UT SOUTHWESTERN MEDICAL CENTER NEWS

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Circuit regulating anti-diabetic actions of serotonin uncovered by UT Southwestern researchers

DALLAS – Nov. 11, 2010 – New findings by researchers at UT Southwestern Medical Center suggest that serotonin – a brain chemical known to help regulate emotion, mood and sleep – might also have anti-diabetic properties.

The findings, appearing online this week in *Nature Neuroscience*, also offer a potential explanation for why individuals prescribed certain kinds of anti-psychotic drugs that affect serotonin signaling sometimes have problems with their metabolism, including weight gain and the development of diabetes.

"In this paper, we describe a circuit in the brain that may explain the anti-diabetic actions of serotonin-receptor signaling," said Dr. Joel Elmquist, professor of internal medicine and pharmacology at UT Southwestern and senior author of the study. "This discovery tells us that drugs that affect serotonin action can have anti-diabetic actions independent of body weight and feeding."

For the current study, the researchers engineered a mouse model in which the expression of a serotonin receptor called 5-hydroxytryptamine 2C was blocked throughout the entire body. Without functioning receptors, the mice developed insulin resistance in their livers.

Previous research has implicated these receptors in the brain in the regulation of energy balance and glucose metabolism throughout the body. When activated by serotonin, this receptor also is known to suppress appetite. Until now, however, it was unclear which type of neuron in the brain mediated the effects of serotonin to regulate glucose, or blood sugar, levels.

To find out, the study authors engineered another set of mice in which the same serotonin receptor was blocked everywhere except within a group of brain cells called pro-opiomelanocortin, or POMC, neurons. The POMC neurons, which are found in the hypothalamus, are also known to play an important role in suppressing appetite and inducing weight loss.

The researchers found that when they reactivated the serotonin receptor only in the POMC neurons, the mice no longer displayed insulin resistance in the liver. Restoring the receptor essentially protected the mice from developing the metabolic problems usually found in mice which lack the receptor throughout the body.

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Dr. Elmquist said that even though the findings are in mice, they do provide potential insight into blood glucose control in humans.

"It also further reinforces our previous findings that specific subsets of POMC neurons within the brain are responsible for the regulation of liver function and blood sugar metabolism," Dr. Elmquist said.

The next step, he said, is to determine what happens to feeding, body weight and liver metabolism in mice engineered to lack this serotonin receptor only in the POMC neurons.

Other UT Southwestern researchers involved in the study included lead author Dr. Yong Xu, instructor of internal medicine; Drs. Eric Berglund, Jen-Chieh Chuang, William Holland and Jong-Woo Sohn, postdoctoral research fellows in internal medicine; Dr. Makoto Fukuda, instructor of internal medicine; Dr. Kevin Williams, assistant instructor of internal medicine; Dr. Jeffrey Zigman, assistant professor of internal medicine and psychiatry; Dr. Philipp Scherer, director of the Touchstone Center for Diabetes Research; and Dr. Jari Rossi, former postdoctoral research fellow in internal medicine. Researchers from Baylor College of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School also contributed to the study.

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