

New drug classes

Thiazolidinediones: an update

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Thiazolidinediones, which are being developed for the treatment of insulin resistance and type 2 diabetes mellitus, bind and activate peroxisome proliferator-activated receptor γ , a nuclear receptor that regulates the expression of several genes involved in metabolism. This receptor controls adipocyte differentiation, lipid storage, and insulin sensitisation. Besides metabolic activities, thiazolidinediones have effects as diverse as the control of host defence, cell proliferation, and tumorigenesis.

Diabetes affects over 140 million people worldwide, 90% of them having type 2 (non-insulin-dependent) diabetes. Rates are soaring in populations becoming westernised. Every year about 3 million people die from the complications of diabetes. The cornerstone of therapy for type 2 diabetes remains exercise and weight reduction. Drug therapy has improved little since the introduction of insulin in 1921 and the antidiabetic sulphonamides and biguanides in the 1950s. The arrival of "glitazones" or thiazolidinediones is therefore an important event.

Peroxisome proliferator-activated receptor γ (PPAR γ)

We will begin with a brief review of recent data on the mechanism of action of PPAR γ and the thiazolidinediones. Older publications are covered elsewhere, including a 1999 review in *The Lancet*.¹⁻³

Upon binding to small lipophilic natural ligands, or synthetic molecules such as the glitazones and certain non-steroidal antiinflammatory drugs, PPAR γ undergoes a conformational change. This stabilises its interaction with the retinoid X receptor and allows the recruitment of cofactors, resulting in the stimulation of transcription of target genes.⁴ PPAR γ is highly expressed in adipose tissue, where it helps to control adipocyte differentiation, the ultimate "thrifty response".^{5,6} The notion that PPAR γ coordinates the thrifty response is supported by human genetic studies and studies in "knock-out" animals (figure). One rare mutation renders PPAR γ more active, leading to increased adipocyte differentiation and obesity.⁷ Another, but much more common, mutation impedes PPAR γ activity and is associated with a lower body mass index, improved insulin sensitivity, and higher plasma HDL-cholesterol.⁸ The association with insulin sensitivity disappears when corrected for body mass index, indicating that the primary effect is on body weight. Homozygous PPAR γ ^{-/-} mice have no adipose tissue;⁹ heterozygotes have reduced adipose tissue⁹⁻¹¹ and, contrary to expectations, significant insulin sensitisation.¹⁰ These heterozygote mice have a deficient PPAR γ system with less adipose tissue and a subsequent improvement in insulin sensitivity.

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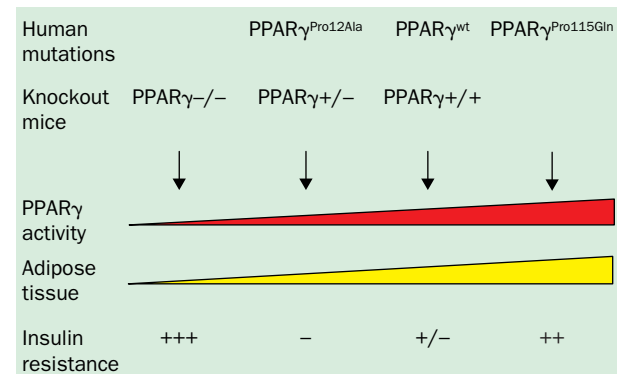
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Adipose tissue seems to be the main site of action for thiazolidinediones. These drugs increase adipose tissue mass, which seems illogical in view of the association of obesity with insulin resistance. On a whole-body level, however, adipose tissue is indispensable for glucose homeostasis, as demonstrated by the link between lipotrophy and insulin resistance,^{12,13} suggesting that the adipogenic activity of PPAR γ contributes to insulin sensitisation. The glitazones induce a "fatty acid steal" by the adipose tissue.^{14,15} The resulting decreased systemic availability of fatty acids and diminished fatty acid uptake by muscle will improve insulin resistance. So, in the short term, storage of excess energy, secondary to PPAR γ activity, ameliorates insulin sensitivity. What we need to know now is whether the resulting adipose tissue accumulation can lead to resistance to insulin and to the action of thiazolidinediones once a critical adipose-tissue threshold has been passed. Genetic studies in man^{7,8} and mouse⁹⁻¹¹ warn that this might be so.

Clinical evidence

Three thiazolidinediones (panel 1) have been approved by the US Food and Drug Administration for type 2 diabetes, and more are being developed. However, few clinical studies have been published and much of the information discussed here has had to come from company websites (www.rezulin.com; www.sb.com/products; www.actos.com). Treatment of type 2 diabetes with these drugs lowers blood glucose, % glycosylated haemoglobin, and serum insulin concentrations as a consequence of enhanced insulin action.¹⁶ This insulin



PPAR γ , a thrifty gene product controlling adipose tissue mass
Effects of PPAR γ mutants in man and mouse on PPAR γ activity, adipose tissue mass, and insulin resistance.

Panel 1: **Thiazolidinediones**

| Name (proprietary name) | Manufacturer | Status |
|-------------------------|--|--------------------------|
| Troglitazone (Rezulin) | Parke-Davis | USA, Japan |
| Rosiglitazone (Avandia) | SmithKline Beecham | USA* |
| Pioglitazone (Actos) | Takeda/Eli Lilly | USA, Japan* |
| MCC 555 | Mitsubishi Chemicals/ Johnson & Johnson | Phase II clinical trials |
| KRP 297 | Kyorin Pharmaceuticals/ Merck | Phase II clinical trials |

*Approval pending in European Union.

sensitisation occurs mainly through an improvement in insulin-stimulated glucose disposal rates in peripheral tissues. It is less clear whether these drugs suppress hepatic glucose output.^{17,18} One attractive feature of the thiazolidinedione insulin sensitisers is their synergism with glucose-lowering drugs that have a different mechanism of action. Synergistic glucose-lowering can be explained by enhanced peripheral glucose disposal in combination with either decreased endogenous glucose production (by metformin)¹⁸ or increased insulin levels (sulphonylureas or insulin).¹⁶ When added to current treatment in patients whose glycaemic control remained unsatisfactory despite sulphonylureas, metformin, insulin, or a combination of these agents, all three thiazolidinediones were effective, as judged by decreases in serum levels of glucose, insulin, and HbA_{1c}.^{19,20} In about one-quarter of patients there is no blood glucose response to these new drugs. Non-responders are more obese and have a longer standing insulin resistance with depleted pancreatic insulin reserves. Combination treatment regimens might convert some non-responders into responders.

Thiazolidinediones profoundly affect lipid metabolism. Patients with insulin resistance and type 2 diabetes often have raised triglycerides and low HDL-cholesterol concentrations. Since these drugs increase the lipolysis of triglycerides in very-low-density lipoproteins (VLDL), they will reduce triglyceride and increase HDL-cholesterol levels.^{16,17} A potential drawback is that during this lipolysis VLDL will be converted into the more dangerous LDL,¹⁶ and treatment with troglitazone¹⁶ and rosiglitazone,²⁰ but not pioglitazone, does seem to be associated with a rise in LDL. Long-term follow-up will show if such a rise in LDL has a negative impact on metabolism and atherosclerosis.

Safety

More than a million patients have now received thiazolidinediones. Few side-effects have been reported (panel 2) but concerns about long-term safety persist. Hepatic dysfunction, seen in about 2% of the patients and sometimes leading to liver failure, is serious problem with troglitazone.^{21,22} Although, this potentially lethal side-

Panel 2: **Potential side-effects**

| Side-effect | Relative frequency |
|---------------------------|--------------------|
| Weight gain | +++ |
| Raised LDL-cholesterol | ++ |
| Fluid retention | + |
| Drug interactions | + |
| Hepatotoxicity | + |
| Cardiac hypertrophy | ? |
| Induction of colon polyps | ? |

effect²² appears to be less frequent with rosiglitazone^{23,24} and pioglitazone, liver function monitoring is recommended, and these tests add to the cost of treatment.

Because of tumour-inducing effects in a murine model for familial adenomatous polyposis and sporadic colon cancer, these drugs should not be prescribed for people from families with adenomatous polyposis coli.^{25,26} Long-term studies should monitor effects on the development of sporadic colon tumours. Fluid retention, haemodilution, and the induction of preload-induced cardiac hypertrophy—all serious side-effects seen in animal studies—should also be looked for. Clinically, however, the rise in plasma volume seems not to be associated with an increase in left-ventricular mass.^{19,20} Nevertheless, glitazones are contraindicated in patients with New York Heart Association class III or IV cardiac status.

Another word of caution concerns drug interactions. Troglitazone and pioglitazone, but not rosiglitazone,¹⁹ induce the cytochrome P450 isoform CYP3A4, which is partly responsible for their metabolism. Safety and efficacy could be affected when these new agents are coadministered with other drugs metabolised via this enzyme, such as erythromycin, astemizole, calcium-channel blockers, cisapride, corticosteroids, cyclosporin, statins, tacrolimus, and triazolam. Blood-glucose should also be monitored more carefully in patients receiving these antidiabetic drugs in combination with inhibitors of CYP3A4 such as ketoconazole or itraconazole. Finally, time will tell whether obesity, and eventual secondary drug resistance, is a serious issue (see above)

Other glitazones

Future PPAR γ modulators may address some of the problems encountered with simple agonists. Novel thiazolidinediones such as KRP-297 and JTT-501^{27,28} and PPAR γ agonists with different structural bases such as BM 17.0744²⁹ with effects on PPAR α and γ have broader tissue-specific activity and different pharmacological properties. Thiazolidinediones such as MCC-555 and L-764486 retain significant antidiabetic properties yet are only weak PPAR γ ligands. They are PPAR γ modulators rather than agonists and can behave as full or partial agonists or antagonists, depending on cell type and sequence-recognition site.^{30,31} Tissue and promoter specific PPAR γ modulators are thus possible, and such agents might, like the selective oestrogen-receptor modulators (SERMs), induce beneficial effects on certain target tissues yet lack activity in other tissues where activation is less desirable.

Activation of thrifty transcription factor PPAR γ ?

During most of evolution, a “thrifty response” was selected for by genetic pressure, allowing survival during famine and combating infection, inflammation, and neoplasia. PPAR γ interfaces with insulin signalling, the pathway which coordinates not only the response to food intake but also energy storage and growth. In *Caenorhabditis elegans*, mutations in the insulin-signalling pathway result in growth arrest, fat accumulation, and a significant extension of the life-span known as “dauer”.³² Wild-type animals also can enter dauer in the absence of adequate nutrition or with overcrowding. Similarly, in *Drosophila* interference with insulin signalling is

characterised by fat accumulation.³³ If PPAR γ is a master controller of a similar thrifty response it is no surprise to learn that PPAR γ expression is part of the set of genes that are modified by caloric restriction.³⁴ The transition from a primitive society, with limited food, to an agricultural and later industrialised society, with ample food and reduced physical activity, occurred late in evolution, and it renders the thrifty response superfluous.

We suggest that a maladapted thrifty response, coordinated by PPAR γ , has contributed to the recent rise in the prevalence of obesity, atherosclerosis and chronic inflammation. If so—and by analogy with SERMs—we predict that partial PPAR γ agonists/antagonists or modulators hold more promise than potent, pure agonists for the disorders of insulin resistance and type 2 diabetes.

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