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NOVEL SOMATOSTATIN RECEPTOR ANTAGONIST IMPROVES GLUCAGON SECRETION IN DIABETIC RATS

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Hypoglycemia is the most serious acute complication for type 1 diabetic (T1D) patients trying to reach optimal glycemic goals. Key to this is loss of the ability to secrete glucagon in response to hypoglycemia, which occurs within 5 years after the onset of diabetes. Glucagon is the primary hormone that helps to raise blood glucose levels back to normal when they begin to fall. Finding pharmacotherapies that can restore glucagon secretion from the pancreatic α-cells is crucial to helping prevent or reduce the incidence of hypoglycemia in patients with T1D.

The regulation of glucagon secretion is controlled by multiple factors, one of which is somatostatin (SST). SST is a hormone that is secreted by pancreatic δ-cells and it acts through SST type 2a receptors (SSTR2a) to suppress glucagon secretion. In T1D, SST levels are elevated and it may contribute to loss of the glucagon response to hypoglycemia. Therefore, antagonists of SSTR2a may be a promising therapy to help restore this response.

Streptozotocin (STZ)-diabetic rats were used to evaluate the efficacy of ZT-01, which is a new SSTR2a antagonist. Surgery to cannulate the left carotid and right jugular vein was performed on the rats one week after induction of diabetes. The animals were then subjected to a hyperinsulinemic-euglycemic-hypoglycemic clamp one week after surgery. The control group received injections of vehicle and the treatment groups received varying dosages of ZT-01 one hour prior to inducing hypoglycemia to find the lowest effective drug dose that would enhance glucagon secretion during hypoglycemia.

We evaluated four different doses of ZT-01 ranging from 0.3mg/kg to 0.1ug/kg. The most promising dose was 0.3mg/kg which increased glucagon secretion by almost 8-fold compared to vehicle-treated STZ rats. Lower doses exhibited a dose-dependent decline in efficacy with 0.1ug/kg showing no effect.

In conclusion, our pre-clinical findings indicate that ZT-01 shows great potential as a therapy to improve glucagon secretion in rats with T1D.