causes an increase in intracellular calcium and stimulation of exocytosis of insulin-containing granules. After ingestion of a mixed meal, the resultant hyperglycemia leads to an increase in malonyl CoA concentration within the β-cell. Malonyl CoA inhibits carnitine palmitoyl transferase-1, thus impairing the transport of fatty acyl CoAs into the mitochondria where they are oxidized in the Krebs cycle. The resulting increase in cytosolic fatty acyl CoAs (*i.e.* consequent to malonyl CoA-induced inhibition of carnitine palmitoyl transferase-1) works in tandem with hyperglycemia to augment insulin secretion. Consistent with these *in vitro* observations, short-term (2- to 6-h) elevation of the plasma FFA concentration in rodents and man has been shown to enhance insulin secretion (32, 43–45), whereas an acute decrease in the plasma FFA

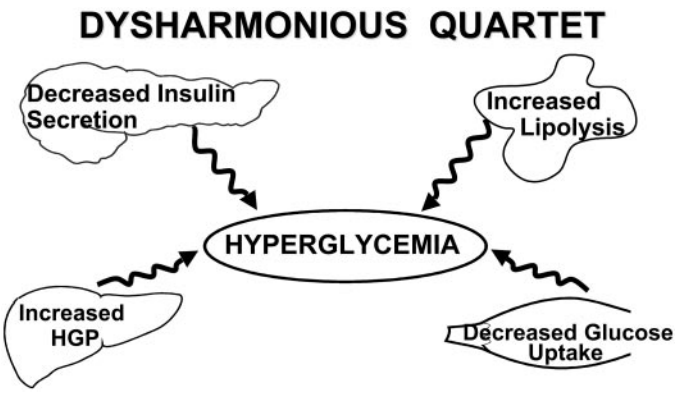

FIG. 1. Pathogenesis of T2DM: the "dysharmonious quartet."

concentration inhibits glucose-stimulated insulin secretion (32, 43).

In contrast to the acute effect of elevated plasma FFA to enhance insulin secretion, longer-term (≥48 h) exposure results in an impaired β-cell response to glucose both *in vitro* and *in vivo* in animals (46–51) and humans (33, 52–54). The inhibitory effect of chronically elevated plasma FFA appears to be more prominent in individuals with a genetic predisposition to develop T2DM (33), but has also been observed in healthy carriers of the $Pro^{12}Ala$ polymorphism of the peroxisome proliferator-activated receptor-γ2 (PPARγ) gene (55). Conversely, a reduction in the plasma FFA concentration in type 2 diabetics has been shown to improve insulin secretion (33, 56, 57). Several groups have shown that chronic (6- to 7-wk) overfeeding of a high fat diet impairs insulin secretion in dogs (58, 59). Elevated plasma FFA levels also have been shown to be a risk marker for the long-term development of impaired glucose tolerance and T2DM (50) in Caucasians (60) and Pima Indians (61). Unger (62) has coined the term lipotoxicity to describe the deleterious effect of chronic FFA elevation on insulin secretion by the pancreatic β-cells. In the Zucker diabetic fatty rat, chronically increased plasma FFA levels initially lead to a physiological impairment in insulin secretion. With time, however, β-cell apoptosis ensues and β-cell mass is reduced by more than 50% (50). Within the β-cell, elevated fatty acyl CoAs increase the formation of ceramide. Ceramide, in turn, augments nitric oxide formation, which is cidal to the β-cell (40). Obviously, similar studies cannot be performed in man *in vivo*, but, at least in the Zucker diabetic fatty rat model, the biochemical/molecular basis of FFA-induced β-cell toxicity has been established. Incubation of human islets with FFA also has been shown to cause β-cell apoptosis (51). Regardless of the mechanism(s) involved, chronic physiological (478–666 μmol/liter) (33) elevation of the plasma FFA concentration in nondiabetic humans has been shown to impair insulin secretion (33, 52–55).

C. FFA and muscle glucose metabolism

Four decades ago, Randle and colleagues (63) proposed that increased FFA oxidation restrains glucose oxidation in muscle by altering the redox potential of the cell and by inhibiting key glycolytic enzymes. Excessive FFA oxidation 1) leads to the intracellular accumulation of acetyl CoA, a potent inhibitor of pyruvate dehydrogenase, 2) increases the NADH/NAD ratio, causing a slowing of the Krebs cycle, and 3) results in the accumulation of citrate, a powerful inhibitor of phosphofructokinase. Inhibition of phosphofructokinase, in turn, causes product inhibition of the early steps involved in glucose metabolism, leading to the accumulation of glucose-6-phosphate (G-6-P), which inhibits hexokinase II. The block in glucose phosphorylation results in a build-up of intracellular free glucose, which restrains glucose transport into the cell via the GLUT4 transporter. The resultant decrease in glucose transport impairs glycogen synthesis, although a direct inhibitory effect of fatty acyl CoAs on glycogen synthase also has been demonstrated (64). This sequence of events, via which accelerated plasma FFA oxidation inhibits muscle glucose transport, glucose oxidation, and glycogen synthesis, is referred to as the Randle cycle (63). It should be noted that the same scenario would ensue if the FFA were derived from triglycerides stored in muscle (34, 35) or from plasma (21, 28, 29).

Felber and co-workers (30, 65, 66) were among the first to demonstrate that in diabetic (and obese nondiabetic) humans, basal plasma FFA levels and lipid oxidation are increased and fail to suppress normally after glucose ingestion. The elevated basal rate of lipid oxidation was strongly correlated with a decreased basal rate of glucose oxidation as well as with the reduced rate of nonoxidative glucose disposal, which primarily reflects glycogen synthesis (24), after ingestion of a glucose load. Further validation of the Randle cycle in man has come from studies employing the euglycemic insulin clamp (67). When Intralipid is infused concomitantly with insulin, either to prevent the decline in plasma FFA concentration or to increase the plasma FFA concentration above basal levels, both glucose oxidation and nonoxidative glucose disposal are inhibited in a dose-dependent fashion (31, 67). Using magnetic resonance imaging, Roden *et al.* (68) have shown that the FFA-induced inhibition of nonoxidative glucose disposal reflects impaired glycogen synthesis.

D. Randle cycle revisited: biochemical/molecular basis of FFA-induced insulin resistance

The Randle cycle was formulated based upon experiments performed in rat diaphragm and heart muscle (63). Recent studies performed in human skeletal muscle implicate mechanisms, in addition to those proposed by Randle, in the FFA-induced insulin resistance (Fig. 2). Several investigators (68–70) failed to observe a rise in muscle G-6-P, an increase in muscle citrate levels, or an inhibition of phosphofructokinase when insulin-stimulated glucose metabolism was inhibited by a lipid infusion to elevate the plasma FFA concentration. Thus, although increased FFA/lipid oxidation and decreased glucose oxidation are closely coupled, as originally demonstrated by Randle, mechanisms other than product (*i.e.* elevated G-6-P) inhibition of the early steps of glucose metabolism must be invoked to explain the defects

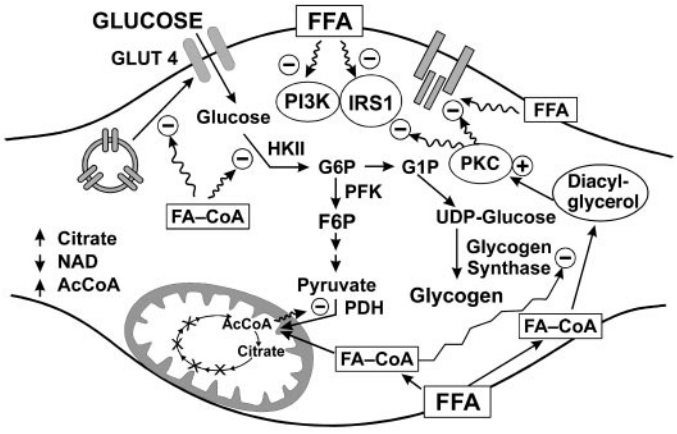

FIG. 2. Randle cycle revisited; see text for a detailed discussion. The negative sign within the enclosed circle indicates a site of inhibition by intracellular metabolites of triglyceride metabolism.

in glucose transport, glucose phosphorylation, and glycogen synthesis.

Studies in humans and animals have shown a strong negative correlation between insulin-stimulated glucose metabolism and increased intramuscular lipid pools, including triglycerides (71–73),[1] diacylglycerol (DAG) (77, 78), and long chain fatty acyl CoAs (FA-CoA) (79). An acute elevation in plasma FFA concentration leads to an increase in muscle fatty acyl CoA and DAG concentrations. Both long chain fatty acyl CoAs and DAG activate protein kinase Cθ (77), which increases serine phosphorylation with subsequent inhibition of insulin receptor substrate-1 (IRS-1) tyrosine phosphorylation (80–82) (Fig. 2). Consistent with this observation, both acute (4 h) and chronic (5 d) elevation in the plasma FFA concentration inhibits insulin-stimulated tyrosine phosphorylation of IRS-1, the association of the p85 subunit of PI-3 kinase with IRS-1, and activation of phosphoinositol 3-kinase in human skeletal muscle (83–85). A direct effect of long chain FA-CoAs on glucose transport (86), glucose phosphorylation (87), and glycogen synthase (64) also has been demonstrated in muscle (Fig. 2). Lastly, increased muscle ceramide levels (secondary to increased long chain FA-CoAs) interfere with glucose transport and inhibit glycogen synthase in muscle via activation of protein kinase B (88, 89) (Fig. 2).

E. FFA and hepatic glucose metabolism

The liver plays a central role in the regulation of glucose metabolism (1, 2). After ingestion of a carbohydrate meal, the combination of hyperinsulinemia and hyperglycemia suppresses basal hepatic glucose production (23). If glucose were to enter the systemic circulation simultaneously from both the gastrointestinal tract and the liver, marked hyperglycemia would ensue. In addition, the liver takes up approximately one third of the glucose in the ingested carbohydrate meal (23, 90). Collectively, suppression of hepatic glucose production and augmentation of hepatic glucose uptake account for the maintenance of about half of the rise in plasma glucose concentration after carbohydrate ingestion (1, 2, 23, 90).

The regulation of HGP is controlled by a number of factors, of which insulin (inhibits HGP) (90, 91) and glucagon and FFA (stimulate HGP) (92) are the most important. *In vitro* studies have demonstrated that plasma FFA are potent stimulators of HGP and do so by stimulating pyruvate carboxylase and phosphoenolpyruvate carboxykinase, the rate-limiting enzymes for gluconeogenesis (93–95), and by increasing the activity of glucose-6-phosphatase, the enzyme that ultimately controls the release of glucose by the liver (96). In normal subjects, an increase in plasma FFA concentration stimulates gluconeogenesis (97, 98), whereas a decrease in the plasma FFA concentration reduces gluconeogenesis (97, 99). Bergman, Cherrington, and colleagues (92, 100) have shown that a significant component of the suppressive effect of insulin on HGP is mediated via inhibition of lipolysis and reduction of the plasma FFA concentration. Moreover, FFA infusion in normal humans under conditions that simulate the diabetic state (101) and in obese insulin-resistant subjects (102) enhances HGP due to stimulation of gluconeogenesis (97).

In type 2 diabetics the fasting plasma FFA concentration and lipid oxidation rate are increased and are strongly correlated with both the elevated fasting plasma glucose concentration and the basal rate of HGP (1, 2, 21, 29, 30, 102, 103). Moreover, reduction of the plasma FFA concentration with nicotinic acid reduces HGP and gluconeogenesis in T2DM subjects (104). In the insulin-resistant, normal glucose-tolerant offspring of two diabetic parents, suppression of HGP by insulin is reduced and basal, and insulin-suppressed rates of plasma FFA and lipid oxidation are impaired (5, 12). In other insulin-resistant states, including obesity and IGT, insulin-suppressed HGP also is reduced and correlates with both the elevated basal FFA levels and the increased lipid oxidation rate (18, 105, 106). In a recent study (106), normal glucose-tolerant, insulin-resistant men demonstrated impaired suppression of HGP and plasma FFA levels by insulin and increased hepatic fat content, with strong correlations among the three independent variables. The relationship among elevated plasma FFA concentration, FFA oxidation, and HGP in T2DM (and obesity) can be explained as follows. 1) Increased plasma FFA, by mass action, augments FFA uptake by hepatocytes, leading to accelerated lipid oxidation and accumulation of acetyl CoA. Increased acetyl CoA stimulates pyruvate carboxylase and phosphoenolpyruvate carboxykinase, the rate-limiting enzymes in gluconeogenesis (94, 95), as well as glucose-6-phosphatase, the rate-controlling enzyme for glucose release from the hepatocyte (96). 2) Increased FFA oxidation provides a source of energy (in the form of ATP) and reduced nucleotides (NADH) to drive gluconeogenesis. 3) Elevated plasma FFA induce hepatic insulin resistance by inhibiting the insulin signal transduction system (80–85, 107, 108). In T2DM patients, these deleterious effects of elevated plasma FFA concentration occur in concert with increased plasma glucagon levels (109, 110), increased hepatic sensitivity to glucagon (110), and increased hepatic uptake of circulating gluconeogenic precursors (111).

III. The Fat Cell as an Endocrine Organ

The preceding discussion emphasized the adipocyte as a storage depot for FFA. In insulin-resistant states, such as T2DM (and obesity), stored FFA are released in excessive amounts and travel to the muscle/liver and pancreas where they induce insulin resistance and impair insulin secretion, respectively. It now is recognized that the adipocyte is a metabolic factory that produces a wide variety of adipocytokines (112). In type 2 diabetics there is a reduction in the production of some factors that normally are synthesized by the adipocyte, *i.e.* adiponectin, whereas there is accelerated release of other adipocytokines, *i.e.* resistin, angiotensinogen,

[1] Trained athletes are an exception. The muscle triglyceride concentration is increased and primarily is located in lipid droplets surrounding the mitochondria, which histologically are enlarged, but otherwise appear normal and have increased oxidative capacity (74, 75). In contrast, lipid droplets are distributed more diffusely throughout the cell in type 2 diabetics and are not in close proximity to the mitochondria, which generally are smaller and display reduced oxidative enzyme activity (76). Enlarged, fractured mitochondria also are present in myocytes of diabetics, and this has been interpreted to represent accelerated apoptosis (76).

plasminogen activator inhibitor-1, TNFα, ILs, leptin, and others. Thus, the fat cell has become "dysfunctional."

A. Adiponectin

Adiponectin (Acrp 30 or AdipoQ) possesses two unique characteristics: 1) it is expressed only in adipocytes, from where it is secreted into the circulation; and 2) it is the only known adipocyte-secreted factor that increases tissue sensitivity to insulin (113–115). Plasma adiponectin levels are markedly decreased in T2DM (and obese) subjects (116–121), and the magnitude of the reduction is strongly correlated with the severity of insulin resistance in peripheral tissues (muscle) (116–119) and liver (120, 121). Recent studies have shown that adiponectin is a potent antiinflammatory agent that inhibits a number of steps involved in the development of atherosclerosis in animals and humans (reviewed in Refs. 122 and 123). In cultured adipocytes, insulin increases adiponectin expression (124). As adipocytes from type 2 diabetics are resistant to insulin (125), one could postulate that the decline in plasma adiponectin concentration in type 2 diabetics results from diminished insulin sensitivity. Alternatively, decreased adiponectin expression could reflect the dysfunctional fat cell syndrome.

B. Resistin

Resistin is a novel protein, discovered in preadipocytes that were undergoing differentiation into mature adipocytes (126). When injected into normal animals, resistin produces insulin resistance. Conversely, neutralization of resistin with antiresistin antibodies leads to a decline in the plasma glucose concentration and enhanced insulin-stimulated glucose uptake in cultured cells (127, 128). Recent studies have demonstrated that in human T2DM (and obesity), circulating resistin levels and resistin expression in fat cells are increased (129–133). In humans with T2DM we and others (Bajaj, M., S. Suraamornkul, L. Hardies, and R. A. DeFronzo, submitted for publication) have shown that plasma resistin levels are elevated and correlate closely with hepatic, but not muscle, insulin resistance (134). Consistent with this observation, infusion of resistin into normal animals causes severe hepatic insulin resistance, but has no effect on muscle insulin sensitivity (135). Resistin also is a member of the FIZZ family of proteins and is a potent inflammatory agent (136). Insulin inhibits resistin expression in adipocytes (137–139). As T2DM individuals have elevated basal plasma resistin levels (133, 134) despite fasting plasma insulin concentrations that are increased 2- to 4-fold (1, 2), this suggests that the inhibitory effect of insulin on fat cell synthesis and/or secretion of resistin may be resistant to the action of insulin.

C. Angiotensinogen

Although the liver is usually thought to be the primary source of angiotensin in the circulation, fat cells from rodents (140) and humans (141) express the message for angiotensin in abundance and represent an important source of angiotensinogen in the body. Although little is known about angiotensinogen expression in fat cells in human T2DM and obesity, angiotensinogen expression in adipocytes and plasma levels of the hormone have been shown to be increased in rodent models of obesity (142). Angiotensin II is a potent vasoconstrictor and has been implicated in the development of atherosclerosis in muscle by inhibiting the insulin signaling cascade (143, 144). Therefore, it is interesting to speculate that the strong associations among insulin resistance, hypertension, and accelerated atherosclerosis in both T2DM and obesity are a manifestation of the dysfunctional fat cell syndrome.

D. Plasminogen activator inhibitor-1 (PAI-1)

PAI-1 is a serine protease that inhibits tissue plasminogen activator, which cleaves plasminogen to plasmin, thus activating the fibrinolytic cascade. Elevated PAI-1 levels upset the balance between the thrombotic and fibrinolytic systems, favoring the formation of microthrombi on blood vessels and accelerating the atherosclerotic process. Both T2DM and obese subjects have elevated PAI-1 levels (145), which are correlated with the development of coronary artery disease and myocardial infarction (146). Adipose tissue is a major source of PAI-1, and PAI-1 expression and secretion by adipocytes are markedly increased in diabetic obese nondiabetic individuals (147, 148). Moreover, insulin, which is characteristically increased in insulin-resistant states, is a potent stimulus for PAI-1 secretion by fat cells (147, 149). Thus, the dysfunctional fat cell through enhancing PAI-1 secretion may provide an important link between accelerated cardiovascular disease and insulin resistance/obesity/T2DM.

E. TNFα

TNFα is an adipocyte-derived cytokine that plays a central role in the insulin resistance of sepsis and cancer (150, 151). When infused into rodents, it produces severe insulin resistance (152), stimulates lipolysis, and activates the inflammatory MAPK isoforms c-Jun N-terminal kinase and p38 MAPK (153). TNFα impairs insulin signaling by inhibiting the function of IRS-1 through serine phosphorylation (154, 155). Neutralization of circulating TNFα enhances insulin sensitivity in insulin-resistant rodent models of diabetes and obesity (153). The role of TNFα in the insulin resistance of human T2DM and obesity is less clear. Circulating TNFα levels are increased in obese nondiabetic (156) and T2DM individuals (157, 158), but the correlation between insulin resistance and plasma TNFα levels is weak in both obese (159) and diabetic (157) individuals. It should be emphasized, however, that TNFα exerts local paracrine effects, and the induction of insulin resistance may be more related to the local tissue TNFα concentration than to the levels in plasma (160). TNFα also is a potent inflammatory cytokine that has been implicated in the development of atherosclerosis in nonhuman models (160).

F. IL-6

IL-6, an inflammatory cytokine, is highly expressed in adipocytes (161) and plays an important role in inflammation and the regulation of T cell and β-cell function (162). In rodent models of diabetes, IL-6 has been implicated in the development of muscle insulin resistance (163) and β-cell

apoptosis (40). In humans with T2DM, IL-6 levels are increased and correlate with the severity of glucose intolerance (164) and with the severity of inflammation, as indicated by the highly sensitive C-reactive protein (CRP) serum concentration (165). The correlation between IL-6 and the CRP reflects both a direct effect of IL-6 on CRP secretion and the inflammatory-provoking actions of IL-6 that secondarily augment CRP secretion.

G. Leptin

Leptin is produced exclusively by adipocytes and secreted into the bloodstream (166). It is an appetite suppressant that exerts its effects by interacting with a type 2 cytokinase receptor in the hypothalamus, where it interacts with neuropeptide Y, melanocyte-stimulating hormone, and the melanocortin-4 receptor (167, 168). Leptin-deficient rodents (167) and humans (169) develop hyperphagia and marked obesity, which are reversed by administration of the cytokine. When administered to rodents, some (170–172), but not all (173), studies have shown an insulin-sensitizing effect in muscle and adipocytes. Although large scale clinical studies in humans have failed to identify an effect of leptin on glucose metabolism in obese and T2DM subjects (174), mutations in the leptin gene in man are associated with severe obesity, glucose intolerance, and insulin resistance, which are reversed by leptin replacement therapy (175, 176).

An interesting aspect of leptin function that has received little attention is its potential role in inflammation. Leptin acts directly on macrophages to augment their phagocytic activity and increase their production of inflammatory cytokines (177). Leptin also is required for macrophages to manifest full immunocompetency (178, 179). Thus, leptin could play an important role in the inflammation associated with T2DM and atherosclerosis (180).

H. Adipsin and acylation-stimulating protein (ASP)

The proteins adipsin and ASP are highly expressed in adipocytes and are integral proximal components of the alternate complement pathway (181, 182). Because adipocytes lack the distal components of the complement pathway, cell lysis does not occur. Rather, ASP increases lipid deposition in adipocytes by enhancing glucose uptake and deposition into triglycerides (182). Consistent with this observation, both ASP (markedly) and adipsin (moderately) levels have been shown to be increased in human obesity and T2DM (183).

I. Inflammation, insulin resistance, and the adipocyte: a hypothesis

Considerable evidence links chronic inflammation, insulin resistance, T2DM, and atherosclerosis (180, 184). Based upon the preceding discussion, it is reasonable to hypothesize that dysfunctional fat cells provide a link that connects these seemingly diverse metabolic and cardiovascular disorders.

Acute phase proteins (CRP, sialic acid, fibrinogen, complement factors, PAI-1, and serum amyloid A) are increased in T2DM subjects and individuals with coronary artery disease (180, 184). Highly sensitive CRP is strongly predictive of the inflammatory atherosclerotic process and future myocardial infarction (185). Many acute phase proteins are stimulated by factors such as TNFα, ILs, and leptin, and they are released from multiple sites, including not only white blood cells, but also adipocytes (see preceding discussion). These fat cell-derived proteins are increased in insulin-resistant conditions, *i.e.* T2DM, obesity, atherosclerosis, and the metabolic syndrome (186, 187), and play important roles in the immune response. Thus, leptin enhances macrophage function and is required for a normal immune response (188). TNFα and IL-6, which also are highly expressed in fat cells, have clear roles in immune modulation (151, 160, 162, 189). The presence in adipose tissue of proteins (adipsin and ASP) in the proximal portion of the alternative complement pathway raises questions about their possible roles in the inflammatory process. Resistin, initially characterized as an insulin resistance factor, is a member of a family of resistin-like molecules that belong to the FIZZ (found in inflammatory zone) protein family (resistin is FIZZ3) (136, 190). Similarly, the adipokines adiponectin (191) and PAI-1 (147) have been implicated in the inflammatory process.

The mechanisms via which chronic inflammation produces insulin resistance in such diverse tissues as liver, skeletal muscle, fat, and vascular smooth muscle cells have yet to be elucidated. One possibility might be related to activation of serine/threonine phosphorylation cascades that lead, on the one hand, to activation of nuclear factor-κB and inflammation-related transcriptional regulation and, on the other hand, to serine phosphorylation of elements of the insulin receptor signaling system, especially IRS-1 (192). Evidence supporting this schema arises from the observation that high dose salicylates can improve insulin sensitivity through a mechanism that involves inhibition of I$\kappa\beta$ kinase (IKK-β) (193). Consistent with this hypothesis, heterozygous IKK-β knockout mice have increased insulin sensitivity, and salicylate administration improves insulin sensitivity in insulin-resistant mice (194). IKK-β induces insulin resistance by causing serine phosphorylation of IRS-1 and subsequent inhibition of the insulin signaling cascade. Salicylates also inhibit the activity of RSK2 (p90 ribosomal S6 kinase) (195), and IRS-1 contains several consensus serine/threonine phosphorylation sites for RSK2. Our laboratory has shown that RSK2 activity is increased 5-fold in skeletal muscle biopsies from patients with T2DM (196). Based upon the preceding discussion, some investigators have proposed an adipocentric view of insulin signaling and intracellular trafficking (197).

IV. Fat Topography: Ectopic Fat, Insulin Resistance, and β-Cell Failure

A. Overview

The association between T2DM and obesity is well established. Cross-sectional (198, 199) and prospective (200, 201) studies have documented that the incidence of diabetes rises steeply with increasing body weight. The diabetogenic effect of obesity is related to three factors: attained body mass index, duration of obesity, and recent increase in body weight (202). Epidemiologic data (203, 204) as well as direct measurement with the euglycemic insulin clamp technique

(205–207) have established obesity as an insulin-resistant state, and both obesity and insulin resistance are risk factors for the development of T2DM (1, 2, 208, 209). Like T2DM (21), the insulin resistance of obesity involves muscle (205, 206, 210), liver (203, 206, 211), and adipocytes (105, 212, 213).

In addition to total fat content, the pattern of fat distribution is also an important predictor of the body's sensitivity to insulin. Individuals with preferential upper body fat accumulation (android) are more insulin resistant, hyperinsulinemic, and dyslipidemia than people with a preponderance of lower body fat (gynecoid) (214, 215). Using magnetic resonance imaging and computed tomography, increased visceral fat has been shown to be specifically related to the presence of insulin resistance (215–219). This association has been attributed to the enhanced lipolytic activity of visceral fat cells, with increased delivery of FFA into the portal (causing hepatic insulin resistance) and systemic (causing muscle insulin resistance) circulations (220, 221). However, there also is evidence to indicate that visceral fat cells produce excessive amounts of insulin-resistant, inflammatory-provoking adipocytokines (*i.e.* resistin, TNFα, IL-6, PAI-1, *etc.*) and undersecrete insulin-sensitizing adipocytokines (*i.e.* adiponectin) (222–225).

B. Ectopic fat deposition: an emerging paradigm

Recent studies have demonstrated that organ-specific deposition of fat is a strong predictor of insulin resistance in muscle and liver. Increased intramyocellular triglyceride content, assessed by muscle biopsy (226) or magnetic resonance/computed tomography (34, 35, 227–230), correlates closely with muscle insulin resistance and is a better predictor of impaired insulin action than visceral adiposity (231). Conversely, a decrease in intramyocellular lipid content brought about by weight loss is a strong correlate of the improved muscle insulin sensitivity (232–234).

Fat accumulation within the liver also is tightly correlated with hepatic insulin resistance. In type 2 diabetics, increased hepatic fat content, quantitated by magnetic resonance spectroscopy, is closely related to the basal hepatic insulin resistance index (HGP $\times$ fasting plasma insulin) and impaired suppression of HGP by insulin (37, 120, 121). Consistent with this observation, insulin requirements in T2DM patients are closely related to the hepatic fat content (235), and in nondiabetic individuals, hepatic fat stores are strongly correlated with hepatic sensitivity to insulin (36).

Inherited forms of lipodystrophy in humans, although rare, provide additional insight into the importance of ectopic fat deposition in the pathogenesis of insulin resistance and glucose intolerance. Human (236, 237) and animal (238) forms of lipodystrophy are characterized by selective loss of sc and visceral fat and are associated with a number of metabolic abnormalities, such as dyslipidemia, hyperglycemia, and insulin resistance. Insufficient adipose tissue mass leads to excessive storage of ingested fat in muscle and liver and the development of severe insulin resistance in these organs. Replacement therapy with leptin mobilizes fat out of the liver and muscle, leading to dramatic improvements in hepatic and muscle sensitivity to insulin and improved glycemic control (239, 240). Additional support for the ectopic fat paradigm comes from transgenic animal models with defects in adipogenesis (241–245). These lipodystrophic animals manifest marked fatty infiltration of the liver and muscle, hepatic and muscle insulin resistance, and IGT. Surgical transplantation of adipose tissue into these lipotrophic animals results in mobilization of fat out of the liver and muscle, improved insulin sensitivity in these organs, and correction of the glucose intolerance (246). Conversely, surgical removal of adipose tissue in normal glucose tolerant hamsters results in fat accumulation in liver and muscle, insulin resistance, and glucose intolerance (247).

The sequence of events by which the inability to store fat in adipose tissue leads to ectopic accumulation of triglycerides in muscle and liver, hepatic and muscle insulin resistance, glucose intolerance, and overt diabetes has been referred to as the overflow hypothesis (248). We believe that the overflow hypothesis has received sufficient scientific validation so that it no longer should be considered hypothetical. The overflow hypothesis also explains the well documented observation that enlarged fat cells correlate better with insulin resistance than any other measure of adiposity (249–252) and that enlarged fat cells are a strong, independent predictor of the development of type 2 diabetes (253). Once the capacity of the fat cell to store triglycerides is exceeded, fat overflows to other tissues (muscle and liver), where the intracellular metabolites of triglyceride metabolism interfere with insulin signaling, glucose transport/phosphorylation, and glycogen synthesis in muscle and augment hepatic gluconeogenesis/total glucose production.

On a more speculative note, there are experimental data in rodent models of diabetes to support the overflow hypothesis of β-cell dysfunction. In the genetically obese Zucker fatty rat, overt diabetes develops at about 10–12 wk of life, and this is associated with a marked increase in islet triglyceride content and FA-CoA levels (40, 46, 49, 50). The rise in β-cell FA-CoA concentration leads to increased ceramide formation, stimulation of inducible nitric oxide synthase, and elevated nitric oxide levels, which, in concert with the release of inflammatory cytokines (TNFα, IL-6, and others), lead to β-cell dysfunction and apoptosis (40, 46, 49, 50). At present, it remains unknown whether a similar sequence of events occurs in human β-cells. However, chronic physiological and pharmacological elevation of the plasma FFA concentration, which would be expected to increase FFA transport into the β-cell by mass action, has been shown to impair insulin secretion (32, 33, 52–54), whereas chronic reduction of the plasma FFA concentration with acipimox in genetically predisposed individuals augments insulin secretion (254).

V. "Dysfunctional" Fat *vs.* "Healthy" Fat

Most type 2 diabetics 1) possess too much fat; 2) have an abnormal distribution of fat with excessive fat deposition in muscle, liver, and visceral adipocytes; and 3) have large, insulin-resistant fat cells whose capacity to store triglycerides is compromised. These dysfunctional fat cells produce excessive amounts of adipocytokines that cause insulin resistance, inflammation, hypercoagulability, dyslipidemia, and possibly hypertension. They also underproduce adipocytokines (adiponectin) that play an essential role in maintaining

normal insulin sensitivity. When viewed in this context, it is clear that the glucose intolerance of T2DM results at least in part secondary to a disordered fat cell metabolism. Because the derangements in adipocyte metabolism are present in normal glucose-tolerant, insulin-resistant, genetically predisposed individuals (5, 7, 12, 73), in people with IGT (11, 13, 29–31, 36, 72, 103, 187), and in insulin-resistant, normal glucose-tolerant obese individuals (30, 34, 36, 65, 66, 105), some authorities have considered disordered lipid/FFA metabolism to represent the primary disturbance in the pathogenesis of T2DM (255).

An important question is whether dysfunctional fat cells can be converted to healthy adipocytes, and whether the abnormal pattern of fat distribution can be reversed, leading to enhanced muscle/hepatic sensitivity to insulin and improved β-cell function. Thiazolidinediones represent a novel class of antidiabetic agents that improve glycemic control (256–260), enhance hepatic and muscle insulin sensitivity (261–268), and improve β-cell function in both human and animal models of T2DM (40, 269–272). A consistent finding in these studies is the association between weight gain and reduction in hemoglobin A_{1c} (HbA_{1c}) with troglitazone (273–276), rosiglitazone (263, 277, 278), and pioglitazone (261, 262, 279). The greater the weight gain, the better the improvement in glycemic control. This observation is paradoxical, because weight gain brought about by overeating is associated with insulin resistance and deterioration in glycemic control (3, 280, 281). It also is noteworthy that obese individuals respond better than lean subjects to thiazolidinediones, and that women, who have a higher percentage of body fat, respond better than men (279, 282).

The glucose-lowering efficacy of the thiazolidinediones is related to their ability to bind to PPARγ (160, 266, 283). Similar beneficial effects on glucose homeostasis can be expected from nonthiazolidinedione PPARγ agonists (283, 284). PPARγ is one of a group of three nuclear receptor isoforms (the other two are PPARα and PPARδ) that are encoded by different genes (284–286). PPARs are ligand-regulated nuclear transcription factors that regulate gene expression by binding to specific peroxisome proliferator response elements within the promoter region (160, 258, 283–285). PPARγ exists as two isoforms, γ1 and γ2. PPARγ1 is primarily and highly expressed in adipose tissue, whereas PPARγ2 is expressed in a wide variety of tissues (160, 283–285, 287–289). Of note is the low expression of both PPARγ1 and PPARγ2 in skeletal muscle (283, 288, 289), making this tissue an unlikely target for any direct action of the thiazolidinediones. PPARs associate with the retinoic acid receptor, and the PPAR/retinoic acid X receptor complex binds with cofactors to initiate gene transcription (160, 266, 283–285). The naturally occurring ligands for the PPARγ are fatty acids and eicosanoids, which are active at micromolar concentrations (283, 284, 290, 291). Thiazolidinediones are synthetic ligands that are potent PPARγ agonists (160, 266, 283–285).

PPARγ is a critical transcription factor in the differentiation of preadipocytes into adipocytes (292–295). Three families of transcription factors play central roles in the differentiation and maturation of preadipocytes into adipocytes: 1) PPARγ; 2) CCAAT/enhancer-binding proteins (C/EBPs) α, β, and δ; 3) a sterol response element-binding protein (296–299). PPARγ is the master regulator of adipogenesis, being both essential and sufficient for adipocyte differentiation (300). C/EBPβ, C/EBPδ, and sterol response element-binding protein-1c act early in adipogenesis to induce PPARγ expression, whereas C/EBPα interacts with PPARγ to facilitate the expression of multiple genes in the mature fat cell, including the insulin-sensitive glucose transport system (301, 302) and other key genes involved in lipid homeostasis (including phosphoenolpyruvate carboxykinase, acyl-CoA synthetase, lipoprotein lipase, and adipocyte P2) (303–306). Each of these genes contains a PPAR response element in its regulatory region. PPARγ also up-regulates the expression of fatty acid transporter proteins (FATP-1 and D036) (307, 308) and c-Cbl-associated protein (309). The net result of these changes is to enhance glucose (providing the carbon skeleton) and FFA transport into the adipocyte and to stimulate triglyceride synthesis. Consistent with these molecular actions, all thiazolidinediones cause a marked reduction in plasma FFA concentration and inhibit lipolysis in T2DM patients (261–266, 268). Thiazolidinediones also inhibit the expression of the leptin gene in adipocytes (160, 228), and the resultant decline in the plasma leptin concentration (157) may increase appetite and contribute to weight gain (167, 169).

In rodents, thiazolidinediones increase the number of small fat cells by stimulating adipogenesis in sc fat depots (295, 310–312). Although PPARγ receptors are present in visceral adipocytes and preadipocytes in rodents, they are not activated to divide. Thiazolidinediones also cause apoptosis of large fat cells in both visceral and sc regions in rodents (295, 311, 312). These observations are consistent with *ex vivo* studies in which thiazolidinediones (rosiglitazone and pioglitazone) were shown to markedly enhance the differentiation of human sc preadipocytes into mature small adipocytes (310). Moreover, prior transfection of these human preadipocytes with a mutant PPARγ blocked this differentiation process (313). Two studies have examined sc abdominal fat cell size in adipose depots after treatment with thiazolidinediones in humans. One study reported a trend toward smaller fat cells (314), whereas the other study reported a slight increase in fat cell size (315). However, the number of diabetics treated with thiazolidinediones in both studies was small, and even if thiazolidinediones caused sc preadipocytes to differentiate into small fat cells, they would eventually accumulate fat and increase in size. Studies using magnetic resonance imaging consistently have shown that troglitazone, pioglitazone, and rosiglitazone cause a shift in fat topography, characterized by a decrease in intraabdominal fat and an increase in sc fat (261–263, 268, 275, 316, 317) (Fig. 3). Whether the increase in sc fat mass observed in humans is due to increased fat cell number (adipogenesis), increased fat cell size (induction of genes involved in lipogenesis and inhibition of lipoprotein lipase), or some combination of the two remains to be determined. As visceral fat is strongly related to increased gluconeogenesis and HGP in T2DM individuals (211), it is not surprising that thiazolidinedione therapy improves hepatic insulin sensitivity and reduces hepatic gluconeogenesis and total hepatic glucose output (261, 262, 264, 265). It is noteworthy that surgical removal of visceral fat in rodent models of type 2 diabetes

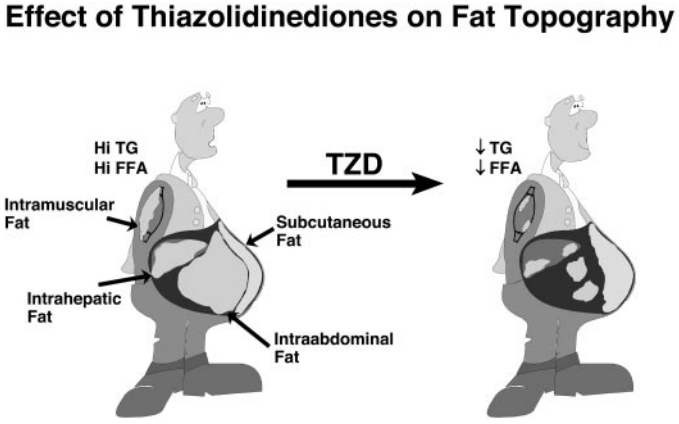

FIG. 3. Effect of PPARγ agonists on fat distribution. [Adapted from Treatment of Type 2 Diabetes Mellitus: A Sound Approach Based upon its Pathophysiology, a CME program sponsored by the Academy of Medicine of New Jersey (Lawrenceville, NJ).]

also improves hepatic insulin sensitivity, reduces HGP and gluconeogenesis, and improves glucose tolerance (277, 318). Although the improvement in hepatic insulin sensitivity has been attributed to decreased portal FFA delivery to the liver from the lipolytically more active visceral fat cells (220, 319–323), one also could postulate that a reduction in insulin-resistant adipocytokines (such as resistin or TNFα) or an increase in insulin-sensitizing adipocytokines (such as adiponectin) is responsible for the improvement in hepatic insulin sensitivity (116, 118, 119). In fat, evidence for this later scenario has been provided in both man (120, 121, 134) and animals (133).

The increase in FFA uptake by sc fat cells (whether due to hyperplasia or hypertrophy) also explains the consistent decrease in plasma FFA concentration observed with all thiazolidinediones and the strong correlation between improved muscle insulin sensitivity and reduction in plasma FFA concentration/FFA turnover (261–263, 265, 268). As the plasma FFA concentration declines, one also would predict a mobilization of fat out of the muscle and liver (Fig. 3), with improved insulin sensitivity in these organs. Indeed, both pioglitazone (120, 121) and rosiglitazone (268) been shown to reduce hepatic fat content in association with an improvement in basal hepatic insulin sensitivity and enhanced insulin-mediated suppression of HGP in T2DM subjects. Pioglitazone therapy also enhances splanchnic glucose uptake of an oral glucose load, although the increased splanchnic glucose uptake correlates more closely with the reduction in HbA_{1c} than the decrease in hepatic fat content (120). In the one published study that examined intramyocellular fat content after rosiglitazone therapy, no change was observed (268). However, it is the decrease in intracellular concentration of metabolites of muscle triglycerides (FA-CoAs, DAG, ceramides, *etc.*) that best predicts the improvement in muscle sensitivity to insulin (71–82, 86–89), and these metabolites were not measured in this study (268). Recently, we have shown that the reduction in plasma FFA concentration is associated with improved insulin sensitivity in muscle and enhanced insulin receptor and IRS-1 tyrosine phosphorylation, increased association of IRS-1 with phosphoinositol 3-kinase, and increased phosphoinositol 3-kinase activity (324).

The sequence of events described above explains why weight gain (261–263, 273, 279) and reduced plasma FFA concentrations (261–263, 265, 268) are strongly correlated with the reduction in HbA_{1c} in T2DM patients treated with thiazolidinediones. In the absence of an isocaloric diet or caloric restriction, weight gain is a predictable consequence of thiazolidinedione therapy. When viewed in this context, weight gain, along with the reduction in plasma FFA concentration, indicates that the thiazolidinedione is working and exerting beneficial effects to improve tissue sensitivity to insulin and glucose homeostasis. Further, the decline in plasma FFA is indicative of a "healthier" fat cell, which now responds well to insulin stimulation of glucose uptake and suppression of lipolysis (263, 324). Other indications that the thiazolidinediones have converted the dysfunctional fat cell in type 2 diabetics into a healthier fat cell include 1) inhibition of resistin, TNFα, and PAI-1 gene expression in adipocytes and reduction in their circulating levels (127, 128, 160, 197, 228, 325, 326), and 2) stimulation of adiponectin gene expression in adipocytes and increase in the plasma adiponectin concentration (121, 326, 327).

In rodent models of diabetes, thiazolidinediones improve β-cell function in concert with a reduction in islet fat content (32, 40, 50) and preserve islet histology and β-cell mass (328, 329). In diabetic rats, thiazolidinediones prevent the loss of β-cell mass by maintaining β-cell proliferation and inhibiting β-cell apoptosis (330). In cultured human islets, FFA downregulate insulin mRNA expression, inhibit glucose-stimulated insulin secretion, and promote β-cell death. All of these deleterious effects of FFA are prevented when islets are incubated with rosiglitazone (331, 332). In humans, thiazolidinedione therapy has been shown to improve the insulinogenic index (incremental insulin response/incremental glucose response during the oral glucose tolerance test) in a dose-dependent fashion (269). In the *T*roglitazone *i*n *P*revention *o*f *D*iabetes (TRIPOD) study, treatment of women with a prior history of gestational diabetes mellitus with troglitazone markedly reduced the conversion rate to T2DM over a 30-month period (333). Although troglitazone consistently improved insulin sensitivity (measured with the frequently sampled iv glucose tolerance test) in gestational diabetes mellitus responders, improved β-cell function was the best predictor of response (333). The protective effect of troglitazone against the development of T2DM and the drug's beneficial effect on β-cell function persisted for an additional 8 months after cessation of troglitazone (333). An improved β-cell response to glucose in subjects with IGT also has been reported by other investigators (334). One could speculate that a mobilization of fat out of β-cells into sc fat depots explains the long-lasting (8 months) beneficial effects of troglitazone on β-cell function as well as on tissue sensitivity to insulin. Moreover, one would predict that as long as the triglyceride remained within sc fat cells, the improvements in β-cell function and tissue insulin sensitivity would persist.

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