Nature Reviews Endocrinology **7**, 630 (2011); published online 27 September 2011; doi:10.1038/nrendo.2011.167

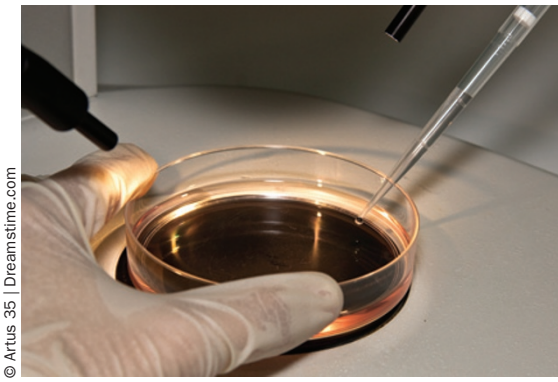
DIABETES

T2DM—PPARγ ligands without the adverse effects?

Thiazolidinediones are agonists for the peroxisome proliferator-activated receptor γ (PPARγ) and are effective agents for the treatment of type 2 diabetes mellitus. Unfortunately, these agents have adverse effects that can include weight gain, fluid retention, an increased risk of congestive heart failure and loss of BMD. Now, Choi *et al.* describe the antidiabetic actions of a nonagonist PPARγ ligand in mice, tempting speculation that a new class of antidiabetic drugs could be developed that would have the antidiabetic actions of thiazolidinediones but not the associated adverse effects.

"We prove that ligands for PPARγ can be antidiabetic without any classical agonism," explains Bruce Spiegelman of Harvard Medical School, one of the study investigators. The researchers describe a novel synthetic compound, SR1664 —a PPARγ ligand that lacks classical transcriptional agonism. Instead, the compound blocks the phosphorylation of PPARγ at serine 273 by cyclin-dependent kinase 5, a mechanism that is now thought to be linked to the therapeutic effects of PPARγ-based agents, including thiazolidinediones.

The investigators show that in mice fed a high-fat diet, SR1664 injected twice daily for 5 days resulted in a trend towards normalization of glucose levels and a significant reduction in fasting insulin levels. Moreover, in treated mice, insulin sensitivity improved. Treatment with SR1664 for 11 days also had antidiabetic actions in leptin-deficient *ob*/*ob* mice, which are obese and insulin resistant. The *ob*/*ob* mice were treated with either the thiazolidinedione rosiglitazone or SR1664. Whereas body weight increase, fluid retention and fat tissue accumulation occurred in the rosiglitazone-treated mice, the SR1664-treated mice experienced none of these adverse effects. Furthermore, SR1664 applied to cells in culture did not affect bone cell mineralization.



Although SR1664 does not have the required pharmacological properties to be administered to patients, Spiegelman comments that the team "will attempt to make ligands with better pharmacology that might be more suitable drug candidates for human therapy". The researchers also want to know how the phosphorylation at serine 273 modifies the function of PPARγ.

Carol Wilson

Original article Choi, J. H. *et al.* Antidiabetic actions of a non-agonist PPARγ ligand blocking Cdk5-mediated phosphorylation. *Nature* doi:10.1038/nature10383