Determining the Impact of GIP Receptor Signaling on α-Cell GLP-1 Production

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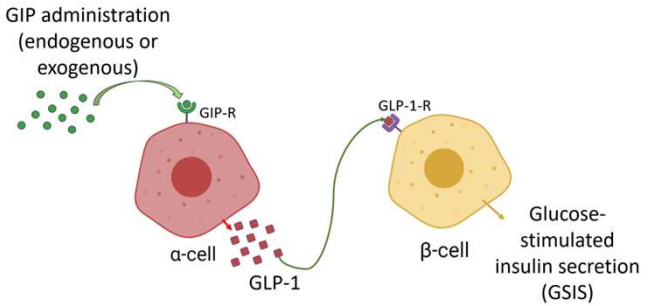
Abstract

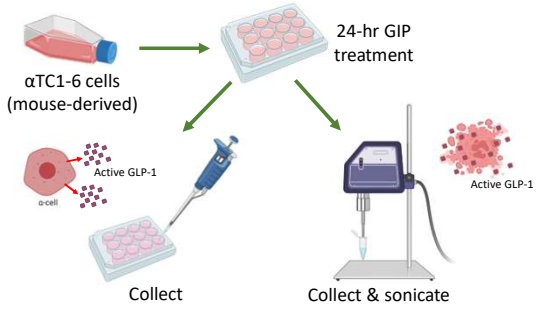
Insulin secretion in response to oral glucose intake is described as the incretin effect and is driven by two gut-derived hormones: glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1). GLP-1 is derived from the protein precursor proglucagon, which can be cleaved into either glucagon or GLP-1 via the PC2 or PC1/3 enzyme, respectively. Traditionally, it was believed that alpha cells express PC2 and not PC1/3, but multiple studies have demonstrated alpha cells can be stimulated to express PC1/3 and consequently produce GLP-1. Because the half-life of active GLP-1 in circulation is extremely short, it is hypothesized that alpha cells contribute to glucose-stimulated insulin secretion (GSIS) via paracrine signaling to beta cells using GLP-1. Indeed, a recent study demonstrated that GIP contributes to GSIS through the alpha cell. We hypothesize alpha cell GIP receptor signaling promotes GSIS by activating the production of GLP-1. The goal of our project is to determine if GLP-1 is released in response to alpha cell GIP receptor signaling, which would give more insight into potential mechanism behind alpha and beta cell communication in GSIS. To achieve this, we are treating alpha TC1-6 cells with GIP under conditions of high and low glucose and measuring the alpha cell response via ELISAs for active GLP-1 and glucagon levels. Additionally, PC1/3 & PC2 mRNA and protein levels will be quantified by qPCR and immunoblotting. Because glucogenic amino acids, such as alanine, are key stimulants of alpha cell hormone secretion, treatments of pancreatic islets with GIP and alanine will be analyzed as described above as well.

Hypothesis

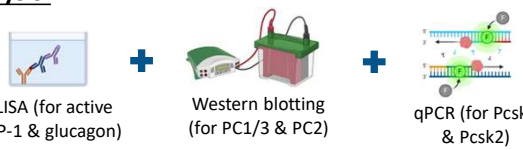


Methods

Study Design:



Analysis:



Results

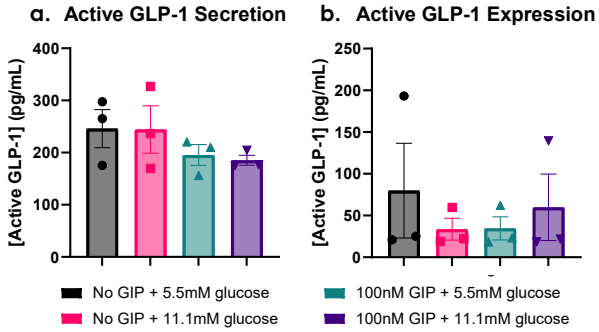


Figure 1. Active GLP-1 Expression and Secretion Following GIP Treatment of αTC1-6 Cells. (a) Active GLP-1 concentrations measured in conditioned media of α-cells treated with GIP; n=3 per group (b) Active GLP-1 concentrations measured in lysates of α-cells treated with GIP; n=3 per group. Active GLP-1 levels quantified via sandwich electrochemiluminescence immunoassay (Meso Scale Discovery). Data are presented as means ± SEM.

Discussion

- ❑ Secretion of active GLP-1 by α-cells does not change in response to GIP treatment under these experimental conditions.
- ❑ Expression levels of active GLP-1 also do not appear to be affected by GIP treatment under these experimental conditions.
- ❑ This experiment will be repeated to increase the sample size to determine any potential significance of our results.
- ❑ We repeated this study in human islets to assess the impact of GIP treatment on alpha cell GLP-1 production in a more translationally relevant model with intact paracrine signaling systems. These results are pending.

Conclusion

- ❑ The α-cell GIP-R plays a role in α/β-cell communication, but further investigation is required to identify the intermediate by which this occurs.

Future Directions

- ❑ Replicate experimental paradigm in human and mouse islets for increased translational and physiological relevance.
- ❑ Explore the role of glucogenic amino acids in glucose-stimulated insulin secretion with GIP administration.

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