



Exploring the relationship between DPP-IV inhibition and PYY mediated control of hyperglycaemia

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Background:

The incretin effect, which in normal health is responsible for ~80% of insulin secretion at mealtimes, is impaired in type 2 diabetes (T2D) (Mari et al., 2013). GLP-1 is thought to be the most important incretin hormone which regulates glycaemia, making it a successful therapy for diabetes (Harris & McCarty, 2015). However, active GLP-1 is prone to rapid degradation by a group of proteolytic enzymes called dipeptidyl peptidase-IV (DPP-IV) (Heard et al., 2013). Thus, prolongation of GLP-1 activity through inhibition of DPP-IV is an attractive therapeutic opportunity for enhancement of insulin secretion in diabetes. Interestingly, the gut hormone peptide tyrosine tyrosine (PYY) is also degraded by DPP-IV action and PYY has been shown to play a vital role in restoration of diabetes following Roux-En-Y gastric bypass (RYGB) (Ramracheya et al., 2016). Recently, in a double-blind randomised control trial, the DPP-IV inhibitor sitagliptin was shown to have no effect on plasma GLP-1 levels but led to an increase in PYY (Aaboe et al., 2010). We have preliminary data demonstrating that PYY is secreted locally by islet cells and it can affect glucose-stimulated insulin secretion (GSIS) in both rat and human islets. In addition, we have observed potentiation of GSIS by sitagliptin in islets isolated from GLP-1 receptor knockout mice. Whilst pancreatic islets express DPP-IV (Omar et al., 2014), its role and function on local GLP-1 or PYY system remain obscure. Further work establishing PYY as a mediator of glycaemic control with DPP-IV inhibition is required, as well as gaining further understanding of DPP-IV action within islets on local GLP-1 and PYY. PYY levels are known to vary with adiposity (Jamie & Cooper, 2014) and non-specific metabolomic analysis of serum pre-and post-surgery in man has shown changes in metabolites suggesting potential lipid biomarkers of diabetes remission following RYGB (Luo et al., 2016). More detailed metabolomic investigation is required on key metabolites involved in glucose and metabolic regulation, and as to whether these could potentially augment reversal of hyperglycaemia post-surgery.

Hypothesis and Aims

The main goals of this project are: 1) investigate the effect of DPP-IV inhibition therapy on plasma PYY and GLP-1 levels in T2D; 2) explore the role of DPP-IV inhibitors on insulin and glucagon secretion and local GLP-1 and PYY levels in mouse and human islets; and 3) metabolomic analysis of human serum

pre-and post-bariatric surgery to determine which metabolic changes could potentially mediate reversal of hyperglycaemia.

Work plan

The project will provide experience of both clinical and basic science research. The study will involve use of serum and plasma samples from patients with T2D undergoing DPP-IV inhibition treatment and RYGB with subsequent application of basic science techniques to explore the role of PYY in DPP-IV action and islet function, providing an excellent opportunity for a clinical fellowship.

Serum samples from patients on DPP-IV inhibition therapy and relevant controls are available via an existing collaboration with Dr Angus Jones (University of Exeter). Samples will be analysed for incretins, insulin and glucagon. Metabolomic analysis will be done on serum samples from patients pre- and post-surgery with samples available via an existing collaboration with Dr John Ryan at the Translational Gastroenterology Unit in Oxford. *In vitro* work will be conducted using isolated mouse and donor human islets using a combination of optical, molecular and genetic approaches to study the mechanisms underlying DPP-IV inhibition on pancreatic islet function. Secretion studies will be performed to investigate the effects of DPP-IV blockers on insulin and glucagon secretion and hormone release will be measured by MesoScale Multiplex platform. Selective inhibitors will be used to study the intracellular signal transduction mechanisms involved in DPP-IV inhibition and GLP-1 and PYY action. The project will also provide training and experience in range of other broad techniques, including light microscopy, islet isolation and hand-picking, cell culture, immunohistochemistry, gene expression and Western blotting and biochemical assays.

Relevance

PYY is currently not used clinically to treat diabetes or obesity – this work may contribute to its use as a potential therapy in diabetes management.

References

1. Mari A, Bagger JI, Ferrannini E, Holst JJ, Knop FK, Vilsbøll T (2013). [Mechanisms of the incretin effect in subjects with normal glucose tolerance and patients with type 2 diabetes](#). *PLoS ONE*, **8**: 73154.
2. Heard KR, Wu W, Li Y, Zhao P *et al.* (2013) [A general method for making peptide therapeutics resistant to serine protease degradation: application to dipeptidyl peptidase IV substrates](#). *J Med Chem* **56**: 8339-51.
3. Harris KB, McCarty DJ (2015) [Efficacy and tolerability of glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes mellitus](#). *Ther Adv Endocrinol Metab.* **6**:3-18.
4. Aaboe K, Knop FK, Vilsbøll T, Deacon CF, Holst JJ, Madsbad S, Krarup T (2010). [Twelve weeks treatment with the DPP-4 inhibitor, sitagliptin, prevents degradation of peptide YY and improves glucose and non-glucose induced insulin secretion in patients with type 2 diabetes mellitus](#). *Diabetes Obes Metab* **12**: 323-333.

5. **Ramracheya RD, McCulloch LJ, et al** (2016) [PYY-Dependent Restoration of Impaired Insulin and Glucagon Secretion in Type 2 Diabetes following Roux-En-Y Gastric Bypass Surgery](#). *Cell Reports* **15**: 944-50.
6. Omar BA1, Liehua L, Yamada Y, Seino Y, Marchetti P, Ahrén B (2014) [Dipeptidyl peptidase 4 \(DPP-4\) is expressed in mouse and human islets and its activity is decreased in human islets from individuals with type 2 diabetes](#). *Diabetologia*, **57**: 1876-83.
7. Jamie A Cooper (2014) [Factors affecting circulating levels of peptide YY in humans: a comprehensive review](#). *Nutrition Reviews* **27**: 186-197.
8. Luo P, Yu H, Zhao X *et al* (2016) [Metabolomics Study of Roux-en-Y Gastric Bypass Surgery \(RYGB\) to Treat Type 2 Diabetes Patients Based on Ultrapformance Liquid Chromatography-Mass Spectrometry](#). *J Proteome Res* **15**:1288-99.

Supervisor's recent relevant publications

1. **Ramracheya RD, McCulloch LJ, et al** (2016) [PYY-Dependent Restoration of Impaired Insulin and Glucagon Secretion in Type 2 Diabetes following Roux-En-Y Gastric Bypass Surgery](#). *Cell Reports* **15**: 944-50. PMID: 27117413.