Diabetes drug side effects traced to fat action

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For better or worse, a popular class of anti-diabetic drugs does more than lower blood sugar. One known as rosiglitazone (trade name Avandia) has been in the spotlight for its possible link to increased cardiovascular events, but it also seems to come with unexplained vascular benefits and an unwelcome tendency for weight gain. Now, two separate studies in the July *Cell Metabolism*, a Cell Press publication, explore those other effects of the drugs known collectively as thiazolidinediones (TZDs), both of which stem from their activity in fat.

The findings offer new biological insights into fat tissue and its role as a central component of metabolic control. They may also pave the way for the development of new and better drugs, according to the researchers.

"TZDs have lots of side effects," said Jonathan Graff of the University of Texas Southwestern Medical Center. "We may find ways to replace them with drugs that have fewer."

Earlier studies showed that TZDs remodel fat (adipose) tissue and that they lead to the recruitment of new fat cells known as adipocytes. "TZDs alter adipose tissue to make you fatter," Graff said.

His team wanted to know whether those effects could be traced to adipose stem cells as the source of all those new adipocytes. Adipose stem cells were earlier identified in the walls of the blood vessels that feed adipose tissue, suggesting they might be an accessible target for therapies.

Indeed, they show in mice that rosiglitazone markedly increases the evolution of adipose stem cells into new adipocytes, perhaps explaining why those taking the drugs tend to put on pounds. After two months on the drug, however, the animals' stem cells were "profoundly altered" both molecularly and functionally. At that point, "they don't proliferate in the same way and they no longer form fat cells," Graff said. It was as if the fat cell progenitors had worked overtime and were spent.

The findings offer important evidence that the biology of fat might be altered for therapeutic ends via stem cells, the researchers say. They also provide important new insight into how TZDs work and how they might be improved.

"Although TZDs are effective at lowering blood glucose levels, side effects and concerns that TZDs increase cardiovascular risk have hastened the need to find alternative therapeutics," Graff's team wrote. "A better understanding of whether and how TZDs modulate the adipose lineage may shed light on their insulin-sensitizing efficacy, and may also help to develop the next generation insulin-sensitizers."

In the second study, Yu Huang of Chinese University of Hong Kong and Aimin Xu of the University of Hong Kong tested whether the vascular benefits of rosiglitazone could be connected to the fat-derived hormone adiponectin. Adiponectin is unusual among fat hormones in that its levels generally decline in those who are obese and many earlier studies by Huang and Xu's team and others suggested it might have a protective effect on blood vessels.

In diabetic mice, the researchers found that adiponectin is required for the vascular benefits of treatment with rosiglitazone. Rosiglitazone treatment also stimulated the release of adiponectin from isolated fat tissue, and fat tissue transplanted from treated mice relaxed the blood vessels of untreated diabetic mice.

" Our study emphasizes the importance of adipose tissue-derived adiponectin in response to TZD," Huang said. "This suggests that development of pharmacological agents that can elevate adiponectin, but avoid the undesirable effects of TZDs, may represent an effective therapeutic approach for treating or preventing vascular diseases induced by obesity and diabetes."

He says they have also identified several natural compounds in edible herbs that boost adiponectin levels by other means. They plan to test whether those compounds might have therapeutic use.

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