

# Scientists uncover novel anti-diabetes mechanism

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In a joint study, scientists from The Scripps Research Institute and the Dana-Farber Cancer Institute at Harvard University have uncovered a novel mechanism that dramatically increases insulin sensitivity and reduces the risk of developing type 2 diabetes and cardiovascular disease.

These findings offer a potent new target in the continuing search for new and improved anti-diabetic treatments. Currently, nearly 24 million children and adults in the United States have some form of the disease, according to the American [Diabetes](#) Association.

The new study, which focuses on controlling a fat-regulating protein known as PPAR $\gamma$ , was published July 22, 2010, in the journal *Nature* (Volume 466, Issue 7304).

"The field has become interested in finding drugs that can promote increased insulin [sensitization](#) but not activate the classical fat cell generating pathway of PPAR $\gamma$ ," said Patrick R. Griffin, chairman of the Department of Molecular Therapeutics at Scripps Florida who headed up the Scripps Research part of the study. "We examined the mechanism of action of compounds that bind to PPAR $\gamma$  that improve [insulin sensitivity](#) but have minimal induction of fat. It was clear from the studies that these compounds have a unique but overlapping mechanism with the class of drugs used clinically that target PPAR $\gamma$ ."

Adipose or fat tissue lies at the center of the metabolic syndrome, a

cluster of risk factors that increases the possibility of [type 2 diabetes](#), as well as stroke, coronary artery disease, even certain cancers. Of those risk factors, excessive body fat is considered the most problematic. PPAR $\gamma$  can be considered the master gene of fat cell biology because it drives the conversion of cellular precursors into fat cells.

The collaborative studies showed obesity causes a modification on PPAR $\gamma$  that leads to alterations in the expression of a number of genes, including a reduction in the production of an insulin-sensitizing protein (adiponectin). This leads to an increase in insulin resistance. The reprogramming of genes controlled by PPAR $\gamma$  occurs when it undergoes phosphorylation (a phosphate group is added to a protein) by the cdk5 kinase, an enzyme that is involved in a number of important sensory pathways and that can be activated by pro-inflammatory proteins.

The scientists were able to use both full and partial agonists (compounds that activate a cellular response) to reverse these phosphorylation effects and improve the production of adiponectin. These results strongly suggest that cdk5-mediated phosphorylation is involved in the development of insulin-resistance and open the door to a novel opportunity for creating an improved generation of anti-diabetic drugs.

## Pointing the Way

In 2007, Griffin and his colleagues published a study in the journal *Structure* (October 16, 2007, Volume 15, Number 10, pp.1258-1271) that explained the difference between how full and partial agonists interacted with PPAR $\gamma$ . Full agonists interacted strongly with a region of the receptor known to be important for the classical fat generation program. On the other hand, partial agonists, which are poor agonists of the receptor, did not interact with this region at all but interacted more strongly with a potentially critical region of the receptor. From a drug development point of view, these results offered a new area of the

[protein](#) to focus on to optimize therapeutic molecules that would be potent insulin sensitizers without driving fat generation.

"Bruce Spiegelman at Dana-Farber was starting to uncover the fact that the phosphorylation of PPAR $\gamma$  takes place in the very region where MRL-24, one of the partial agonists interacted," Griffin said. "I suggested that compounds like MRL24 might be better at antagonizing the cdk5 site given their strong interaction in this region of the receptor. For the new study, we provided significant amounts of compound to support the animal studies and provided an plausible mechanism for how partial agonists might recruit co-activator proteins to the cdk5 surface of PPARg."

While the team found that PPAR $\gamma$  phosphorylation effects were reversed by both full and partial agonists, partial agonists indeed accomplished this as well or better than the full agonists. Mimicking the effects of just blocking the phosphorylation event by mutation of the site on the receptor showed improvements in the production of adiponectin.

The new study also suggests a unified framework for understanding the relationship between [fat cell](#) dysfunction in obesity and anti-diabetic therapies based on PPAR $\gamma$ . In animal studies, high fat diets activate the cdk5 kinase, initiating phosphorylation, disrupting a number of key metabolic regulators including adiponectin and adipsin, a fat cell-selective gene whose expression is altered in obesity.

"The great paradox of this whole effort is we're targeting a receptor critical for fat production to offset the problem of fat overproduction," Griffin said. "Unfortunately, current drugs that target PPARg increase fat as one of their unwanted long-term side effects."

While the study is a big step forward, important questions still remain such as does a high fat diet and obesity lead to activation of cdk5 in non-

fat tissues, Griffin said, since the negative effects of obesity extend far beyond metabolic syndrome to diseases like cancer and neurodegeneration.

**More information:** "Anti-diabetic drugs inhibit obesity-linked phosphorylation of PPAR $\gamma$  by Cdk5," Jang Hyun Choi, et al. *Nature* Volume 466, Issue 7304

Provided by The Scripps Research Institute

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