



Thiazolidinediones – mechanisms of action

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Summary

The thiazolidinediones (or 'glitazones') are a new class of drugs for the treatment of type 2 diabetes. They bind avidly to peroxisome proliferator-activated receptor gamma in adipocytes to promote adipogenesis and fatty acid uptake (in peripheral but not visceral fat). By reducing circulating fatty acid concentrations and lipid availability in liver and muscle, the drugs improve the patient's sensitivity to insulin. Thiazolidinediones favourably alter concentrations of the hormones secreted by adipocytes, particularly adiponectin. They increase total body fat and have mixed effects on circulating lipids.

Key words: hypoglycaemic drugs, insulin, diabetes, pioglitazone, rosiglitazone.

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Introduction

Despite the explosion in the prevalence of type 2 diabetes in the last 50 years, there has been a distinct lack of progress in the development of new therapies. Together with decreased insulin secretion, insulin resistance, or a reduction in the biological activity of endogenous insulin, is a key component in the development of type 2 diabetes and 'prediabetic' states, such as impaired glucose tolerance. As the thiazolidinediones (or 'glitazones') improve insulin sensitivity through actions which are completely different from those of other oral hypoglycaemic drugs, there has been a lot of interest in their potential role in type 2 diabetes.¹

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 (PPAR γ)²
- improve insulin sensitivity in parallel with a major change in fat metabolism, including a substantial reduction in circulating free fatty acids.³

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. Unfortunately, troglitazone caused uncommon but serious liver toxicity, leading to its withdrawal from use. It seems likely that this toxicity was related to the vitamin E-like part of the molecule.⁴ Hepatotoxicity does not seem to be associated with the other two compounds, but regular liver function tests are recommended.¹

Molecular mechanisms of action

PPAR γ is a member of a family of nuclear receptors. Another member of this class, peroxisome proliferator-activated receptor alpha (PPAR α), is predominantly expressed in the liver and is thought to mediate the triglyceride lowering actions of fibrates.⁵ PPAR γ is expressed in many tissues, including colon, skeletal muscle, liver, heart and activated macrophages, but is most abundant in adipocytes.¹

Thiazolidinediones are selective agonists of PPAR γ . When activated by a ligand, such as a thiazolidinedione, PPAR γ binds to the 9-*cis* retinoic acid receptor (RXR [retinoid X receptor]) to form a heterodimer.¹ This binds to DNA to regulate the genetic transcription and translation of a variety of proteins involved in cellular differentiation and glucose and lipid metabolism.⁶

Biological effects

Thiazolidinediones have several biological actions. Although the precise mechanism by which the thiazolidinediones improve insulin sensitivity is still not completely understood, a large part of their action is thought to be mediated by changes in body fat and its distribution.

Fat redistribution

One result of PPAR γ activation is enhanced differentiation and proliferation of preadipocytes into mature fat cells, particularly

in non-visceral (peripheral or subcutaneous) fat depots. There is an upregulation of enzymes/transporters in adipocytes to facilitate their uptake of fatty acids (for example, increases in lipoprotein lipase, fatty-acid transporter 1 and glycerol kinase).⁵

It is notable, and probably important, that most of these consequences of PPAR γ stimulation are **not** seen in visceral adipocytes, even though these cells have abundant PPAR γ receptors. Visceral adipocytes are also metabolically quite different to peripheral adipocytes in other ways, for example they are less responsive to insulin and more responsive to catecholamines. Increased fatty acid storage in subcutaneous adipocytes results in a 'lipid-steal' phenomenon, leading to lower circulating fatty acids and reduced concentrations of triglycerides in muscle and liver (Fig. 1).^{1,2} Studies in animals and humans have shown that thiazolidinediones only improve insulin action (and glycaemic control in diabetes) in the presence of insulin resistance.³ This may be explained by the fact that the effects of these drugs on lipid redistribution are only beneficial if there is excess tissue lipid availability. The 'lipid-steal' effect of thiazolidinediones may therefore be a major contributor to improved insulin action in muscle (enhanced glucose utilisation) and liver (reduced hepatic glucose output), as the direct effects of PPAR γ stimulation in muscle and liver are unclear. The potential role of the thiazolidinediones in reducing hepatic lipid content in non-alcoholic steatohepatitis is under investigation.

The thiazolidinediones do not increase insulin secretion. On the contrary, thiazolidinediones reduce insulin levels acutely, which may be a consequence of improved insulin sensitivity and/or reduced circulating fatty acids (as fatty acids stimulate insulin secretion). In the longer term, thiazolidinediones arrest the

decline in β -cell function that occurs in type 2 diabetes, perhaps by protecting the β -cell from lipotoxicity.⁷ The thiazolidinediones are of no use in type 1 diabetes or in the occasional lean insulin-deficient (but insulin-sensitive) patient with type 2 diabetes.

Adipokines and transporters

In addition to promoting adipogenesis and fatty acid uptake, thiazolidinediones are thought to improve insulin sensitivity by altering hormone production by adipocytes. Adipocytes secrete a number of important hormones, referred to as 'adipokines', including leptin, adiponectin, resistin and tumour necrosis factor- α (TNF- α).⁶ The thiazolidinediones, again via PPAR γ activation, substantially increase the production of adiponectin (which has been shown to increase fat oxidation, improve insulin action and to have anti-atherogenic properties). They also reduce the secretion of substances which impair insulin action such as TNF- α and, possibly, resistin (Fig. 1).^{2,4}

There has been an interesting discussion about the degree to which the improved insulin response induced by thiazolidinediones is mediated by increased glucose processing molecules (such as the insulin regulated glucose transporter, GLUT 4, and pyruvate dehydrogenase activity) in adipocytes.⁵ As adipocytes only account for a small component of insulin-induced glucose disposal, it seems likely that the effects of thiazolidinediones on these glucose handling proteins are not a major component of their activity.

Other biological effects

The effect of the thiazolidinediones on lipid concentrations is complex (Table 1). HDL cholesterol concentrations tend to

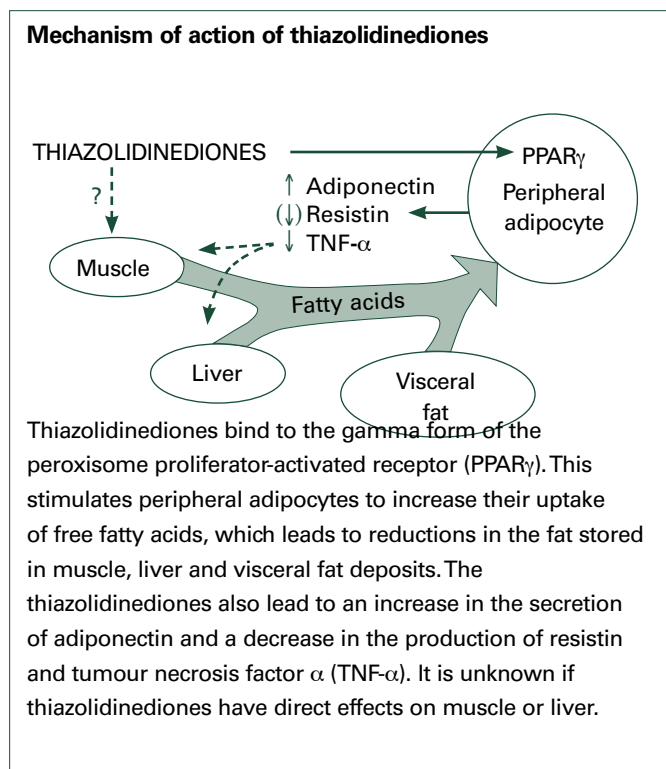


Table 1

Additional biological effects of the thiazolidinediones⁷

- Increased HDL cholesterol concentrations
- Increased LDL cholesterol concentrations
- Increased LDL cholesterol particle size
- Reduced triglyceride concentrations (particularly pioglitazone)
- Small reduction in blood pressure
- Reduced incidence of microalbuminuria
- Decrease in plasminogen activator inhibitor-1 and fibrinogen
- Vasorelaxation
- Increase in vascular reactivity
- Anti-inflammatory effects

All of these effects, except for increased LDL cholesterol concentrations, would be regarded as potentially beneficial in regard to the metabolic syndrome and cardiovascular disease.

Fig. 1

increase while triglyceride concentrations decrease.¹ Although LDL cholesterol concentrations may increase initially, this effect lessens over time and particles are now larger and more buoyant.^{2,4} The outcomes of ongoing large clinical trials may clarify the effect of thiazolidinediones on cardiovascular risk. Pioglitazone has some PPAR α activity, which may account for the data suggesting a more favourable effect on triglyceride and LDL cholesterol levels.⁷

Most of the other biological effects of the thiazolidinediones are potentially beneficial and related to improvements in parameters of the insulin resistance syndrome (Table 1). Many of these effects are probably due to changes in lipid metabolism or adipokines, although detailed mechanisms are not fully understood. These changes have generally only been recorded in animal or human models of insulin resistance. Another reported effect, which may not be mediated by PPAR γ , is a degree of anti-inflammatory activity and reduction in macrophage function.² Limited evidence also suggests that the thiazolidinediones may improve insulin resistance and ovulatory function in women with polycystic ovary syndrome.⁷

Mechanisms of adverse effects

Given the effect of the thiazolidinediones on adipocyte differentiation and proliferation, particularly in peripheral adipocytes, it is not surprising that an adverse effect of thiazolidinedione treatment is a gain in weight and peripheral fat mass. In fact, there tends to be a correlation between increasing peripheral fat and clinical improvement in insulin sensitivity and glycaemia in type 2 diabetes. On the other hand, visceral fat, which appears far more metabolically 'harmful' than peripheral fat, is not increased and may, in fact, decrease with thiazolidinedione therapy.²

An adverse effect, which may preclude the use of the thiazolidinediones in patients with moderate to severe cardiac failure, is fluid retention. This is an important class effect, which may result in peripheral oedema, particularly in patients taking concomitant insulin therapy (which may itself cause some increase in interstitial fluid). An increase in plasma volume results in a small drop in haemoglobin concentrations due to haemodilution. This is rarely clinically significant.

Pharmacokinetics and drug interactions

The thiazolidinediones are rapidly absorbed and reach peak concentrations within a few hours.⁴ 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.⁴ 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.

Conclusion

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 PPAR γ 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. A second aspect of their action is the modification of adipokine secretion.

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Further reading

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Professor Chisholm has received research funding for preclinical studies on thiazolidinediones and has given lectures for and participated in advisory boards for both Eli Lilly and GlaxoSmithKline, marketers of pioglitazone and rosiglitazone. He has no beneficial interest and does not receive consultancy payments from either company other than for lectures and advisory board meetings.

Self-test questions

The following statements are either true or false (answers on page 79)

5. Treatment with thiazolidinediones leads to weight reduction in patients with type 2 diabetes.
6. Haemoglobin concentrations may fall during treatment with thiazolidinediones.



Experimental and clinical pharmacology

Clinical indications for thiazolidinediones

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Summary

Undertreatment of hyperglycaemia in type 2 diabetes is a major therapeutic problem. This is partly because reduced insulin sensitivity and beta cell failure become resistant to current therapies. The thiazolidinediones are a new class of drugs that improve insulin sensitivity. However, large-scale clinical trials are needed to assess their clinical roles and whether they have microvascular protective effects beyond those associated with lowering blood glucose. Trials with clinical end-points are also required to determine if thiazolidinediones reduce macrovascular disease. Thiazolidinediones can cause delayed-onset hypoglycaemia, especially in combination with other oral hypoglycaemic drugs, weight gain and fluid retention. The fluid retention may precipitate heart failure so careful monitoring of weight gain and peripheral oedema is required.

Key words: diabetes, hypoglycaemic drugs, pioglitazone, rosiglitazone.

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Introduction

Lifestyle changes including weight loss and increased activity are the primary recommendations for treatment of type 2 diabetes.

However, because of the progressive nature of the disease, the treatment of type 2 diabetes usually requires the stepwise introduction of oral hypoglycaemic drugs followed by insulin.¹ Despite this approach less than 10% of patients with type 2 diabetes maintain their concentration of glycated haemoglobin (HbA1c) below 7%, which is still about two standard deviations above the upper limit of the normal range. The reasons for this are complex and include factors relating to organisations, doctors, patients and deficiencies in drug efficacy. These may arise from a delay in the translation of new guidelines into clinical practice, patient resistance to starting insulin and secondary failure of existing oral hypoglycaemic drugs.

The thiazolidinediones are a recent addition to the list of hypoglycaemic drugs (Table 1). Rosiglitazone and pioglitazone are now listed on the Australian Pharmaceutical Benefits Scheme (PBS) for the treatment of type 2 diabetes.

Mechanism of action

Thiazolidinediones do not stimulate insulin secretion. They act by improving insulin sensitivity via activation of the nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR γ). There is an increase in glucose utilisation by skeletal muscle and fat cells, increased uptake of free fatty acids and reduced lipolysis by fat cells, and to possibly a lesser extent a reduction in hepatic gluconeogenesis. For fat cells the ratio of adipogenesis to apoptosis is also differentially altered favouring apoptosis of larger insulin-resistant cells and the proliferation of smaller insulin-sensitive adipocytes. This is accompanied by a shift in the distribution of fat from central to peripheral depots.