Insulin resistance, characterized by reduced responsiveness to normal circulating concentrations of insulin, is a common feature of almost all patients with type II diabetes. The presumed central roles of both peripheral and hepatic insulin resistance suggest that the enhancement of insulin action might be an effective pharmacological approach to diabetes. Thiazolidinediones are a new class of orally active drugs that are designed to enhance the actions of insulin. These agents reduce insulin resistance by increasing insulin-dependent glucose disposal and reducing hepatic glucose output. Clinical studies in patients with type II diabetes, as well as other syndromes characterized by insulin resistance, have demonstrated that thiazolidinediones may represent a safe and effective new treatment. Although the precise mechanism of action of these drugs remains unknown, transcriptional changes are observed in tissue culture cells that produce enhanced insulin action. This regulation of gene expression appears to be mediated by the interactions of thiazolidinediones with a family of nuclear receptors known as the peroxisome proliferator-activated receptors (PPARs). The further elucidation of the molecular actions of these drugs may reveal much about the underlying mechanisms of insulin resistance. Diabetes 45:1661-1669, 1996

The pathophysiology of type II diabetes involves characteristic defects in three main organ systems that conspire together to produce abnormal glucose metabolism. Although there is uncertainty regarding the primary lesion, metabolic defects in the liver, peripheral target tissues, and the pancreatic β-cells all contribute to the syndrome (Fig. 1).

A characteristic trait of type II diabetes is the overproduction of glucose by the liver. Increased hepatic glucose output (HGO) correlates well with fasting glucose levels and is the main cause of fasting hyperglycemia in type II diabetic patients. Increased levels of glucagon and free fatty acids (FFAs), as well as the recycling to the liver of three carbon gluconeogenic precursors such as lactate and pyruvate, all contribute to elevated HGO. Hepatic insulin resistance is also known to play an important role. The second defect occurs at the level of peripheral target tissues. From 80 to 90% of insulin-stimulated glucose uptake occurs in skeletal muscle. The stimulation by insulin of skeletal muscle glucose disposal is significantly reduced in type II diabetic subjects. Indeed, garden-variety type II diabetic patients commonly demonstrate a 60-80% deficiency in this action of insulin. Finally, impaired β-cell function is commonly found in established type II diabetes, usually coincident with fasting hyperglycemia. However, this defect is relatively glucose specific, since the insulin secretory responses to nonglucose stimuli are often preserved. In prediabetes, or mild type II diabetes, absolute levels of insulin secretion can be normal or even elevated.

Prospective epidemiological studies across a number of population groups have indicated that insulin resistance may be the primary defect in type II diabetes, since it can be detected long before deterioration of glucose tolerance occurs, often at a time when insulin secretion is actually increased. Thus, in many populations and patient groups, insulin resistance and hyperinsulinemia precede the development of type II diabetes and can be identified in most prediabetic individuals (Fig. 2). Moreover, insulin resistance can be further exacerbated during the progression of the disease because of the dysregulation of lipid and carbohydrate metabolism. The β-cells normally respond to peripheral insulin resistance by increasing basal and postprandial insulin secretion to compensate for the insulin-resistant state, maintaining normal or impaired glucose tolerance but preventing frank deterioration of glucose homeostasis and type II diabetes. Eventually, the β-cells are no longer able to compensate for insulin resistance by secreting increased amounts of insulin. At this stage, glucose-induced insulin secretion falls, allowing glucose homeostasis to deteriorate and leading to the subsequent development of frank diabetes.

It is clear that the treatment of insulin resistance has great therapeutic potential for the amelioration of type II diabetes. Although currently available pharmacological modalities are not directed to the treatment of impaired insulin action, recent efforts have focused on the deve-
CAUSES OF HYPERGLYCEMIA IN NIDDM

FIG. 1. Summary of the metabolic abnormalities in NIDDM that contribute to hyperglycemia. Increased hepatic glucose production, impaired insulin secretion, and insulin resistance caused by receptor and postreceptor defects all combine to generate the hyperglycemic state.

THIAZOLIDINEDIONES IMPROVE GLUCOSE AND LIPID HOMEOSTASIS IN ANIMAL MODELS OF DIABETES

Thiazolidinediones appear to enhance insulin action without directly stimulating insulin secretion. As such, these drugs have been used to assess the impact of improving insulin resistance on a variety of pathophysiological processes. Thiazolidinediones markedly decrease plasma glucose, insulin, and triglyceride levels in genetically insulin-resistant animals, including the KKA, ob/ob, and db/db mouse, the Zucker fa/fa rat, and others (1-3). With these observations, it became clear that thiazolidinediones are effective in improving insulin sensitivity in various rodent models of insulin resistance (4-7).

The distinguishing feature of these insulin-sensitizing agents: the apparent lack of hypoglycemic activity in euglycemic animals, despite the potent sensitization of insulin action. As insulin resistance improves, insulin secretion falls in a corresponding manner. Since the negative-feedback systems between glucose and insulin levels remain intact, hypoglycemia does not occur.

The effects of thiazolidinediones on insulin sensitivity have been studied with the euglycemic-hyperinsulinemic clamp. Treatment with thiazolidinediones restored the ability of insulin to suppress HGO and increase peripheral glucose disposal in various rodent models of insulin resistance (8-9). These metabolic effects were accompanied by a dramatic improvement in insulin sensitivity in isolated fat and muscle tissue, normalizing glucose and insulin levels and preventing the progression to diabetes (8-12).

While thiazolidinediones in general do not directly modulate insulin secretion in islet cells, the amelioration of insulin resistance exerts insulin-sparing effects, reducing elevations in insulin levels. In diabetic animals, this can restore the responsiveness of desensitized islets to insulinotropic stimuli. Troglitazone produced a marked regranulation of pancreatic islets in severely diabetic db/db mice, restoring cellular insulin content (13). This response typifies those effects of the thiazolidinediones that are exerted indirectly through amelioration of glucose toxicity. To explore the mechanisms involved in the reduction of fasting insulin levels, Seenan et al. (14) investigated insulin secretion rates in perfused pancreases from troglitazone-treated normal, fatty, and diabetic Zucker rats. Troglitazone markedly lowered basal secretion rates in both normoglycemic fatty and diabetic
rats, and it subsequently increased the ability of the perfused pancreas to respond to glucose. Although these effects may simply reflect the decreased requirement for insulin, the possibility remains that these drugs may directly influence the islet to correct metabolic abnormalities associated with the insulin-resistant phenotype by altering the expression of enzymes involved in glucose metabolism or correcting the dysregulation of basal insulin secretion caused by high levels of ambient FFAs.

Hypertriglyceridemia is a characteristic trait of many insulin-resistant rodents and may be an important risk factor for atherosclerosis, especially in type II diabetic patients. Plasma triglyceride and FFA levels are markedly reduced in a number of diabetic rodent models by treatment with thiazolidinediones (2-4,8,9,15). These effects are observed in both insulin-resistant and insulin-deficient animals, suggesting that the triglyceride-lowering actions of these drugs may not be related to the sensitization of insulin action. The attenuation of hyperlipidemia by troglitazone results from inhibition of triglyceride synthesis in the liver, as well as increased clearance in the periphery (2). Moreover, the antihyperglycemic effects of the drug were not due to decreases in circulating FFAs or triglycerides, since treatment of fructose-fed rats with bezafibrate produced lowering of plasma lipids similar to that seen with troglitazone without improving insulin sensitivity (16). Thiazolidinediones also modulate lipoprotein profiles in rodents. Although total plasma cholesterol does not respond dramatically to these agents, increased HDL cholesterol and decreased LDL and VLDL cholesterol have been observed, along with some changes in circulating lipoproteins (17).

**THIAZOLIDINEDIONES CAN REVERSE INSULIN RESISTANCE IN TYPE II DIABETES**

Since insulin resistance plays such a prominent role in the pathophysiology of type II diabetes, it is clear that pharmacological agents that improve insulin action could be of benefit in the treatment of this disease. Treatment of Japanese type II diabetic patients with troglitazone for 12 weeks led to an improvement in hyperglycemia with a concomitant reduction in circulating insulin levels (18). This simultaneous fall in both glucose and insulin levels in response to troglitazone is consistent with an overall improvement in insulin action.

This proposition has been directly demonstrated in more mechanistically based clinical research studies (19). A series of metabolic measurements, including glucose clamp studies, glucose and meal tolerance tests, and measures of lipid values, were conducted in obese type II diabetic patients hospitalized in a metabolic ward. After the establishment of baseline values, patients were treated for 3 months with 400 mg/day troglitazone, during which time diet, body weight, and physical activity were kept constant. The effect of the drug on fasting and postmeal glucose levels is seen in Fig. 4. Of the patients, 75% responded to the drug, whereas 25% exhibited no glucose-lowering effects. Analysis of the responder group revealed a 35% reduction of fasting glucose levels (from 12.7 to 8.3 mmol/l) and a 34% reduction in postprandial glycemia. A striking 50% reduction in insulinemia also occurred (Fig. 5), indicating that this drug worked by improving insulin resistance. This was directly demonstrated by analyzing the results of the individual glucose clamp studies, performed at insulin infusion rates of 40 and 120 mU · m·min⁻¹. Figure 6 shows the individual data before and after drug treatment. Insulin resistance improved in every subject at both insulin infusion rates. Overall, drug treatment led to a 60% increase in the stimulation by insulin of glucose disposal. Additionally, troglitazone treatment led to a striking decrease in HGO from 2.5 to 1.8 mg · kg⁻¹ · min⁻¹, approaching the normal mean value of 1.6. This reduction in HGO accounts for the significant decrease in fasting hyperglycemia seen with the drug.

Note that 25% of the patients in this study did not show a glucose-lowering effect with drug treatment. A similar percentage of nonresponders has been noted in larger clinical trials (20,21). An analysis of the individual data (Fig. 6) revealed that all patients showed an improvement in insulin resistance after drug treatment. However, in the nonresponders, it was noted that these patients exhibited the lowest levels of insulin secretion at the onset of the study. In a larger study, a similar nonresponder group was identified, and most of them exhibited minimal β-cell function, characterized by a fasting C-peptide level of <1.5 ng/ml (20). This is consistent with the hypothesis that thiazolidinediones improve insulin resistance in essentially all type II diabetes patients, but that improved insulin action will not lead to a beneficial effect on glycemia without sufficient circulating levels of insulin. Thus, it may be possible to predict which patients...
FIG. 4. Glucose profiles during 7-h meal tolerance tests. Eleven NIDDM patients were fed mixed meals, and mean serum glucose levels (± SE) were sampled for 7 h. In B, the eight responders were analyzed separately.

are more likely to respond to the drug as monotherapy, based on fasting C-peptide levels or other measures of pancreatic β-cell function.

In addition to the beneficial effects of troglitazone treatment on glucose metabolism, the drug had profound effects on circulating lipids. Elevated triglycerides and reduced HDL levels are commonly seen in type II diabetic subjects. Drug treatment caused a 20% decrease in triglyceride levels, as well as a statistically significant 10% increase in HDL cholesterol (19).

Larger-scale clinical trials have now been completed in both the U.S. (20) and Europe (21) that have sustained the results of these earlier pilot studies. These placebo-controlled studies have demonstrated a dose-dependent reduction in HbA\textsubscript{1c}, fasting blood glucose, hyperinsulinemia, and hypertriglyceridemia. Studies are underway to evaluate in more detail the mechanistic aspects of these effects. Moreover, troglitazone has appeared to be well tolerated, with few reports of drug-related adverse events. At the therapeutically effective doses, the side effect profile has been the same as that in the placebo-control groups. Importantly, these longer-term large studies have revealed no weight gain or evidence for drug-related hypoglycemia. Furthermore, in contrast to observations with sulfonylurea or biguanide drugs, there has thus far been no indication of secondary failure with this drug (M. Ghazzi, T. Antonucci, J. Driscoll, S. Huang, B. Faja, J. Perez, P. Dandona, M. Wilson, J.B. McGill, C. Burant, R. Lang, R.H. Rao, J. Gorscan, M. Rendell, S. Mohiuddin, R. Whitcomb, unpublished observations).

Thus, troglitazone treatment consistently reduces glucose and insulin levels in a variety of type II diabetic populations, with the collateral benefit of lowered triglyceride and increased HDL levels.

Since troglitazone potentiates insulin action, it is reasonable to speculate that combination therapies using troglitazone with either insulin or sulfonylureas might prove especially efficacious. Moreover, it is possible that thiazolidinedione therapy might reduce insulin requirements for those type II diabetic patients on insulin therapy. Clinical trials to test these ideas are ongoing.

USE OF THIAZOLIDINEDIONES IN NONDIABETIC INSULIN-RESISTANT STATES

While insulin resistance is an important component of type II diabetes, it is also a key feature of several other human disease states, such as obesity, hypertension, impaired glucose tolerance, and polycystic ovarian syndrome (23). Initial studies have now been conducted in some of these conditions, with promising results (24). Obese patients with or without impaired glucose tolerance (IGT) were treated with troglitazone for 3 months. These patients were insulin resistant before treatment, and drug therapy essentially normalized insulin sensitivity, as measured by both the euglycemic clamp technique and the frequently sampled intravenous glucose tolerance test–derived insulin sensitivity index, S\textsubscript{I} (Fig. 7). This enhanced insulin action led to a striking improvement in glucose tolerance, accompanied by a 41% reduction in fasting and postprandial insulinemia (Fig. 8). Of the patients who met the criteria for IGT, 80% demonstrated normal glucose tolerance at the end of the treatment period. Interestingly, a significant reduction in both systolic and diastolic blood pressure was also observed. Thus, in this group of nondiabetic individuals with insulin resistance and hyperinsulinemia, the metabolic abnormalities associated with syndrome X (28), including hypertension and dyslipidemia, were largely corrected with troglitazone. These findings suggest that insulin resistance may indeed be the underlying cause of this syndrome or that another thiazolidinedione-responsive metabolic defect gives rise to these symptoms.

The beneficial effect of troglitazone treatment in patients with IGT has potential implications for disease...
prevention. It is now well recognized that many patients with IGT are prediabetic. In the U.S. population, it is estimated that 7% of all subjects with IGT will convert to type II diabetes each year. Since patients with IGT tend to be insulin resistant and hyperinsulinemic before the onset of type II diabetes, it is logical to speculate that treatment of insulin resistance in the prediabetic state might prevent or delay the ultimate development of type II diabetes. Indeed, this hypothesis will be tested in a large-scale, National Institutes of Health–sponsored, multicenter study in which a large number of IGT patients will be treated with troglitazone as one arm of the study to determine whether diabetes can be prevented.

Polycystic ovarian syndrome (PCOS) is another condition characterized by insulin resistance. The cellular mechanisms of this insulin-resistant state appear to differ from that seen in obesity and type II diabetes. Cells from PCOS patients show a unique desensitization mechanism for uncoupling between insulin receptor activation and stimulation of glucose transport. A majority of PCOS patients are insulin resistant independent of obesity, since lean PCOS subjects are more resistant than lean control subjects and obese PCOS subjects are more insulin resistant than obese subjects without PCOS. It has been proposed that insulin resistance and hyperinsulinemia are primary events in PCOS that somehow lead to hyperandrogenism and the subsequent reproductive endocrine abnormalities. In support of this, a recent study (26) found that treatment of PCOS patients with troglitazone led to the amelioration of insulin resistance and hyperinsulinemia, with the concomitant reduction of elevated testosterone and luteinizing hormone levels toward the normal range. In some of these women, ovulation also occurred during the period of drug therapy.
several candidate pathways that involve a complex series of molecular actions of these drugs. Although the precise mechanisms underlying the actions of thiazolidinediones have been difficult in animal models, because glucose and lipid metabolism is regulated by complex feedback systems, molecular changes induced by drugs or hormones are rapidly counteracted. Such homeostatic loops are generally not present in tissue culture cells, offering an opportunity to study specific responses to defined stimuli. Three such cell lines—the 3T3-L1 mouse fibroblast, which can differentiate into insulin-responsive adipocytes; HepG2, a human hepatoma cell line; and L6 rat myocytes—have been used as model systems to evaluate the effects of thiazolidinediones on fat, liver, and muscle to probe the molecular actions of these drugs. The cellular actions of insulin are characterized by a wide variety of effects, initiated by the tyrosine kinase activity of the receptor. Although the precise mechanisms involved in the regulation of intermediary metabolism by insulin are not precisely understood, there are several candidate pathways that involve a complex series of protein phosphorylations (27). The effects of thiazolidinediones on these pathways have been evaluated extensively. These agents have little, if any, direct effects on the early phosphorylation events induced by insulin, although longer-term exposure to these drugs can, in some cases, increase receptor and IRS-1 tyrosine phosphorylation and facilitate the activation of phosphatidylinositol 3'-kinase. However, numerous investigations suggest that the insulin-sensitizing actions of thiazolidinediones do not primarily involve mobilization of early signaling events in insulin action. A number of the thiazolidinediones have been shown to significantly increase both basal and insulin-stimulated uptake of glucose in 3T3-L1 adipocytes and L6 myocytes (28–30), correlating with enhanced expression of the transporters GLUT1 and GLUT4 (29). Increases in GLUT1 mRNA levels have been observed in both adipocytes and myocytes (22), although these increases may not result from a direct effect of thiazolidinediones on the GLUT1 promoter. Increased GLUT4 expression in 3T3-L1 cells appears to occur secondarily to the acceleration of fat cell differentiation (22). Pioglitazone, troglitazone, and BRL49653 dramatically increase the number of and rate at which fibroblasts are converted to adipocytes (22,32–34). This effect is absolutely dependent on insulin and perhaps accounts for the observed increase in adiposity of young rodents treated with these drugs. Indeed, expression of other fat cell–specific genes is increased by these agents, including lipoprotein lipase, AP-2, acyl CoA synthase (ACS), malic enzyme (MAL1), and adipin (32–34). The regulated expression of some of these proteins may contribute to the stimulation of triglyceride clearance by thiazolidinediones. The effects of thiazolidinediones described above are likely to reflect an early transcriptional event in fat cell differentiation that requires a target already present in preadipocytes. One family of candidates for such a target was recently identified as the peroxisome proliferator–activated receptors (PPARs), members of the steroid/thyroid hormone receptor superfamily of transcription factors (35–37). Thus far, three major PPAR family members have been identified, α, γ, and δ (also known as Nuc-1 or FAAR, for fatty acid–activated receptor) (Fig. 9). These family members share considerable sequence homology in their activation and DNA-binding and ligand-binding domains. The precise roles of these receptors in the biological actions of thiazolidinediones have yet to be clarified. PPARα is known to be a receptor for the fibrate class of lipid-lowering drugs, mediating the regulation of lipoprotein gene expression. Recent studies have implicated both PPARγ and PPARδ as promising candidates for thiazolidinedione-activated receptors. Both pioglitazone and BRL49653 have been shown to directly bind to PPARγ with high affinity and low capacity. This interaction occurs over a concentration range similar to that required for transactivation of a heterologous promoter (38). Moreover, some evidence suggests an approximate correlation between PPARγ binding affinity and in vivo activity of thiazolidinediones (39), although these studies have compared oral bioactivity rather than effective blood levels of drug. The role of PPARδ in the action of thiazolidinediones remains controversial. Although some studies have failed to detect binding to or transactivation of this family member by thiazolidinediones (38), a chimeric glucocorticoid receptor/PPARδ construct was activated by BRL49653, troglitazone.
tazone, and pioglitazone, and PPARδ was suggested to be involved in the effect of these agents on transcription of the AP-2 gene (40). However, it is likely that these cells expressed low levels of PPARγ that could account for the transcriptional effects.

Although there is uncertainty about the relative roles played by PPAR subtypes, a general model for the activation of these receptors by thiazolidinediones has emerged (Fig. 10). PPARs exist in a heterodimer with another nuclear receptor, retinoic acid X receptor (RXR). An additional “co-repressor” protein in this complex may serve to maintain the receptor in an inactive state, analogous to what has been described for other nuclear receptors (41). Binding of this complex by the ligand induces a conformational change, displacing the co-repressor or allowing for the binding of a coactivator. The “activated” receptor interacts with specific DNA sequences in responsive genes and subsequently activates or represses transcription. Although the identity of thiazolidinedione-responsive elements in genes that are involved in restoring insulin sensitivity remains unknown, a number of generic PPAR-response sequences have been found (42).

In addition to our lack of knowledge regarding the identity of relevant thiazolidinedione-responsive genes, there remains much to learn about the initial sites of action of these drugs. Early studies suggested that PPARγ is expressed mainly in adipose tissue, but lower levels were later detected in other tissues, notably in cells of the immune system (43). In a recent study, significant levels of PPARγ2, an alternatively spliced form, were found in skeletal muscle of mice (44). PPARα is found in liver and, to a lesser extent, in kidney, gut, and adipose tissue, while PPARδ is ubiquitously expressed, with significant amounts found in liver, fat, and muscle (43,45). The restricted expression of these family members illustrates the difficulty in determining the relative roles of these tissues in mediating the effects of these drugs, although thiazolidinediones clearly exert direct effects on liver and muscle. It is possible that other
nuclear receptors, including some not yet identified, may play important roles in the regulation of glucose and lipid metabolism by thiazolidinediones.

The profound effects of the thiazolidinediones suggest that the modulation of PPARs by endogenous ligands might play a critical role in hormonal regulation of intermediary metabolism. The PPARs were originally thought to interact with fatty acids and their metabolites, although the identity of authentic endogenous ligands for these receptors remains a mystery. Recent studies (46,47) indicate that PPARγ may interact with metabolites of arachidonic acid, particularly prostanooids of the J2 series. However, a number of other metabolites can activate or bind to these receptors, suggesting that identification of the true ligand may be difficult. While the relative importance of these putative ligands awaits further investigation, it is tempting to speculate that alterations in their synthesis or metabolism may contribute to the development of insulin resistance in humans and perhaps account for a common underlying defect in some cases of syndrome X.

In addition to enhancing glucose disposal, troglitazone has also been shown to facilitate insulin-dependent inhibition of HGO, presumably because of attenuation of glucoseogenesis and/or activation of glycolysis (48). Effects of the drug on gene expression were evaluated in HepG2 or H35 cells transfected with the promoters for known insulin-responsive genes, such as glucokinase and PEPCK. While the PEPCK promoter was unresponsive to the compound, transcription of the glucokinase gene in HepG2 cells was rapidly stimulated by troglitazone, even in the absence of insulin (W.W. Li, T. Leff, unpublished observations). Comparison of the troglitazone-responsive promoter in the glucokinase gene to genes responding in fat cells may lead to a more complete understanding of the precise molecular mechanisms of the drug, particularly regarding the role of PPAR subtypes.

THIAZOLIDINEDIONES MAY DIRECTLY AMELIORATE GLUCOSE TOXICITY

In addition to the primary insulin resistance that precedes the development of type II diabetes, there is a secondary resistance that appears to result from the metabolic changes associated with diabetes, particularly hyperglycemia. Indeed, insulin receptor tyrosine phosphorylation is significantly reduced in diabetic subjects (50). Moreover, fibroblasts exposed to high ambient glucose levels exhibit reduced receptor tyrosine phosphorylation, which might be mediated through an inhibitory serine phosphorylation of the receptor (51). Troglitazone restored the hyperglycemia-induced reduction of receptor phosphorylation in diabetic rats (52) and was shown to prevent the glucose-induced inhibition of insulin receptor tyrosine phosphorylation in cultured cells after only a 20-min preincubation (53). While this effect of the drug may not be relevant to its insulin-sensitizing effects in normoglycemic paradigms, it may contribute in some way to the antihyperglycemic actions of the drug. Moreover, the rapid onset of this effect on receptor phosphorylation suggests that it may be mechanistically distinct from the transcriptional effects described above.

FUTURE PROSPECTS

Although a number of pharmacological approaches to the treatment of type II diabetes are currently available, it is clear that none are ideal for the treatment of the great majority of type II diabetes patients. Thus, the development of novel therapeutic approaches remains highly desirable. While a number of strategies are under investigation to attack the metabolic abnormalities that contribute to diabetes or the cluster of risk factors that are associated with the disease, thiazolidinediones represent the first therapeutic attempt to directly target one of the major underlying causes of the disease, insulin resistance. In theory, this approach offers numerous advantages, primarily because it targets the primary metabolic characteristic of type II diabetes, as well as related disorders. Moreover, the development of insulin sensitizers exploits the normal homeostatic mechanisms that regulate glucose and lipid metabolism, attenuating the risk of drug-induced hypoglycemia. Furthermore, this therapeutic approach might lead to the preservation of pancreatic islet cell function. Treatment of prediabetic individuals with a drug that can ameliorate insulin resistance has the potential of preventing the eventual development of type II diabetes. Ongoing clinical studies will more precisely reveal whether these drugs can provide a safe and effective means for treating type II diabetes, as well as related non-diabetic syndromes associated with insulin resistance. A better understanding of the precise mechanism of action of thiazolidinediones should lead to the development of even more effective treatments for diabetes and may contribute to a better understanding of the underlying molecular abnormalities of this disease.

REFERENCES