Scientists establish a new class of anti-diabetic compound

September 4 2011

In a joint study, scientists from The Scripps Research Institute and Harvard University's Dana-Farber Cancer Institute have established a new class of anti-diabetic compound that targets a unique molecular switch.

The finding paves the way for the development of anti-diabetic therapeutics with minimal adverse side effects plaguing currently available drugs such as Avandia (rosiglitazone), scheduled to be removed from pharmacy shelves this fall due to concerns about increased risk of heart attack.

The new study, led by Patrick R. Griffin, professor and chair of the Department of Molecular Therapeutics at Scripps Florida, Bruce Spiegelman, professor of cell biology at the Dana-Farber Cancer Institute, and Theodore Kamenecka, associate scientific director of medicinal chemistry at Scripps Florida, was published September 4, 2011, in the journal *Nature*. The study describes a new compound known as SR1664.

"In this study, we demonstrate that we have discovered novel compounds that work effectively through a unique mechanism of action on a well-validated clinical target for diabetes," said Griffin. "This unique mechanism of action appears to significantly limit side effects associated with marketed drugs. This study is a great example of interdisciplinary, inter-institutional collaboration with chemistry, biochemistry, structural biology, and pharmacology."

"It appears that we may have an opportunity to develop entire new classes of drugs for diabetes and perhaps other metabolic disorders," said Spiegelman.

Diabetes affects nearly 24 million children and adults in the United States, according to the America Diabetes Association.

A Viable Therapeutic Target

The study follows previous research by the authors published last year in Nature (Volume 466, Issue 7305, 451-456) that suggested an obesity-linked mechanism that may be involved in the development of insulin-resistance. In that research, the team found disruptions in various genes when a protein known as PPARγ undergoes phosphorylation (when a phosphate group is added to a protein) by the kinase Cdk5, an enzyme involved in a number of important sensory pathways.

The new study confirms that blockage of Cdk5's action on PPARG is a viable therapeutic approach for development of anti-diabetic agents. The new SR1664 compound is a potent binder to the nuclear receptor PPARG, but does not activate gene transcription via the receptor's normal mechanism.

While Griffin stressed the difficulty of fully assessing side effects of new compounds such as SR1664, the new research is extremely positive in that it clearly demonstrated fewer of the major well-documented side effects, such as weight gain or increased plasma volume, from SR1664 as compared to Avandia in diabetic mice.

While both the mice treated with Avandia and those treated with SR1664 demonstrated improved blood sugar levels, those treated with Avandia showed weight gain and increased fluid retention within a few days of beginning treatment; those being treated with SR1664 showed

none of these side effects. In cell culture studies, SR1664 also appeared to have little effect on bone formation, nor did it increase fat generation in bone cells, another side effect of current therapies such as Avandia.

While S1664 likely will not be developed as a drug, it now serves as a molecular scaffolding for the creation of similar compounds with potential to treat diabetes. "With data in hand showing that our compounds are as efficacious as the currently marketed PPARG modulators, while demonstrating a significant improvement of side effects in limited studies, we are now advancing newer compounds with improved pharmaceutical properties into additional studies," Griffin said.

More information: "Anti-Diabetic Actions of a Non-Agonist PPARG Ligand Blocking Cdk5-Mediated Phosphorylation," by Jang Hyun Choi, Alexander S. Banks, et al, *Nature*.

Provided by The Scripps Research Institute