The Abstract

New mechanisms of incretins in diabetes and bariatric surgery

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Background & aim: In health, blood glucose levels are regulated by the joint actions of insulin and glucagon secreted from the pancreatic beta- and alpha-cells, respectively. Thus, hyperglycaemia does not arise due to insulin deficiency alone. Dysregulation of glucagon secretion occurs in all forms of diabetes and elevated glucagon levels can aggravate hyperglycaemia. Bariatric surgery is described as a miracle cure for type 2 diabetes (T2D) and is being offered as a treatment option for the disease. This phenomenon occurs independently of weight loss via a combination of factors, including changes in incretins. However, the impact of the surgery on islet function has not been explored in depth. Incretins also play a crucial role in glucose homeostasis but the role of gut peptides such as GLP-1 and PYY on glucose-mediated glucagon release remains uncharacterised. The aim of this study was to elucidate the physiological relevance of GLP-1 and PYY on glucagon secretion in bariatric surgery and in health and in diabetes.

Methods: Donor human islets obtained with ethical consent from the Oxford Islet Isolation and Transplantation Centre and isolated mouse islets were used for secretion studies. Secreted hormones were analysed by means of radio-immunoassays.

Results: GLP-1 potently inhibited glucagon secretion in isolated mouse and donor human islets. In parallel, we have also shown that peptide tyrosine tyrosine (PYY) is capable of suppressing glucagon release although PYY receptors are restricted to beta-cells. Using a T2D rat model, we show that bariatric surgery leads to marked beneficial metabolic effects and reversal of T2D within just 10 days post operation. The restoration of deranged islet secretory function upon RYGB was linked to marked elevations in PYY and persisted in the presence of GLP-1R inhibition. Moreover, chronic treatment of diabetic rat and human islets with exogenous PYY improved insulin and glucagon release. These findings suggest that PYY is the humoral factor which mediates the anti-diabetic effects of RYGB and restoration of dysregulated insulin and glucagon secretion in diabetes.

Conclusion: Since impairment of glucagon regulation constitutes a major fifty percent of the pathogenesis of diabetes, addressing both the insulin and glucagon defects would effectively 'cure' the disease. To date, very few anti-diabetic drug therapies target both hormonal impairments. This is well illustrated by the remarkable success rate of GLP-1-based therapies. However, the unpleasant side-effects associated with these treatments have hampered their suitability for many patients. Thus, the fact that PYY is also capable of restoring both defective insulin and glucagon release, is of significant clinical relevance. This lecture will first, explore the regulation of pancreatic hormone release by GLP-1 and PYY, and subsequently discuss their roles in glucose homeostasis, diabetes and bariatric surgery.