THE FEASIBILITY OF USING A NOVEL SOMATOSTATIN RECEPTOR 2 INHIBITOR TO PREVENT HYPOGLYCEMIA IN TYPE 2 DIABETES
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Loss of the ability to secrete glucagon, a hormone that is important to help raise blood glucose levels, in patients with advanced type 2 diabetes (T2D) places them at greater risk for experiencing hypoglycemia. Although the mechanism underlying this loss is currently not known, elevated somatostatin levels in poorly controlled T2D may play a role as it binds to type 2 somatostatin receptors on pancreatic alpha-cells to inhibit glucagon secretion. The current study evaluates whether a new somatostatin receptor 2 antagonist, ZT-01, can be used to help restore glucagon secretion in response to hypoglycemia in advanced T2D rats. In addition, we also examine whether ZT-01 affects metabolic parameters under hyperglycemic conditions. Sprague-Dawley rats placed on a high-fat diet and given a low-dose of streptozotocin were used to model advanced late stage T2D in humans. These animals underwent either a hyperinsulinemic-hypoglycemic or hyperglycemic clamp following the administration of ZT-01 to evaluate the effect of the drug on glucagon and insulin secretion, respectively. In response to hypoglycemia, plasma glucagon responses were almost completely absent in the T2D animals, whereas treatment with ZT-01 improved glucagon responses in the diabetic rats. Under hyperglycemic clamp conditions, we observed a significant and unexpected rise in plasma insulin levels that was accompanied by a rise in glucagon than was observed in response to hypoglycemia. Based on the data collected, ZT-01 appears to be effective at enhancing glucagon secretion in advanced T2D rats during hypoglycemia but surprisingly, it also stimulated insulin secretion under hyperglycemic conditions, which may prove to be an advantageous therapy in maintaining metabolic control in T2D.