

A promising new pathway to treating type 2 diabetes

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Benjamin Renquist, an association professor in the UArizona School of Animal and Comparative Biomedical Research. Credit: University of Arizona

This year marks the 100th anniversary of the discovery of insulin, a scientific breakthrough that transformed Type 1 diabetes, once known as juvenile diabetes or insulin-dependent diabetes, from a terminal disease into a manageable condition.

Today, Type 2 diabetes is 24 times more prevalent than Type 1. The rise in rates of obesity and incidence of Type 2 diabetes are related and require new approaches, according to University of Arizona researchers, who believe the liver may hold the key to innovative new treatments.

"All current therapeutics for Type 2 diabetes primarily aim to decrease blood glucose. So, they are treating a symptom, much like treating the flu by decreasing the fever," said Benjamin Renquist, an associate professor in the UArizona College of Agriculture and Life Sciences and BIO5 Institute member. "We need another breakthrough."

In two newly published papers in *Cell Reports*, Renquist, along with researchers from Washington University in St. Louis, the University of Pennsylvania and Northwestern University, outline a new target for Type 2 diabetes treatment.

Renquist, whose research lab aims to address obesity-related diseases, has spent the last nine years working to better understand the correlation between obesity, [fatty liver disease](#) and diabetes, particularly how the liver affects insulin sensitivity.

"Obesity is known to be a cause of Type 2 diabetes and, for a long time, we have known that the amount of fat in the liver increases with obesity," Renquist said. "As fat increases in the liver, the incidence of diabetes increases."

This suggested that fat in the liver might be causing Type 2 Diabetes, but how fat in the liver could cause the body to become resistant to insulin or cause the pancreas to over-secrete insulin remained a mystery, Renquist said.

Renquist and his collaborators focused on fatty liver, measuring neurotransmitters released from the liver in animal models of obesity, to

better understand how the liver communicates with the brain to influence metabolic changes seen in obesity and diabetes.

"We found that fat in the liver increased the release of the inhibitory neurotransmitter Gamma-aminobutyric acid, or GABA," Renquist said.

"We then identified the pathway by which GABA synthesis was occurring and the key enzyme that is responsible for liver GABA production—GABA transaminase."

A naturally occurring amino acid, GABA is the primary inhibitory neurotransmitter in the central nervous system, meaning it decreases nerve activity.

Nerves provide a conduit by which the brain and the rest of the body communicate. That communication is not only from the brain to other tissues, but also from tissues back to the brain, Renquist explained.

"When the liver produces GABA, it decreases activity of those nerves that run from the liver to the brain. Thus, fatty liver, by producing GABA, is decreasing firing activity to the brain," Renquist said. "That decrease in firing is sensed by the central nervous system, which changes outgoing signals that affect glucose homeostasis."

To determine if increased liver GABA synthesis was causing insulin resistance, graduate students in Renquist's lab, Caroline Geisler and Susma Ghimire, pharmacologically inhibited liver GABA transaminase in animal models of Type 2 diabetes.

"Inhibition of excess liver GABA production restored insulin sensitivity within days," said Geisler, now a postdoctoral researcher at the University of Pennsylvania and lead author on the papers. "Longer term inhibition of GABA-transaminase resulted in decreased food intake and weight loss."

Researchers wanted to ensure the findings would translate to humans. Kendra Miller, a research technician in Renquist's lab, identified variations in the genome near GABA transaminase that were associated with Type 2 [diabetes](#). Collaborating with investigators at Washington University, the researchers showed that in people with insulin resistance, the [liver](#) more highly expressed genes involved in GABA production and release.

The findings are the foundation of an Arizona Biomedical Research Commission-funded clinical trial currently underway at Washington University School of Medicine in St. Louis with collaborator Samuel Klein, co-author on the study and a Washington University professor of medicine and nutritional science. The trial will investigate the use of a commercially available Food and Drug Administration-approved inhibitor of GABA transaminase to improve insulin sensitivity in people who are obese.

"A novel pharmacological target is just the first step in application; we are years away from anything reaching the neighborhood pharmacy," Renquist said. "The magnitude of the obesity crisis makes these promising findings an important first step that we hope will eventually impact the health of our family, friends and community."

More information: Caroline E. Geisler et al, A critical role of hepatic GABA in the metabolic dysfunction and hyperphagia of obesity, *Cell Reports* (2021). [DOI: 10.1016/j.celrep.2021.109301](https://doi.org/10.1016/j.celrep.2021.109301)

Provided by University of Arizona

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