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HIV Drugs Interfere With Blood Sugar, Lead to Insulin Resistance

The same powerful drugs that have extended the lives of countless people with HIV come with a price -- insulin resistance that can lead to diabetes and cardiovascular disease.

Now, researchers at Washington University School of Medicine in St. Louis have determined why that happens. Their research shows that HIV protease inhibitors directly interfere with the way blood sugar levels are controlled in the body. This leads to insulin resistance, a condition that occurs when the body produces enough insulin but doesn't use it properly.

This confirmation provides the potential to develop safer antiviral drugs.

Paul Hruz, MD, PhD, assistant professor of pediatrics and of cell biology and physiology at the School of Medicine, and his team found that first-generation protease inhibitors, including the drug ritonavir, block GLUT4, a protein that transports glucose from the blood into the cells where it is needed. This raises blood sugar levels -- a hallmark of diabetes.

"Our lab has established that one of the effects of these drugs is blocking glucose transport, one of most important steps in how insulin works," says Hruz, senior author of the study published in the Nov. 19 Journal of Biological Chemistry. "Now that we've identified the main mechanism, we will look to develop new drugs that treat HIV but don't cause diabetes."

Hruz's lab made the discovery in mice that lacked the GLUT4 protein. When researchers gave these mice ritonavir, the drug had no effect on their glucose tolerance. However, when they gave the drug to normal mice, their blood glucose shot up very quickly, showing that the drugs impair glucose

tolerance and promote insulin resistance.

"What we saw were very acute effects on insulin sensitivity that we could reverse in the mice," Hruz says. "But when insulin resistance goes on for a long time, secondary changes develop, such as high triglycerides, and those are harder to reverse," he says.

The finding will help researchers better understand the role of glucose transporters in health and disease, including the epidemic of type 2 diabetes in HIV negative patients, says Hruz. He expects the results will help scientists better understand how to develop new diabetes drugs and the role of glucose transport in diseases such as heart failure.

Hruz and his team are now studying at the molecular level how the HIV drugs inhibit GLUT4.

"We'd like to figure out exactly how these drugs interact with the transporter to aid the development of better HIV drugs," he says. "We want to find problems in glucose transport that lead to diabetes in the preclinical stage of drug development."

The team already is working with a drug developer to create a new HIV drug that the virus does not develop resistance to and does not block GLUT4.

Vyas A, Koster J, Tzekov A, Hruz, P. Effects of the HIV Protease Inhibitor Ritonavir on GLUT4 Knock-out Mice. Journal of Biological Chemistry. Nov. 19, 2010.

Editor's Note: This article is not intended to provide medical advice, diagnosis or treatment.