

# Research team tests alternative approach to treating diabetes

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In a mouse study, scientists at Mayo Clinic Florida have demonstrated the feasibility of a promising new strategy for treating human type 2 diabetes, which affects more than 200 million people worldwide.

In type 2 diabetes, the body stops responding efficiently to insulin, a hormone that controls [blood sugar](#). To compensate for the insensitivity to insulin, many [diabetes drugs](#) work by boosting [insulin levels](#); for example, by injecting more insulin or by increasing the amount of insulin secreted from the pancreas. The new study, published in the June 9 issue of *PLoS ONE*, showed that a different approach could also be effective for treating diabetes - namely, blocking the breakdown of insulin, after it is secreted from the [pancreas](#).

"Insulin levels in the blood reflect the balance between how much is secreted and how fast it is broken down," says the study's lead researcher, Malcolm A. Leissring, Ph.D., from Mayo Clinic's Department of Neuroscience. "Blocking the breakdown of insulin is simply an alternative method for achieving the same goal as many existing diabetes therapies."

The researchers tested this idea by studying mice in which insulin-degrading enzyme (IDE) was "knocked out," or deleted genetically. IDE is a molecular "machine" that normally chews up the insulin hormone, breaking it down into smaller pieces. Levels of insulin in the blood are controlled, in part, by this process.

Compared to normal mice, IDE knockout mice had more insulin overall, weighed less, and were more efficient at controlling their blood sugar. They were, in effect, "super mice" with respect to their ability to lower their blood sugar after a meal, the process that is disrupted in diabetes, explains Dr. Leissring.

These findings suggest that drugs that inhibit IDE could be useful in treating diabetes. Dr. Leissring's team is actively working to develop such drugs. As reported in a separate study in *PLoS ONE* last year, Dr. Leissring and colleagues developed the first potent and selective inhibitors of IDE. The Mayo team has now developed more drug-like IDE inhibitors that they are preparing to test in animal models of diabetes.

"The reason we studied IDE knockout mice was to help us understand whether IDE inhibitors would be useful for treating diabetes," says Samer Abdul-Hay, Ph.D., first author on the study. But the IDE knockout mice are not a perfect model of how a drug will perform, he notes. "They are actually a better model of overdosing on an IDE inhibitor. We would never want a drug that inhibits IDE 100 percent in all tissues throughout life."

The effect of deleting all IDE in the mice was so strong, in fact, that the effect eventually backfired, the researchers say. Despite being "super mice" when young, as the IDE knockout mice aged, they slowly became resistant to the elevated insulin, gained weight, and lost control of their blood sugar. As a result, the older mice developed classic type 2 diabetes.

"The finding that older IDE knockout mice develop diabetes has confused a lot of people," says Dr. Leissring. "It's an example of too much of a good thing becoming bad for you." Drugs that inhibit IDE only partially or only transiently would not be expected to cause diabetes,

he says. "Deleting all IDE is overkill."

The researchers say the Mayo study also has interesting implications for understanding how diabetes starts. "Deleting IDE produces elevated insulin levels - a condition known as hyperinsulinemia. Diabetes is usually believed to cause hyperinsulinemia, not the other way around," Dr. Leissring says. Nevertheless, in the IDE [knockout mice](#), chronic hyperinsulinemia seemed to actually cause diabetes. As they aged, the mice appeared to adapt to the chronically high insulin levels, for example, by reducing the number of receptors for insulin in their tissues. "These adaptations make the mice less sensitive to [insulin](#), which is the exact cause of [type 2 diabetes](#)."

Whether these findings apply to humans is unclear, Dr. Leissring cautions. He says these novel findings "represent early, but exciting days" in a new avenue of diabetes research. Dr. Leissring was recently awarded a five-year career development grant from the American [Diabetes](#) Association, which will help support this line of research.

Provided by Mayo Clinic

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