Manipulating key protein in the brain holds potential against obesity and diabetes

25 July 2014

A protein that controls when genes are switched on or off plays a key role in specific areas of the brain to regulate metabolism, UT Southwestern Medical Center researchers have found.

The research potentially could lead to new therapies to treat obesity and diabetes, since the transcription factor involved – spliced X-box binding protein 1 (Xbp1s) – appears to influence the body's sensitivity to insulin and leptin signaling. Insulin and leptin are hormones central to the body's regulation of food intake and sugar disposal, and obesity and diabetes are conditions under which the body develops resistance to their actions.

"This study identifies critical molecular mechanisms that link the brain and peripheral endocrine tissues and that ultimately contribute to the regulation of body weight and glucose metabolism," said Dr. Kevin Williams, Assistant Professor of Internal Medicine and co-first author of the study with Dr. Tiemin Liu, a postdoctoral research fellow in Internal Medicine.

Researchers found that over-expression of the gene Xbp1s in mice that were fed a high-fat diet protected them against obesity and diabetes, according to the recent study, published online in *Cell Metabolism*. On average, these mice were 30 percent leaner than mice fed the same food. The gene's actions took place in pro-opiomelanocortin (Pomc) neurons in the hypothalamic region of the brain. Elevated Xbp1s levels in Pomc neurons mimicked a "fed" signal, resulting in improved body weight, decreased blood glucose levels, and improved insulin sensitivity in the liver.

"Manipulating this one gene in the brain affected metabolism in the liver. This result shows that the brain is controlling glucose production by the liver," said Dr. Joel Elmquist, Director of the Division of Hypothalamic Research, Professor of Internal Medicine, Pharmacology, and Psychiatry, and holder of the Carl H. Westcott Distinguished Chair in Medical Research, and the Maclin Family Distinguished Professorship in Medical Science, in Honor of Dr. Roy A. Brinkley.

Dr. Elmquist was co-senior author of the study, along with Dr. Philipp Scherer, Director of the Touchstone Center for Diabetes Research, Professor of Internal Medicine and Cell Biology, and holder of the Gifford O. Touchstone, Jr. and Randolph G. Touchstone Distinguished Chair in Diabetes Research. No drug form of Xbp1s currently exists that could be used to test whether the gene is a target for the treatment of diabetes or obesity, though researchers see such a drug as a potential outgrowth of their research. Dr. Williams said other transcription factors involved in the same metabolic pathway will be studied to see if they have similar effects.

"We have studied one transcription factor out of many that participate in a large, complex cellular process," said Dr. Williams of Xbp1s and its role during times of cellular stress.

Provided by UT Southwestern Medical Center