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The Journey of Thiazolidinediones as Modulators of PPARs for the Management of Diabetes: A Critical Review

Munwar S* and Ilango K

Interdisciplinary Institute of Indian System of Medicine (IIISM), Department of Pharmaceutical Chemistry, SRM Institute Science and Technology, Kattankulathur, Tamil Nadu, India

Abstract

Thiazolidinediones are a class of well-established antidiabetic drugs, also named as glitazones. Thiazolidinedione structure has been an important structural domain of research, involving design and development of new drugs for the treatment of type 2 diabetes. Extensive research on the mechanism of action and the structural requirements has revealed that the intended antidiabetic activity in type 2 diabetes is due to their agonistic effect on peroxisome proliferator-activated receptor (PPAR) belonging to the nuclear receptor super family. Glitazones have specific affinity to PPARγ, one of the subtypes of PPARs. Certain compounds under development have dual PPARα/γ agonistic activity which might be beneficial in obesity and diabetic cardiomyopathy. Interesting array of hybrid compounds of thiazolidinedione PPARγ agonists exhibited therapeutic potential beyond antidiabetic activity. Pharmacology and chemistry of thiazolidinediones as PPARγ agonists and the potential of newer analogues as dual agonists of PPARs and other emerging targets for the therapy of type 2 diabetes are presented. This review highlights the possible modifications of the structural components in the general frame work of thiazolidinediones with respect to their binding efficacy, potency, and selectivity which would guide the future research in design of novel thiazolidinedione derivatives for the management of type 2 diabetes.

Keywords: Insulin • Thiazolidinediones • PPARγ agonists • Type 2 diabetes mellitus (T2DM).

Introduction

Thiazolidinediones (TZDs) were first reported as insulin-sensitizing drugs in the early 1980s by the pharmaceutical company Takeda [1], but their mechanism remained a mystery until the mid-1990s, when they were found to be ligands for the nuclear receptor transcription factor PPARγ [2]. PPARγ is expressed at high levels in adipose tissue, where it functions as a master regulator of adipocyte differentiation, and at much lower levels in other tissues [3]. The simplest model for TZD function involves PPARγ agonism in adipose tissue.

Thiazolidinediones (TZDs), or "glitazones," were first introduced for the treatment of type 2 diabetes in 1996, when troglitazone was approved by the Food and Drug Administration. Since the introduction of this unique class of compounds, many clinicians have embraced their use, whereas others have debated the role of insulin-sensitizing therapy for the management of type 2 diabetes.

Literature Review

Before the introduction of glitazones, conventional management of type 2 diabetes involved stepwise addition of medical nutrition therapy, sulfonylureas, and metformin. Despite broader use of early drug therapy, many patients do not achieve adequate blood glucose control [4]. Even in those who do achieve treatment targets, a gradual deterioration in blood glucose control is often seen [5]. These observations have prompted clinicians to use newer therapies, such as the glitazones, and have increased the use of early combination therapy to achieve glycemic targets (Figure 1).

Glitazones uniquely target insulin resistance-a core physiologic defect

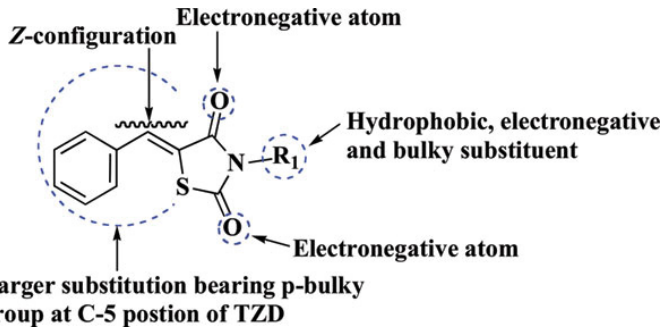

Figure 1. Structure of thiazolidinedione.

in those with type 2 diabetes and by so doing significantly improve glucose control. Glitazones improve insulin action in muscle, adipose, and hepatic tissue by acting as agonists of peroxisome proliferator–activated receptor-γ (PPAR-γ) nuclear receptors. Activation of PPAR-γ results in a myriad of both metabolic and vascular effects by upregulating and downregulating expression of numerous genes, including genes known to regulate lipid and glucose metabolism, vascular function, thrombotic function, and the inflammatory response. Glitazones increase nonoxidative glucose disposal, increase triglyceride synthesis, and improve free fatty acid (FFA) metabolism [6]. Glitazones also lower blood pressure, improve lipid metabolism (raising HDL cholesterol, reducing triglyceride levels, and increasing concentrations of large, buoyant LDL particles), and improve vascular reactivity and rheologic abnormalities common to type 2 diabetes and insulin resistance [7].

Glitazones' unique effects suggest that these compounds may have significant advantages over other commonly used glucose-lowering therapies. The potential of several of these advantages are outlined below and establish both the clinical benefit of glitazone therapy and the clinical potential of these and other insulin-sensitizing therapies.

Who?

- Thiazolidinediones are recommended for persons with type 2 diabetes who have poorly controlled blood glucose and high Hb A1c levels.

What?

- Oral tablet – There are two types of thiazolidinediones that are currently available:
- Pioglitazone (marketed as Actos)

***Address for Correspondence:** Munwar S and Ilango K, Interdisciplinary Institute of Indian System of Medicine (IIISM), Department of Pharmaceutical Chemistry, SRM Institute Science and Technology, Kattankulathur, Tamil Nadu, India, Tel: 8466860416, E-mail: pharmacy14443@gmail.com*

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- Rosiglitazone (marketed as Avandia).
- Combination pills containing pioglitazone and rosiglitazone along with other diabetes medications such as metformin are available

Where?

- These pills work primarily by enhancing the body's ability to respond to insulin.

When?

- The treatment plan will differ for each patient, but in general:
- Pioglitazone is taken once a day; the typical dose is 15, 30 or 45 mg daily
- Rosiglitazone is generally taken once or twice daily starting with 2-4 mg once or twice daily to a maximum daily dose of 8 mg.

Why?

- These medications typically lower A1c levels by 1 – 1.5%.
- When taken alone, these medications do not usually lead to low blood glucose levels.
- Rosiglitazone and pioglitazone may cause or worsen heart failure and are not recommended in persons with history of severe heart failure.
- Patients may experience fluid retention and weight gain while taking thiazolidinedione drugs.
- Studies suggest that pioglitazone may be linked to the development of bladder cancer but evidence is not conclusive.
- Women who take these drugs may be more prone to bone fractures.

Members of the class

- Chemically, the members of this class are derivatives of the parent compound thiazolidinedione, and include:
- Pioglitazone (Actos), France and Germany have suspended its sale after a study suggested the drug could raise the risk of bladder cancer [8].
- Rosiglitazone (Avandia), which was put under selling restrictions in the US and withdrawn from the market in Europe due to some studies suggesting an increased risk of cardiovascular events. Upon re-evaluation of new data in 2013, the FDA lifted the restrictions.
- Lobeglitazone (Duvie), approved for use in Korea

Experimental, failed and non-marketed agents

- Ciglitazone
- Darglitazone
- Englitazone
- Netoglitazone
- Rivoglitazone
- Troglitazone (Rezulin), withdrawn due to increased incidence of drug-induced hepatitis.
- Balaglitazone

- Ciglitazone (INN) is a thiazolidinedione. Developed by Takeda Pharmaceuticals in the early 1980s, it is considered the prototypical compound for the thiazolidinedione class.

Ciglitazone was never used as a medication, but it sparked interest in the effects of thiazolidinediones. Several analogues were later developed, some of which-such as pioglitazone and troglitazone-made it to the market.

Ciglitazone significantly decreases VEGF production by human granulosa cells in an *in vitro* study, and may potentially be used in ovarian hyperstimulation syndrome. Ciglitazone is a potent and selective PPARγ ligand. It binds to the PPARγ ligand-binding domain with an EC50 of 3.0 μM. Ciglitazone is active *in vivo* as an anti-hyperglycemic agent in the murine model. Inhibits HUVEC differentiation and angiogenesis and also stimulates adipogenesis and decreases osteoblastogenesis in human mesenchymal stem cells.

- Darglitazone (previously known as CP 86325-2) is a member of the thiazolidinedione class of drugs and an agonist of peroxisome proliferator-activated receptor-γ (PPAR-γ), an orphan member of the nuclear receptor superfamily of transcription factors. It has a variety of insulin-sensitizing effects, such as improving glycemic and lipidemic control, and was researched by Pfizer as a treatment of metabolic disorders such as type 2 diabetes mellitus.

  Its development was terminated on November 08, 1999.

Mechanism of action of thiazolidinedione

Thiazolidinediones or TZDs act by activating PPARs (peroxisome proliferator-activated receptors), a group of nuclear receptors, specific for PPARγ (PPAR-gamma, PPARG). They are thus the PPARG agonists subset of PPAR agonists. The endogenous ligands for these receptors are free fatty acids (FFAs) and eicosanoids. When activated, the receptor binds to DNA in complex with the retinoid X receptor (RXR), another nuclear receptor, increasing transcription of a number of specific genes and decreasing transcription of others. The main effect of expression and repression of specific genes is an increase in the storage of fatty acids in adipocytes, thereby decreasing the amount of fatty acids present in circulation. As a result, cells become more dependent on the oxidation of carbohydrates, more specifically glucose, in order to yield energy for other cellular processes (Figure 2).

PPARγ transactivation

Thiazolidinedione ligand dependent transactivation is responsible for the majority of anti-diabetic effects. The activated PPAR/RXR heterodimer binds to peroxisome proliferator hormone response elements upstream of target genes in complex with a number of coactivators such as nuclear receptor coactivator and CREB binding protein, this causes upregulation of genes (Figure 3).

- Insulin resistance is decreased
- Adipocyte differentiation is modified [9]
- VEGF-induced angiogenesis is inhibited
- Leptin levels decrease (leading to an increased appetite)
- Levels of certain interleukins
- Antiproliferative action
- Adiponectin levels rise

TZDs also increase the synthesis of certain proteins involved in fat and glucose metabolism, which reduces levels of certain types of lipids, and circulating free fatty acids. TZDs generally decrease triglycerides and increase high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C). Although the increase in LDL-C may be more focused on the larger LDL particles, which may be less atherogenic, the clinical

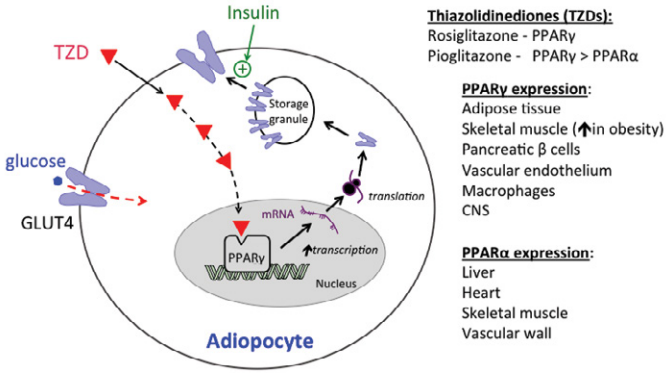

Figure 2. Mechanism of action of thiazolidinedione.

significance of this is currently unknown. Nonetheless, rosiglitazone, a certain glitazone, was suspended from allowed use by medical authorities in Europe, as it has been linked to an increased risk of heart attack and stroke.

PPARγ transrepression

Thiazolidinedione ligand dependent transrepression mediates the majority of anti-inflammatory effects. Binding of PPARγ to coactivators appears to reduce the levels of coactivators available for binding to pro-inflammatory transcription factors such as NF-κB; this causes a decrease in transcription of a number of pro inflammatory genes, including various interleukins and tumour necrosis factors (Figure 4).

The development of the thiazolidinediones

The discovery of thiazolidinediones and a substantial amount of the early developmental work occurred in Japan. The first compound, ciglitazone, improved glycaemic control in animal models of insulin resistance, but its mechanism of action was poorly understood and toxicity prevented trials in humans. Other compounds were subsequently developed with less toxicity in animals, and two important findings led to a rapid increase in our understanding of their mode of action.

These findings were that thiazolidinediones:

- Bind avidly to peroxisome proliferator-activated receptor gamma (PPARγ)
- Improve insulin sensitivity in parallel with a major change in fat metabolism, including a substantial reduction in circulating free fatty acids.
- Three compounds - troglitazone, pioglitazone and rosiglitazone - have entered clinical practice and there has been a steadily increasing understanding of the multiple biological effects of these drugs.

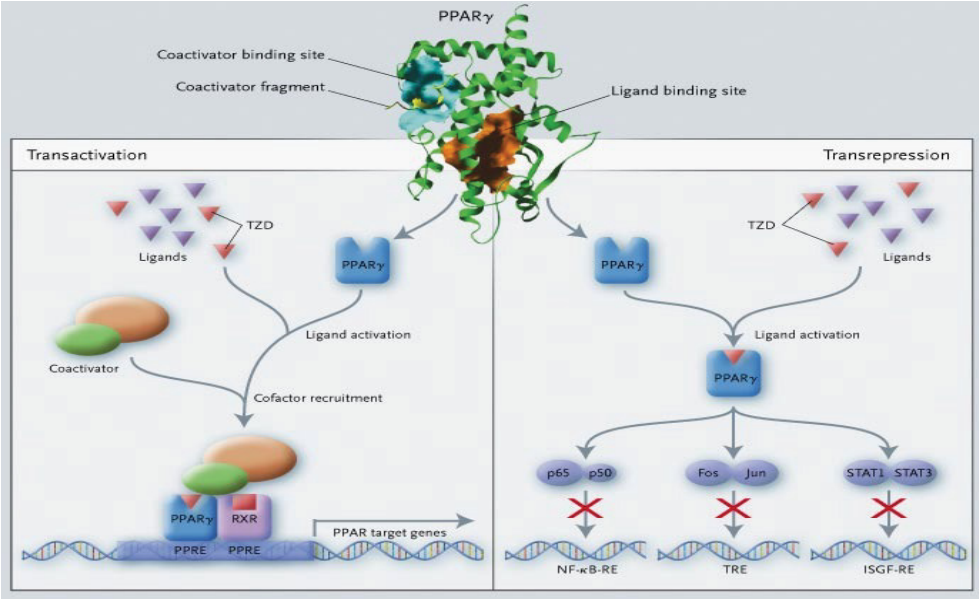

Figure 3. PPARγ trans-activation and PPARγ trans-repression.

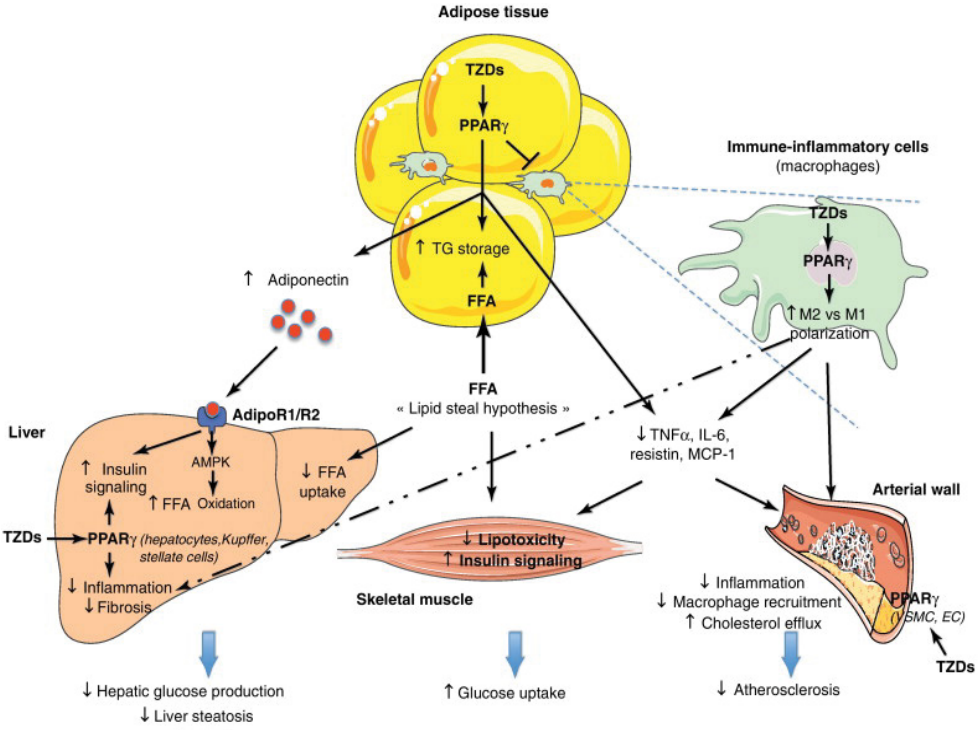

Figure 4. Thiazolidinediones and PPARγ agonists.

Glitazones as glucose-lowering therapy: Achieving and sustaining control

Intensive glucose control is the accepted standard for management of patients with type 2 diabetes. The landmark U.K. Prospective Diabetes Study (UKPDS) confirmed that intensive glycemic control can significantly reduce the risk of complications of diabetes [10]. However, no single therapy (either oral hypoglycemic agents or insulin) proved superior with regard to achieving intensive treatment goals. However, UKPDS also confirmed that type 2 diabetes is a progressive disease, with deterioration in glycemic control observed in all treatment groups regardless of the initial therapy used. By 6 years of treatment, >50% of intensively treated subjects had HbA_{1c} (A1C) values that exceeded 8%. The deterioration in blood glucose control in type 2 diabetes is now felt to result from a decline in β-cell secretory function over time. Impaired insulin secretion, superimposed upon a background of continued insulin resistance, persists and can worsen with the use of sulfonylureas, metformin, or low-dose insulin therapy [11,12].

What added advantages does glitazone treatment offer when used either as monotherapy or in combination that might further benefit patients with type 2 diabetes? All commonly used oral agents, including the glitazones, have similar glucose-lowering effects (generally reducing A1C levels by □1–2 percentage points). The glitazones uniquely target insulin resistance and thereby achieve stable blood glucose control over periods of ≥ 2 years [13,14]. This sustained improvement in glucose control results in great part from an improvement in β-cell secretory function over time. The ability of glitazones to improve insulin secretion is unique among current diabetes therapies [15,16]. The mechanism(s) by which glitazones improve insulin secretion is not fully understood, although improvement in FFA metabolism appears to play an important role in this unique beneficial effect. One theory is that glitazones reduce the "lipotoxic" effect of elevated FFAs in the bloodstream, resulting in improved β-cell secretory function and β-cell mass. Large-scale clinical trials are currently underway to further define the role of glitazone therapy in maintaining glycemic control and sustaining β-cell secretory function [17]. Current data support the use of glitazones in any patient with insulin resistance or in whom deterioration of blood glucose control is seen.

Glitazones and diabetes prevention

The prevalence of type 2 diabetes continues to increase, and recent estimates of the number of people in the U.S. with either diabetes or pre-diabetes may exceed 25 million. More effective therapies to prevent type 2 diabetes are being sought in hopes of limiting the impact of this epidemic. Both intensive lifestyle changes [18,19] and pharmacologic therapies can reduce the risk of type 2 diabetes in high-risk individuals with pre-diabetes or a history of prior gestational diabetes. One common feature of the most effective preventive therapies is their ability to target insulin resistance. Intensive lifestyle changes, including moderate weight loss and increased physical activity (both of which improve insulin sensitivity), reduce the risk of progression to type 2 diabetes by >50% [20].

Pharmacologic therapies, including metformin [21] and the glitazones can also significantly reduce the risk of progression to type 2 diabetes in those at high risk. Metformin therapy reduces risk by □30%; however, this benefit is less than that seen with intensive lifestyle changes [22]. Is metformin preventing diabetes or is it merely masking diabetes? It has been suggested that at least a portion of the benefit derived from metformin therapy is in fact a result of early treatment rather than a true decrease in the risk of diabetes. This observation is supported by data from the Diabetes Prevention Program (DPP), where □25% of metformin-treated subjects developed diabetes quickly after discontinuation of the drug [23]. In contrast, in at least one study, glitazones have been shown to reduce the risk of diabetes by >50% (8), an effect similar in magnitude to that observed with intensive lifestyle changes. Furthermore, in those with a history of prior gestational diabetes, glitazones appear to both prevent and delay diabetes onset rather than simply mask hyperglycemia. In contrast, the development of diabetes following discontinuation of troglitazone in those with impaired glucose tolerance in the Diabetes Prevention Program (DPP) resulted in an increase in diabetes onset that paralleled the rate seen in placebo-treated patients [24]. These contrasting results suggest that while glitazone therapy may be an effective means of diabetes prevention, active treatment may be required to truly prevent diabetes. It must be noted that the populations in the TRIPOD (Troglitazone in Prevention of Diabetes) study and the Diabetes Prevention Program (DPP) differ substantially; with those in TRIPOD receiving treatment before the onset of glucose intolerance, whereas subjects in the DPP were enrolled after glucose intolerance was present. Whether earlier treatment will in fact enhance the effectiveness of TZD therapy for diabetes prevention remains to be determined.

Why the difference between metformin and glitazones? Whether the greater benefit of glitazone therapy is a consequence of specific improvements in insulin resistance, an improvement in β-cell secretory function or other effects is not known. However, one plausible mechanism is explained by an "off-loading" of the β-cell due to reduced insulin requirements resulting from increased insulin sensitivity in peripheral tissue [25]. Theoretically, off-loading preserves β-cell mass and improves secretory response, allowing secretion of insulin for a longer period (effectively preventing the development of diabetes).

Although no diabetes medication is presently approved for the treatment of pre-diabetes or for diabetes prevention, data from these clinical trials support the use of therapies that improve insulin sensitivity, including intensive lifestyle change and pharmacological insulin-sensitizing therapy to achieve maximal risk reduction. In years to come, the early identification of insulin resistance should allow for more directed use of glitazone therapy in diabetes prevention. Again, long-term clinical trials that will further clarify the role of glitazone therapy for diabetes prevention are underway.

Pharmacokinetics and drug interactions

The thiazolidinediones are rapidly absorbed and reach peak concentrations within a few hours [26,27]. Steady-state is usually reached within one week, but perhaps because of the importance of fat redistribution, the full benefit may take 4-12 weeks to become evident. Rosiglitazone and pioglitazone are strongly protein bound in the circulation, predominantly to albumin. No significant drug interactions have been reported with the thiazolidinediones, but it should be noted that in combination with the sulfonylureas, hypoglycaemia may occur due to the combination of enhanced insulin sensitivity (thiazolidinediones) and enhanced insulin secretion (sulfonylureas). Thiazolidinediones are metabolised by cytochrome P450 2C8 (and by CYP3A4 for pioglitazone), but at conventional doses apparently do not affect the activity of those enzymes. Caution should still be exercised when using thiazolidinediones in combination with drugs metabolised by these enzymes.

Adverse effects

Thiazolidinediones now carry a "black box" warning of congestive heart failure and myocardial ischemia. The risk is greater with rosiglitazone. There is also weight gain and a risk of edema, osteoporosis, and fractures. Hepatotoxicity is also a possible adverse effect [28-30].

A) Hepatotoxicity and liver failure

- Associated with Troglitazone use
- Rosiglitazone and Pioglitazone may also cause this
- Follow Liver Function Tests closely
- Especially follow in first year

B) Fluid retention

- Congestive Heart Failure risk
- Peripheral Edema (in 3-5% of patients)
- Moderate weight gain (1-3 kg)
- Mild Anemia

C) Variable lipid effects

- Pioglitazone (Actos)

- Lowers Triglycerides by 9-12%
- Raises HDL Cholesterol by 12-19%
- Rosiglitazone (Avandia):
- Raises Triglycerides by 15%
- Raises HDL Cholesterol by 8-19%
- Raises LDL Cholesterol

D) Risks of adverse effects compounded with Insulin

- Weight gain (3-4 kg)
- Edema (8-10% of cases)
- Congestive Heart Failure
- Observe patients with CHF risk closely
- Hypoglycemia risk

E) Decrease Bone Density (Osteoporosis risk)

- Class effect
- Odds Ratio approaches 2.5 for Glitazone use >8 months

F) Cardiovascular risk

- Rosiglitazone (Avandia) appears to increase CAD risk
- No longer recommended as a first-line agent
- Pioglitazone (Actos) may slightly decrease CAD risk
- Atherosclerosis may be slowed by Actos

G) Bladder Cancer risk

- Risk of up to 11 per 10,000 cases per patients taking Pioglitazone (actos) >1 year

Discussion

TZDs are an important class of drugs that act by increasing the transactivation activity of PPARs, as a result of which, they reduce hepatic glucose production, increase peripheral utilization of glucose and lipid metabolism. These actions, therefore, reduce the preload and after load on b-cells and lipid homeostasis. As a result, the effect of endogenous insulin improves so as to maintain the level of blood glucose. Unfortunately, the clinically used TZDs, Troglitazone, Pioglitazone and Rosiglitazone, suffered from some serious side effects like idiosyncratic hepatotoxicity, fluid retention and weight gain, as a result of which Troglitazone and Rosiglitazone were banned and the Pioglitazone label was updated for the risk of bladder cancer. The TZDs that were withdrawn and restricted from clinical use were developed at a time when not much was known about the role and assembly of PPARs through which the modulation of molecular mechanisms and biological responses of TZDs are mediated. Based on the recent advances and a better understanding of structure and functions of other antidiabetic targets, rationalized approaches have been used to further develop this class of antidiabetic agents. These newer approaches are based on the structural considerations of the ligands, the receptors and ligand-receptor interactions. These include the development of PPAR-a/c dual agonists, PPAR-a/d dual agonists PPAR-d/c dual agonists, PPAR pan agonists, selective PPAR-c modulators and partial agonists. Moreover, TZDs have also been reported as inhibitors of aldose reductase (ALR2), protein tyrosine phosphatase 1B (PTP1B) and a-glucosidase. In addition, studies on TZDs as free fatty acid receptor (FFAR1) and G-protein coupled receptor 40 (GPR40) agonists have also been reported. Today, however, studies on TZDs by investigators are declining.

Conclusion and Future Perspectives

All these alternatives can, therefore, attract the attention of investigators for developing newer agents for T2DM. These targets, either individually and/or through mutiple action, can no doubt create enormous possibilities of developing novel TZDs devoid of unwanted side effects. The discovery and development of the thiazolidinediones represent a significant advance in our understanding of the aetiology of insulin resistance, particularly in relation to adipocyte biology. The thiazolidinediones are a new mode of therapy for type 2 diabetes. Their action, in large part, is mediated by activation of PPARγ and involves redistribution of surplus fatty acids to peripheral fat. This reduces fatty acid availability in the circulation as well as in liver and muscle - thus improving insulin sensitivity.

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