Food additive may one day help control blood lipids and reduce disease risk

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Scientists at Washington University School of Medicine in St. Louis have identified a substance in the liver that helps process fat and glucose. That substance is a component of the common food additive lecithin, and researchers speculate it may one day be possible to use lecithin products to control blood lipids and reduce risk for diabetes, hypertension or cardiovascular disease using treatments delivered in food rather than medication.

"Currently, doctors use drugs called fibrates to treat problems with cholesterol and triglycerides," says the study's co-first author Irfan J. Lodhi, Ph.D., a post-doctoral fellow in endocrinology and metabolism. "By identifying this substance that occurs naturally in the body — and also happens to be used as a food additive — it may be possible to improve the treatment of lipid disorders and minimize drug side effects by adding particular varieties of lecithin to food."

Lecithin is found at high concentrations in egg whites. It also is in soybeans, grains, fish, legumes, yeast and peanuts. Most commercially used lecithin comes from soybeans. Lecithin can alter food taste and texture and also can be mixed with water to disperse fats, making it a common additive in margarine, mayonnaise, chocolate and baked goods. Lecithin is a mixture of fatty compounds called phosphatidylcholines. Various types of phosphatidylcholines house different kinds of fatty molecules linked to a common core.

This new study demonstrates that in the liver, a specific type of lecithin

binds with a protein called PPAR-alpha, allowing PPAR-alpha to regulate fat metabolism. Scientists long have known that PPAR-alpha is involved in lipid and glucose metabolism. When doctors prescribe fibrate drugs to lower triglycerides and elevate good cholesterol in the blood, those drugs work by activating PPAR-alpha.

Although fibrates activate the protein, no one previously had identified any naturally occurring substance that could perform that task. Reporting in the Aug. 7 issue of the journal *Cell*, the Washington University research team describes how it found the link between lecithin and PPAR-alpha.

They first created a strain of mice that could not make fatty acid synthase in the liver. When humans or animals eat, we take in sugars. Fatty acid synthase converts those sugars to fatty acids in the liver, where they play important roles in energy metabolism.

"To our surprise, animals missing fatty acid synthase in the liver were just like animals that couldn't make PPAR-alpha. They had lower fasting insulin levels, and they were prone to develop fatty liver disease," says senior investigator Clay F. Semenkovich, M.D., the Herbert S. Gasser Professor and chief of the Division of Endocrinology, Metabolism and Lipid Research. "When we gave the animals fibrate drugs that activated PPAR-alpha, the mice returned to normal, leading us to suspect that fatty acid synthase also was involved in the activation of PPAR-alpha. Although we knew that fibrate drugs would regulate PPAR-alpha, we also knew that our ability to regulate the metabolism of fats and sugars was in place long before humans started making drugs. But until now, no one had identified how it worked."

Semenkovich, Lodhi, John Turk, M.D. Ph.D., professor of medicine and of pathology, and the rest of the team used mass spectrometry and gene expression studies to isolate the phosphatidylcholine, or lecithin

compound, that activated PPAR-alpha in the liver.

One reason fatty acid synthase had never been connected to PPAR-alpha function was the distance of the two proteins from each other, according to Semenkovich. PPAR-alpha is a nuclear receptor. That is, it's housed in the nucleus of the cell. Fatty acid synthase, on the other hand, lives out in the cell body, or cytoplasm.

"The neighborhoods where PPAR-alpha and fatty acid synthase live aren't very close together," says Semenkovich. "The synthase is way out in the cytoplasm — that's like being in the suburbs — whereas the PPAR-alpha lives right in the middle of the 'city.' These are all microscopic distances, but to the cell, they're worlds apart, so it's amazing that the two are linked."

It's also fortunate, he says, that an extremely common compound like lecithin binds to a key drug target like PPAR-alpha.

"That information could be used to make better drugs or even to develop what people sometimes refer to as nutriceuticals — nutrients that have pharmaceutical-like properties," Semenkovich says.

More information: Chakravarthy MV, Lodhi IJ, Malapaka RV, Xu HE, Turk J, Semenkovich CF. Identification of a physiologically relevant endogenous ligand for PPARα in liver. *Cell*, vol. 138, pp. 1-13, Aug. 7. 2009

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