Scientists find unsuspected molecular link between obesity and insulin resistance

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A new understanding of insulin resistance and the action of diabetes drugs such as Avandia and Actos could pave the way for improved medications that are more selective and safer, say scientists from Dana-Farber Cancer Institute and The Scripps Research Institute.

"Our findings strongly suggest that good and bad effects of these drugs can be separated by designing second-generation drugs that focus on the newly uncovered mechanism," said Bruce Spiegelman, PhD, of Dana-Farber, senior author on a report appearing in the July 22 issue of *Nature*.

Avandia and Actos, known generically as rosiglitazone and pioglitazone, are widely used to counteract the obesity-related abnormalities in insulin response that lead to diabetes. The drugs act on a master regulatory protein called PPAR-gamma, primarily in fat cells, which governs genes involved in the body's response to insulin.

Obesity resulting from a high-fat diet alters the function of PPAR-gamma and disrupts the expression of those insulin response genes, including adipsin and adiponectin. Avandia and Actos work by binding to PPAR-gamma and reversing the gene expression changes.

The drugs were believed to work by stimulating or "agonizing" the PPAR-gamma receptor, causing it to rev up some genes and dampen the activity of others.

In the Nature report, however, the researchers say they have identified "an entirely new and surprising mechanism by which PPAR-gamma can control whole-body insulin sensitivity." It is mainly through this mechanism, they found, that the diabetes drugs counteract insulin resistance - not their agonist effect on PPAR-gamma. Moreover, they say, agonism of PPAR-gamma may be largely responsible for the harmful drug side effects.

The newly identified pathway linking obesity and insulin response involves cdk5, a protein kinase, or molecular "switch." When cdk5 is activated by the development of obesity in mice, it causes a chemical change in PPAR-gamma called phosphorylation. In contrast to agonism of PPAR-gamma, phosphorylation has a narrow effect, disrupting a smaller set of genes that lead to insulin resistance.

In addition to agonizing PPAR-gamma, Avandia and Actos also block the phosphorylation of PPAR-gamma by cdk5. It's this latter effect that accounts for most of the drugs' anti-diabetic benefits, the authors contend. "Agonism may not be therapeutically necessary and likely results in a lot of the toxicities," Spiegelman said.

The strength of various drugs' agonist effects on PPAR-gamma doesn't correlate with how well they work, the researchers observe; instead, it is their ability to block cdk5 phosphorylation that counts. In support of this assertion, the paper describes the researchers' findings from patients treated with Avandia in a German clinical trial. It showed that improvements in insulin sensitivity were tightly correlated with decreased phosphorylation of PPAR-gamma.

"I think this is a really important finding, and potentially very timely in light of the current discussions about Avandia," commented Jeffrey Flier, MD, Dean of the Harvard Medical School, a leading researcher in obesity, insulin resistance, and diabetes.

"It may motivate pharmaceutical companies to take another look at compounds acting through PPAR-gamma that were taken to various stages of development but put on hold because they did not demonstrate strong agonism of PPAR-gamma," Flier said. "People may have been focusing on the wrong outcomes."

Avandia and Actos belong to a relatively new class of compounds called thiazolidinediones, the first medications that can reverse insulin resistance. They have been widely used to treat Type 2 diabetes since being approved in 1999. However, in recent years they have been linked in some patients to heart attacks, heart failure, and strokes. Thousands of lawsuits have been filed against the maker of Avandia, and the US Food and Drug Administration is currently weighing whether it should be taken off the market.

Provided by Dana-Farber Cancer Institute