New biological pathway discovery may help scientists redesign certain diabetes drugs to reduce adverse side effects

October 9 2012

University of Iowa team discovers new biological pathway in blood vessel cells, which may contribute to the blood pressure-lowering effects of TZD drugs used to treat Type 2 diabetes. This finding may help to develop new therapies that retain the beneficial effect of TZDs but eliminate the adverse side effects.

Many drugs work by "fixing" a particular biological pathway that's gone awry in a disease. But sometimes drugs affect other pathways too, producing undesirable side effects that can be severe enough to outweigh the drug's benefits.

Such is the case for the thiazolidinedione drugs (also known as TZDs), which are used to treat type 2 diabetes. These are highly effective in controlling blood glucose levels and have an added benefit of lowering blood pressure in some patients. However, TZDs cause unrelated but potentially severe side effects in some patients, including heart failure, bone fracture, and to a lesser degree heart attack or bladder cancer depending on the specific TZD. The actual risks vary depending upon a patient's specific circumstances. Nonetheless, because of increased recognition of these unwanted effects, the rate of new TZD prescriptions is on the decline.

"We wanted to discover how TZDs lower blood pressure, so that more specific drugs might be developed that retain the beneficial effect of

TZDs but eliminate the detrimental side effects," says Curt Sigmund, Ph.D., professor and head of pharmacology at the UI Carver College of Medicine, and senior author of a new study published Oct. 3 in the journal Cell Metabolism.

The TZD drugs activate a protein called PPAR-gamma. Genetic mutations in this protein disrupt the normal function of blood vessels and cause high blood pressure in people.

Sigmund and his colleagues wanted to home in on the function of PPAR-gamma in blood vessel, so they created a genetically modified mouse where the PPAR-gamma expressed in the blood vessels was mutated. These mice developed high blood pressure.

Using these mice to study how disruption of PPAR-gamma leads to high blood pressure, the researchers uncovered a new biological pathway (called the Cullin-3 pathway) in blood vessels, which may be the key to the blood pressure-lowering effects of TZD drugs.

The study showed that the activity of Cullin-3 in blood vessels is important for maintaining normal blood pressure, and decreased activity of Cullin-3, through disruption of PPAR-gamma, leads to increased blood pressure.

The study results may also help explain another recent finding that mutations in Cullin-3 cause early onset hypertension in people.

Sigmund notes that early research in mice has shown that new molecules, which target PPAR-gamma in new ways, do not have the side effects of TZDs. Whether these new drugs work through the Cullin-3 pathway identified by the UI team will require additional research, he says.

"Our study has added importance because some drugs, which target

Cullin-3 and other Cullin proteins, are currently being tested as chemotherapies," adds Sigmund, who also directs the Center for Functional Genomics of Hypertension. "Our findings suggest that blood pressure will have to be monitored in patients undergoing these treatments."

Provided by University of Iowa