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Title of project: Can somatostatin antagonism be developed for type 2 diabetes therapy?

ABSTRACT

Aims: To investigate if manipulation of somatostatin receptor signalling in the gut and in the brain, respectively can improve glucose control in experimental diabetes models. **Background:** Somatostatin (SS) may act as a paracrine regulator of glucose metabolism through mechanisms in the gut and in the brain. In the gut, SS inhibits secretion of the incretins, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1). The incretins importantly regulate insulin secretion, and exogenous GLP-1 receptor agonists may, to some extent, restore the insulin deficiency in type 2 diabetes. Therefore finding a pharmaceutical way to increase the secretion of endogenous incretins is currently of major scientific interest. Since SS strongly inhibits incretin secretion, antagonizing SS action might enhance endogenous incretin release. SS binds to five different receptor subtypes and my preliminary data suggest that receptor subtype 5 (SSTr5) is of great importance for GLP-1 secretion. SS regulation of GIP is however, largely uninvestigated. The present project will investigate in detail SS's regulation of incretin secretion and action, using isolated perfused preparations of mouse small intestine and calcium imaging of primary cells. Furthermore, the ability of selective SS receptor antagonists to improve glucose regulation in experimental diabetes models will be investigated. SS is also located in areas of the brain involved in food intake and glucose metabolism, and activation of the SS neurons here appears to promote food intake. My study will also investigate the effects of ICV administrations of subtype specific SS receptor antagonists on the brain's regulation glucose homeostasis and food intake.
Expected outcome: My project will provide insight into the importance of SS receptor signalling and its role in glucose control, mediated by the gut and brain. Ultimately the goal is to treat type 2 diabetes with a selective somatostatin receptor antagonist.