Pill that targets gut receptor treats fatty liver disease, obesity in mice

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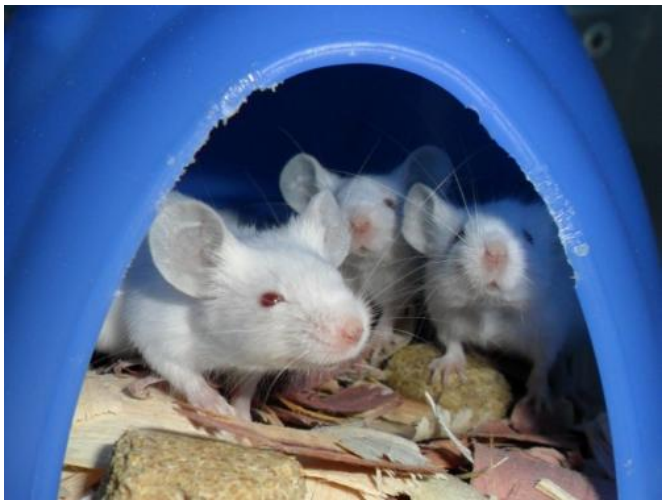

Credit: Martha Sexton/public domain

A bile acid that can turn off a receptor in the gut has prevented and reversed fatty liver disease in mice, according to an international team of researchers. The compound may help treat certain metabolic disorders, such as Type 2 diabetes and obesity, as well.

Obese and diabetic mice fed glycine-beta muricholic acid—Gly-MCA—pills with a high-fat diet had significantly less fat and less insulin resistance than the untreated control group, according to Andrew Patterson, associate professor of molecular toxicology, Penn State.

The researchers, who report their findings today (Dec. 15) in *Nature Communications*, showed that Gly-MCA can inhibit the farnesoid X receptor—FXR—a transcription factor that regulates the expression of certain genes in tissues like those of the intestine and liver.

"Depending on the balance of conjugated and unconjugated bile acids, bacteria can modify these bile acid pools and turn off or turn on this receptor—FXR—in the gut," said Frank Gonzalez, chief of the laboratory of metabolism, National Cancer Institute.

FXR plays a key role in maintaining metabolism by sensing and regulating bile acids, fats and glucose in the body, Gonzalez said. He added that the receptor's role in the production and metabolism of fat may help explain part of the treatment's anti-obesity effect, although that will be the subject of future research.

Patterson said the mice ate only a small amount of the compound to lead to metabolic benefits. For a human, the equivalent would be a single dose in pill form once a day. He added that the treatment worked for both diet- and genetic-based forms of fatty liver disease and obesity.

Previous research identified FXR as a possible target for fatty liver disease and obesity treatment, but the researchers faced several challenges in finding a compound that could operate in the complex and chaotic intestinal system, Gonzalez said.

A group of researchers at Penn State Hershey College of Medicine who helped create the drug are hopeful that larger quantities could be produced economically.

"The preparation of a large quantity of the drug constituted a big challenge since very limited information was available in the literature and the drug was not commercially available," said Dhimant Desai, associate professor of pharmacology, Penn State University College of Medicine, who worked with Gonzalez and Patterson.

Because bacteria, such as Lactobacillus, typically break down the bile acids that inhibit FXR, the researchers had to screen a large group of these bile acids to find ones that were bacteria-resistant.

Gly-MCA was resistant to the enzymatic activity of Lactobacillus, Patterson said.

"Ideally what we would like to do is start looking at whether we can improve upon the current molecule to make more effective derivatives of Gly-MCA that are more resistant to bacterial hydrolyses and more potent at selectively inhibiting FXR," Patterson said.

Other compounds—and, perhaps more effective ones—are the focus of future research, as well.

"The direction of this study is innovative and may open new avenues towards treating fatty liver, a very prevalent metabolic disorder in humans," said Desai.

While the researchers are hopeful for a pill that could treat fatty liver disease in humans, Patterson cautioned that a lot of work remains to better understand this mechanism. The compound must also be tested in multiple species and then pass human trials before it is approved.

The use of bile acids as medicine is rare in Western cultures, but they have been used in a variety of medical treatments in Asian cultures and in ancient medical practices, according to Patterson.

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