Treatment corrects severe insulin imbalance in animal studies

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Researchers have used a drug to achieve normal levels of blood sugar in animals genetically engineered to have abnormally high insulin levels. If this approach succeeds in humans, it could become an innovative medicine for children with congenital hyperinsulinism, a rare but potentially devastating genetic disease in which insulin levels become dangerously high.

"There is currently no effective medical treatment for children with the most common type of congenital hyperinsulinism," said study leader Diva D. De León, M.D., a pediatric endocrinologist at The Children's Hospital of Philadelphia. "This type of congenital hyperinsulinism is caused by mutations in genes that encode important potassium channels in the pancreatic beta cells." The study team, from Children's Hospital and the University of Pennsylvania School of Medicine, published their report online on July 17 in the *Journal of Biological Chemistry*.

In congenital hyperinsulinism (HI), genetic mutations damage the insulin-secreting beta cells in the pancreas. Insulin levels rage out of control and severely reduce blood glucose, a condition called hypoglycemia. If untreated, hypoglycemia may cause irreversible brain damage or death in children. Congenital HI occurs in an estimated one in 50,000 U.S. children, with a somewhat higher incidence among certain groups, such as Ashkenazic Jews.

For the past 20 years, the standard medical treatment for some forms of HI has been the drug diazoxide, which controls insulin secretion by

opening up crucial potassium channels in beta cells. However, this drug does not work in the most common and severe forms of HI, in which mutations prevent those channels from forming.

When the abnormal beta cells are confined to a discrete portion of the pancreas, as occurs in approximately half of HI cases, precise surgery on the tiny organ can remove the lesion and cure HI. The Children's Hospital of Philadelphia is a world leader in diagnosing such lesions and performing the curative surgery on newborns.

However, when abnormal cells are distributed throughout the pancreas in so-called diffuse HI, surgeons must remove nearly all the pancreas. This relieves HI in about a quarter of cases, but leaves the majority of patients at high risk for insulin imbalance, in which blood glucose levels are too low (hypoglycemia) or too high, resulting in diabetes.

The new study makes use of a peptide (an amino acid compound) called exendin-(9-39) that blocks the action of a specific hormone receptor in beta cells. Building on their previous work using exendin-(9-39) on normal mice, De León's study team studied the peptide's effect on a strain of mice that had been genetically engineered to mimic the defect found in children with congenital HI.

When researchers withhold food from those mice, their blood glucose levels become low, a condition called fasting hypoglycemia. Mice who had received exendin-(9-39), however, had significantly higher levels of fasting blood glucose compared to mice that were not treated with the peptide, and reached levels comparable to those in normal, healthy animals. Further studies identified the mechanisms in the hormone signaling system that malfunctions in HI.

The next step, says De León, is a pilot study now under way to test the effect of exendin-(9-39) in children and adults with congenital HI. If

results from the pilot study are promising, her study team expects to progress to a larger clinical trial. "If this peptide can be developed into a treatment for children with this common form of HI, we may have a new tool for controlling their insulin levels and managing their disease," added De León.

The Congenital Hyperinsulinism Center at Children's Hospital has worldwide prominence in diagnosing and treating this genetic disease. Much of its work builds on pioneering research by Charles A. Stanley, M.D., in identifying the specific gene defects that cause HI. Stanley is a co-author of the current study.

Source: Children's Hospital of Philadelphia