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New diabetes treatment lowers blood sugar with less need for insulin

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Diabetes can result from either a deficiency of insulin (type 1 or insulin-dependent diabetes) or decreased sensitivity to insulin (type 2 diabetes). Researchers at Children's Hospital Boston have discovered a mechanism for normalizing blood sugar that doesn't involve insulin and could offer a new therapeutic approach to both kinds of diabetes.

Reporting in Nature Medicine online on February 13, Umut Ozcan, MD, and colleagues in Children's Division of Endocrinology show that a regulatory protein called XBP-1s, when activated artificially in the liver, can normalize high blood sugar in both lean, insulin-deficient type 1 diabetic mice and obese, insulin-resistant type 2 diabetic mice. This suggests that approaches aimed at increasing XBP-1s activity may benefit patients with either type of diabetes.

In previous work, Ozcan's lab identified XBP-1s as a key to the body's sensitivity to insulin, and shown that its function is impaired in the presence of obesity. Initially, XBP-1s was thought to increase insulin sensitivity and normalize blood glucose by binding to DNA and relieving stress on the endoplasmic reticulum, a cellular organ that assembles and folds proteins. When XBP-1s was artificially activated, "blood sugars in obese mice with type 2 diabetes came down abruptly," Ozcan says.

In the new study, Ozcan and colleagues show that XBP-1s regulates blood sugar in a second way: It causes the degradation of a protein, FoxO1, whose actions include increasing glucose output from the liver and stimulating feeding behavior in the brain. This degradation of

FoxO1, the researchers show, is independent of XBP-1s' effect on the insulin signaling system, and by itself leads to a reduction in blood glucose levels and increased glucose tolerance (more rapid clearing of glucose from the blood).

"Activating XBP-1s could be another approach to type 2 diabetes, and could be very beneficial for type 1 diabetes, too," says Ozcan. "Even in mice with no insulin, increased expression of XBP-1s lowered the blood glucose level significantly. This suggests that approaches that activate XBP-1s in the liver of type 1 diabetics could control blood glucose levels, with potentially much less requirement for insulin."

Ozcan's lab is now seeking practical ways to activate XBP-1s that would lend themselves to clinical development. Currently the only treatment for type 1 diabetes is insulin, which requires injections and requires close monitoring to avoid hypoglycemia. Drugs are available for type 2 diabetes, but it remains difficult to control.

Provided by Children's Hospital Boston