

The San Diego
Union-Tribune.

Scientists make advance against Type 2 diabetes

By: Bradley Fikes | March 27, 2017

Type 2 diabetes has been reversed in mice with a new, orally available drug, according to a study led by San Diego scientists. The study suggests a path for developing human therapies based on the drug. The drug protected mice from high-fat induced diabetes without affecting body weight, according to the study. It also reversed signs of the disease in mice who already had it.

Type 2 diabetes is caused by insulin resistance. While the pancreatic islets still make insulin, the hormone doesn't work as well. Cells sense insulin through receptors, which become less effective in this type of diabetes. Scientists led by physician-researcher Nunzio Bottini countered insulin resistance by designing a drug that restored the effectiveness of insulin receptors.

The scientists are seeking pharmaceutical industry partners to help turn the research into a commercializable drug, Bottini said. He estimated that once a deal is reached, it would take about two years to complete the additional work needed to get approval to start a human clinical trial. Bottini conducted the research at the La Jolla Institute for Allergy & Immunology, where he holds an adjunct appointment, and at UC San Diego School of Medicine, his primary appointment.

The drug inhibits an enzyme called a low-molecular-weight protein tyrosine phosphatase, or LMPTP. It's part of a family of enzymes that inactivates the insulin receptor. By inhibiting this particular enzyme in the liver, insulin receptor effectiveness was restored.

"Our findings suggest that LMPTP activity plays a key role in the development of insulin resistance and that LMPTP inhibitors would be beneficial for treating type 2 diabetes," the study stated.

The study was published Monday in Nature Chemical Biology. It can be found at j.mp/diabetestyr. Bottini was senior author. Stephanie M. Stanford, also of the La Jolla Institute and UCSD, was first author.

A choosy molecule

"This work occurred through a wonderful collaboration between our group and a team led by Tony Pinkerton at the Sanford Burnham Prebys Medical Discovery Institute," Bottini said.

While the role of protein tyrosine phosphatases in Type 2 diabetes has been known for years, many enzymes in this family perform other functions, and drugs against these enzymes may also affect other targets.

“They are traditionally considered very difficult enzymes to drug, because it’s very hard to get a compound which is selective for one of those enzymes vs. others,” Bottini said. The drug arising from the research is exceptionally selective in its activity, the researchers said, reducing the chance of side effects.

“We envision that the information we collected about its mechanism of action and binding mode will pave the way for development of LMPTP inhibitors suitable for therapeutic testing in human diabetes,” the study stated. “Since LMPTP has also been proposed to promote heart failure and tumor growth, such inhibitors are predicted to have a wide range of therapeutic applications.”

Stroke, Alzheimer’s disease, cognitive decline and polycystic ovary syndrome are among the other diseases that have been linked to insulin resistance. “We hope there will be additional indications from this compound,” Bottini said. “We are looking into heart failure.” Deletion of the gene for LMPTP protects against heart failure, although the mechanism isn’t clear, he said.

Promising outlook

The study points to an important potential route for relieving Type 2 diabetes, said Athena Philis-Tsimikas, M.D., corporate vice president for the Scripps Whittier Diabetes Institute.

“Two defects underlie the development of diabetes; an increase in insulin resistance and, simultaneous reduction in insulin secretion from beta cells,” said Philis-Tsimikas, who was not involved in the study, by email. “So, any improvements in insulin resistance would be very valuable in improving diabetes. The mechanism described in the paper is fascinating and has potential for improving glucose control.”

Some existing medications relieve insulin resistance and reduce blood sugar levels, she said, but they have unpleasant side effects such as fluid retention and weight gain. So new medications that can address the disease mechanism with fewer side effects are always needed. Scripps Whittier Diabetes Institute does a lot of Phase 2 and 3 trials, and has seen a number of experimental drugs get marketing approval, she said.

“The mechanisms for these new agents look promising, and it is encouraging that the science is progressing especially here in San Diego,” she said. “Researchers started their search by screening 364,168 small-molecule compounds from the National Institutes of Health Molecular Libraries Small Molecule Repository.

They found three “hits,” or molecules active against the target. One was selected for further study because of its potency and specificity. Using medicinal chemistry, the researchers tweaked the molecule to make it more potent. One of the resulting compounds was then tested in live mice.

The La Jolla Institute for Allergy and Immunology and Sanford Burnham Medical Discovery Institute hold a pending patent on the discovery. The researchers were funded by grants from the National Institutes of Health and the American Diabetes Association.