Genetically engineered mice don't get obese (w/Podcast)

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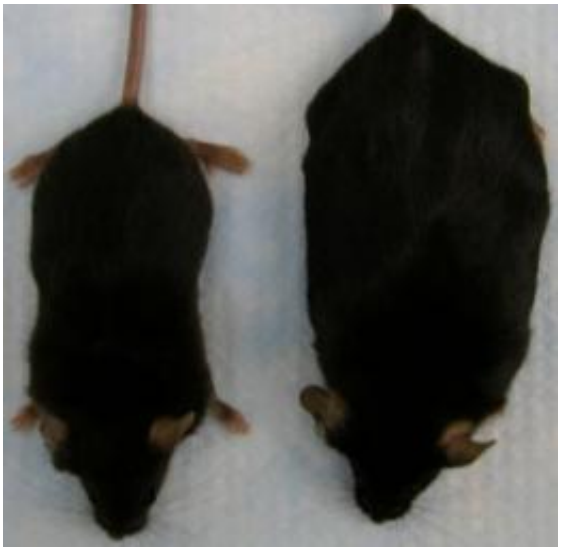

Mice lacking the L-Fabp gene (left) don't become obese on a high-fat diet like normal mice. But while they remain lean, the L-Fabp mice do develop gallstones at high rates. Credit: Washington University School of Medicine

Obesity and gallstones often go hand in hand. But not in mice developed at Washington University School of Medicine in St. Louis. Even when these mice eat high-fat diets, they don't get fat, but they do develop gallstones. Researchers say the findings offer clues about genetic factors related to gallstones, and they believe better understanding of those factors may one day allow physicians to monitor people at risk and even, perhaps, to intervene before gallstones become a serious problem.

Learning more about susceptibility to gallstones is an important public health issue, particularly in the United States. Between 16 million and 22 million Americans have gallstones, which are deposits of cholesterol or calcium salts that form in the gallbladder or in the bile ducts. In many cases, people require surgery, and more than half a million undergo operations to treat gallstones and remove the gallbladder each year.

"Gallstones form when cholesterol is secreted in bile from the liver at high concentrations, and that typically happens in patients who are obese, who have diabetes, take estrogens or who have lost a lot of weight very rapidly," says senior investigator Nicholas O. Davidson, M.D., D.Sc., a Washington University gastroenterologist at Barnes-Jewish Hospital. "Since these mice don't become obese, we thought they might be protected against gallstones. But we found that they were dramatically more susceptible."

The researchers studied a strain of mice without a substance called liver fatty acid binding protein (L-Fabp). Davidson's group compared those genetically engineered mice to their healthy, normal littermates. Both groups of mice ate either a standard chow diet or a more typical "Western" diet that provided about 20 percent of its calories in the form of fat and cholesterol.

After two weeks on the Western diet, only one in 17 of the normal mice developed gallstones, but six of the eight mice without L-Fabp had gallstones. Davidson's team reports its findings in the May issue of the *Journal of Lipid Research*.

Davidson says in addition to risk factors such as diabetes and obesity, these experiments show genetic factors play a role in gallstone risk. The L-Fabp gene, which both mice and humans have, may be a key to understanding how genes can predispose to cholesterol gallstone formation.

"The L-Fabp gene is located in a part of the mouse genome that appears likely to be involved in genetic susceptibility to gallstones," Davidson says. "We believe it also may be involved in gallstone susceptibility in humans."

He says that although minimally invasive gallbladder surgery has made gallstone problems much less serious than in the past, sometimes the symptoms can be severe and dramatic.

"Patients can develop acute pancreatitis or ascending cholangitis, which occurs when gallstones obstruct the pancreatic or bile duct and become infected," he explains. "Even without those problems, gallstones can cause severe, recurrent abdominal pain in a very large number of people. So better understanding who is susceptible and learning how to safely intervene could be very important for people at risk."

How the L-Fabp protein may be contributing to gallstone formation in the genetically engineered mice is likely to be complex. Davidson believes the problem may be related to abnormal processing of cholesterol and altered bile metabolism in the small intestine and liver of these genetically engineered mice. The mice also are lean, and he expects that whatever is happening in these mice to produce gallstones will involve complex interactions of other genes that regulate energy utilization and feeding behavior.

Davidson says more studies of the mice lacking L-Fabp may provide scientists with tools that separate obesity from obesity-related problems. For example, prior to this gallstone finding, the team reported L-Fabp deficient mice on a high-fat diet also develop insulin resistance like their normal littermates.

"That finding demonstrated that although these mice remain lean and have less fat in the liver, they still develop insulin resistance, a problem

usually associated with obesity," Davidson says.

Why the mice don't become obese is not yet known. Davidson says part of the reason may be the mice burn energy more efficiently or they may not eat as much as their normal littermates. He believes the mechanisms likely will take time to sort out.

Davidson's team now is working to determine how L-Fabp operates in the digestive tract. His group is studying mice with tissue-specific deletion of the fatty acid binding protein in either the liver or the small intestine to see how that affects gallstone risk. He also plans to study variations in the human gene to see whether those genetic changes affect the risk of gallstone development.

More information: Xie Y, Newberry EP, Kennedy SM, Luo J, Davidson NO. Increased susceptibility to diet-induced gallstones in liver fatty acid binding protein knockout mice. *Journal of Lipid Research*, vol. 50, pp. 977-987, May 1, 2009.

Source: Washington University School of Medicine (news : web)