

The role of PYY in pancreatic islet physiology and surgical control of diabetes

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Abstract

Bariatric surgery in obese individuals leads to rapid and lasting remission of type 2 diabetes (T2D). This phenomenon occurs independently of weight loss possibly via a combination of factors. The incretin hormone GLP-1 has been recognized as a critical factor. However, recent data have indicated that the beneficial effects of surgery on glucose homeostasis may not be dependent on alterations in GLP-1 levels and that elevation in another gut hormone, peptide tyrosine tyrosine (PYY), may drive these effects. PYY is mainly released from the intestinal L-cells in response to nutrient transit. Its function is well characterized in appetite regulation through NPY receptors. PYY is also locally expressed in the pancreas where it has been shown to modulate islet structure and its secretory properties via unknown mechanisms. Both impaired insulin and glucagon release in diabetic islets are restored by PYY pre-treatment, demonstrating that PYY can correct both hormonal defects associated with diabetes. Here we discuss recent findings on PYY-mediated control of glucose homeostasis and its role in diabetes, in context of what is known for GLP-1. Identification of factors that increase the expression of PYY following bariatric surgery and elucidation of its role in diabetes reversal may have clinical relevance as a non-surgical therapy for T2D.

Keywords: bariatric surgery, diabetes, incretins, PYY

Trends:

- Bariatric surgeries are weight loss interventions, which result in a spectacular reversal of type 2 diabetes (T2D) and associated metabolic benefits in man
- The gut hormone, GLP-1 has been considered as the ‘holy grail’ of this phenomenon and the involvement of other incretins, namely PYY which is also expressed in the pancreatic islets, has been largely overlooked and under-rated.
- PYY is a key factor in diabetes remission ~~following~~[after](#) bariatric surgery in rats. Moreover, elevated PYY levels in patients after surgery are associated with improved glucose responses.
- PYY modulates insulin and glucagon secretion in isolated rat and human islets via unidentified mechanisms and it is critical for the preservation of islet morphology and secretory function.
- Like GLP-1, PYY has been associated with proliferative and protective effects on pancreatic beta-cells.

- The impact of PYY in mediating the anti-diabetic effects of gastric bypass surgery implies that a pharmacological agent enhancing PYY release or its action could provide an effective and non-surgical therapy for T2D

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Outstanding questions:

- What is the mechanism by which PYY enhances insulin secretion? Does it involve proliferation or preservation of beta-cell mass?

- How does PYY modulate glucose-induced stimulated glucagon suppression response? The absence of NPY receptors on alpha-cells points to an indirect effect that may be secondary to insulin or somatostatin secretion.

- What causes PYY elevation after bariatric surgery? Is there a role of bile acids and/or gut microbiota?

- Are PYY levels in the pancreatic islets altered by bariatric surgery? Do they increase as in the circulation plasma?

- What are the other factors contributing to diabetes remission post bariatric surgery?

- Does chronic PYY chronic treatment with PYY restore islet morphology as observed in diabetic rats after RYGB?

Glossary:

Bariatric surgery: surgical procedures designed to achieve weight loss in obese patients. They include purely restrictive procedures which re-size the stomach volume (gastric binding, sleeve gastrectomy) or restrictive and malabsorptive procedures which divert the distal part of the small intestine to a small stomach pouch, bypassing the duodenum and jejunum (biliopancreatic diversion, gastric bypass).

Incretins: hormones released after a meal, which stimulate the glucose-dependent secretion of insulin from beta-cells. Main examples are glucose-dependent insulintropic peptide (GIP) and glucagon-like peptide-1 (GLP-1).

Bariatric surgery as a treatment for diabetes treatment

The first line of evidence demonstrating improved glucose tolerance after bariatric surgery dates back to 1984[1]. Reversal in type 2 diabetes (T2D) was subsequently observed in 78% of patients post gastric bypass, triggering the interesting hypothesis that the metabolic defect in T2D lies between the gut and the islets[2, 3]. More recently, findings from a meta-analysis of 10000 patients have confirmed the high rate of diabetes remission and described additional beneficial effects of weight-loss surgery on metabolism[4]. Elevated insulin levels in diabetic patients return to normal

within just a week of surgery and this phenomenon is sustained after 3 months[5]. Although weight loss may constitute an important component in the reversal of hyperglycaemia[6], it has a negligible impact on early correction of diabetes which is documented to occur well before significant weight reduction. In addition, the restoration of insulin secretion in response to oral glucose following gastric bypass is not observed in patients after equivalent diet-induced weight loss[7]. On the whole, the beneficial effects of bariatric surgery have been so compelling that metabolic surgery is now being incorporated in the treatment algorithm of T2D[8-10]. Thus, new guidelines from the Second Diabetes Surgery Summit (DSS-II) recommends diabetes treatment by bariatric surgery for clinically obese patients as well as patients with a lower BMI of 30.0–34.9 kg/m² when hyperglycemia is inadequately controlled by medical therapy.

Several mechanisms and a combination of factors rather than a single one are likely to mediate the postoperative improvements in glucose homeostasis, including changes in bile acid metabolism and intestinal microbiome as recently reviewed[11]. However a strong positive association is observed between diabetes remission and surgical procedures that specifically modify the gut anatomy and nutrient transit in the duodenum indicating that gut-related factors may be critical. Gut hormone alterations after bariatric surgery have been extensively reported[12-14], of which the incretin hormone glucagon-like peptide 1 (GLP-1) has been rated as a pivotal modulator[15]. However, the role of GLP-1 as the principle mediator of surgery-associated benefits remains inconclusive. On the other hand, recent findings have highlighted another intestinal hormone, peptide tyrosine tyrosine (PYY), as a crucial humoral factor in the recovery of impaired islet secretory functions and reversal of diabetes following RYGB in a rat model of T2D[16]. Nevertheless, its role on glucose homeostasis and in the pancreas remains underrated. The current review addresses this gap by a critical analysis of findings from human and rodent studies. In addition, it analyses the effects of PYY on pancreatic beta-cell renewal and secretory functions, in relation to its well-studied counterpart, GLP-1.

The importance of gut hormones: PYY is an underestimated key factor

The relevance of gastrointestinal factors in diabetes remission is emphasized by analysis of beta-cell function years after gastric bypass in diabetic patients[17]. Thus, Dutia et al. have reported that insulin response to isoglycemic intravenous glucose clamp remains impaired three years after surgery despite documented remission of diabetes within just a month. However, this dysfunction is fully reversed by oral glucose stimulation, highlighting the critical role of the oral route and gut-derived factors in the improvement of beta-cell secretory capacity after RYGB.

Among the gut peptides, GLP-1 has been deemed as a master regulator, initially based on bariatric surgery studies reporting elevated levels of the incretin in non-diabetic subjects in combination with enhanced insulin secretion and reduced circulating glucose concentrations in response to test meals[18]. ~~Exaggerated GLP-1 production has also been suggested to cause hyperinsulinemic hypoglycaemia, a complication usually diagnosed 1-5 years after gastric bypass~~[19]. The causal relationship between the increase in GLP-1 and improvement in beta-cell function after bariatric surgery has been demonstrated by blocking the GLP-1 receptor with exendin (9-39) infusion resulting in a significant blunting of the beneficial effects on glucose tolerance and postprandial insulin secretion[20-22].

On the other hand, a number of studies have mechanistically and directly investigated the role of endogenous GLP-1 on metabolic effects of bariatric surgeries in rodents. Thus, an *in vivo* study with chronic infusion of exendin-(9-39) in RYGB rats has been reported by the Berthoud and Drucker Lab[23]. The data reveal that central GLP-1 receptor signalling is not critical for the beneficial effects of RYGB. Moreover, it was shown that RYGB was just as effective in GLP-1 receptor-deficient mice compared to wild-type mice, suggesting that signalling through this receptor, whether centrally or peripherally, is not required for the beneficial effects of RYGB[24]. In addition, Mokadem et al[25] have demonstrated that attenuated secretion of GLP-1 (including that of its bioactive metabolites) and lack of classical GLP-1 receptor signalling do not prevent the overall beneficial effect of RYGB in mice using two models of functional GLP-1 deficiency. Complementary observations by three independent studies in humans also report that, despite a rapid reduction in plasma glucose levels and improvement in insulin resistance, fasting GLP-1 levels do not change significantly in the first 2-3 weeks of gastric bypass surgery[26-28]. Moreover, causation between elevations in postprandial GLP-1 levels and the metabolic benefits of surgery has been questioned at both short and long term time points in man[29, 30].

In line with these findings, Ramracheya et al., have recently shown that although diabetic GK rats subjected to RYGB do not have increased circulating GLP-1 levels, they exhibit marked beneficial metabolic effects such as decreased plasma glucose concentrations[16]. ~~It should be noted that the GK rat is a lean model of T2D, which in man is associated with a more rapid beta cell failure[31, 32] and which further excludes weight-dependent changes.~~ In this rat model, the restoration of deranged islet secretory function following RYGB is mediated by marked elevations in another incretin, PYY and persists in the presence of GLP-1R inhibition, further excluding GLP-1 as an important mediator in this process. Moreover, ~~treatment of islets with serum obtained from RYGB rats improved glucose-induced glucagon and insulin secretion to the same extent observed following surgery. Importantly, these effects were reversed by immunoneutralisation of PYY. Finally, chronic treatment of rat islets with exogenous PYY potentiates/improves~~ insulin and glucagon release, an observation which was also confirmed in human islets. Taken together these results suggest that factors other than GLP-1, may be accountable for diabetes correction after bariatric surgery. In particular, PYY stands out as the humoral factor which mediates the anti-diabetic effects of RYGB and also capable of restoring dysregulated glucose-induced insulin and glucagon secretion in islets isolated from severely diabetic rats.

PYY, a regulator of glucose homeostasis

The relevance of PYY in bariatric surgery has so far been attributed to a reduction of food intake and subsequent weight loss[33] (**Text Box 1**) which are synergistically achieved in association with GLP-1 in humans[34, 35]. However the expression of PYY in the pancreas of rodents and higher mammals [36-40] alludes to a potential additional extra-role of the peptide in glucose regulation (Figure 1). Although it is well established that PYY is not co-localized in pancreatic islet beta-cells, its specific localization in other islet cell types ~~remains controversial~~ has been reported. ~~However~~ Thus, PYY expression in alpha-cells appears to be species-specific and mostly limited to rodents[37]. It is thought that expression in the alpha-cells decreases by half during pancreatic development[39] whilst it is maintained in islet delta- and polypeptide- cells. PYY signals via the NPY family of

receptors. In human and rodent islets, NPY receptor expression has only been demonstrated at mRNA levels ~~has been demonstrated in human and rodent islets~~ [38, 41]. Among the receptors expressed, NP2YR has the lowest expression levels, implying that the effects of PYY on pancreatic islet secretion and glucose regulation occur via a pathway different distinct from appetite regulation. The effects of PYY on glucose homeostasis and diabetes were described by Pittner *et al* in 2004. Using a number of obese and diabetic rodent models, the authors investigated the effect of chronic administration of PYY (3-36) and reported a significant reduction in HbA1c level as well as improvements in glycaemic parameters. In contrast, there was no effect on plasma glucose following an acute treatment of 60 minutes with PYY, suggesting that the glycaemic benefit of PYY may lie in its long-term chronic rather than acute effect-[42].

- PYY and insulin secretion

Direct insulinostatic effects of PYY were first reported in 1989 where co-injection with PYY (1-36) and glucose in mice, resulted in reduced plasma insulin levels[36]. However, in a more recent study neither circulating glucose nor insulin levels were significantly affected by PYY administration in mice, whilst acute inhibition of insulin release was observed in isolated islets and a human beta-cell line[38]. Interestingly, the same study also demonstrated that high concentrations of PYY induced proliferative and anti-apoptotic effects in the human beta-cell line, in conflict with their report observation of insulin suppression. Undoubtedly However, these results remain to be validated in primary human islets as data from healthy volunteers demonstrates that acute intravenous infusion of PYY does not influence insulin secretion following glucose stimulation[43].

In contrast, insulinotropic effects of PYY have been demonstrated in two different transgenic mouse models. In particular, overexpression of PYY in mouse islets leads to improved glucose-mediated insulin responses, in association with an enlarged beta-cell mass and an increase in islet number and size[44]. Consistent with this finding, PYY ablation in the gut and in the pancreas results in a drastic disruption of islet structure and decrease in beta-cell mass, triggering marked impairments in insulin secretion. Importantly, the deranged beta-cell mass and lack of insulin release were reversed by treatment with a long-acting PYY (1-36) analogue[45]. In agreement with these reports, we have recently demonstrated that chronic treatment with PYY can potentiate glucose-induced insulin secretion from human islets as well as normalise impaired insulin release from severely diabetic rat islets, consistent with the restoration of impaired pancreatic islet secretory function potentially mediated by PYY post RYGB[16].

The discrepancies in the literature on the effects of PYY on insulin release may be due to major differences in experimental conditions, such as concentrations and the duration of PYY treatment of islets and variations in *in vitro* methods. Thus, further investigations are required before a consensus can be attained.

The mechanism by which PYY enhances insulin response remains to be elucidated. However, one hypothesis is that PYY exerts neogenic or mitogenic effects, resulting in the enlargement of beta-cell mass and elevated insulin release. A role of PYY in cell renewal and growth factor response has been demonstrated during pancreatic epithelium regeneration in adult transgenic mice undergoing spontaneous pancreata hyperplasia and neogenesis during adult life[46]. Data from another mouse model engineered to overexpress PYY also support proliferative effects of PYY as previously discussed[44], however in both cases neither has causality been established nor the signalling

pathway identified. NPY receptors are coupled to the heterotrimeric $G_{\alpha i}$ subunit which leads to the inhibition of adenylyl cyclase and subsequent reduction of cAMP and PKA signalling. PKA-mediated phosphorylation is required for various functions including glucose-stimulated insulin secretion[47, 48]. Therefore, inhibition of PKA signalling upon PYY-induced activation of NPY1R would contradict the reported enhanced effects on insulin secretion. On the other hand, interaction of NPYRs with different G subunits additionally leads to protein kinase C activation, which mediates mitogen-activated protein kinase (MAPK) phosphorylation[49] and activates ERK1/2 signalling and beta-cell replication[50]. Although this has also been reported in mouse islets, trophic effects mediated by the NPY system are mainly established in neuronal precursor cells[51] and intestinal epithelium[52, 53], where it is mostly coupled to NPY1R receptor engagement. A more detailed characterisation of these pathways have been described for GLP-1 and its mechanism of action in the pancreas has been extensively studied[54]. A common consensus posits that GLP-1 stimulates beta-cell replication in several healthy and obesity-induced diabetic animal models[55]. In contrast, data from human studies are less clear. Such a discrepancy also applies to the investigation of beta-cell growth after gastric bypass. RYGB in a porcine model leads to an an two-fold increase in beta-cell mass, elevated islet numbers per pancreas and more insulin and glucagon-positive cells[56]. In contrast, islet-cell hypertrophy and hyperplasia are commonly observed in patients who develop hyperinsulinemic hypoglycaemia after surgery[57-59]. Regardless, whether the beneficial metabolic effects of bariatric surgery are due to beta-cell expansion or mediated by changes in PYY levels, remain to be proven.

A second plausible hypothesis for PYY-mediated potentiation of insulin secretion is that PYY plays a role in preventing beta-cell death, thus ameliorating islet functions. Protective effects of PYY were first demonstrated against necrotizing pancreatitis in rats with cerulein-induced acute pancreatitis[60]. In addition, specific ablation of PYY-expressing cells has been shown to reduce beta-cell mass by promoting apoptosis. This effect was rescued by treatment with a PYY (1-36) analogue with high affinity for NPY1R and NPY2R. Beneficial effects of this analogue were also observed against streptozotocin-induced beta-cell apoptosis[45]. Consistent with this finding, Khan et al.[38] have recently demonstrated that streptozotocin alters PYY co-localization in delta- and pp-cells and its dramatic negative effects on beta-cell viability can be reversed by co-treatment with either PYY (1-36) or PYY (3-36). Importantly, the level of protection conferred by exogenous PYY has been reported to be markedly superior to that of GLP-1. More than a decade ago, similar results were described for the GLP-1 analogues[61] and its well-known agonist exendin-4. Thus, its administration decreased streptozotocin-induced hyperglycemia in mice by reducing islet apoptosis, but without cell proliferation. Moreover, overexpression of GLP-1 in pancreatic beta-cells enhances GSIS and improves islet survival and function in transplanted animals[62].

Another possibility is PYY-induced upregulation of insulin secretion without alteration in beta-cell mass, occurs ring via PI3-Ky activation. PI3Ky is the only member of the class1B of PI3Kinases and can only be activated by G-protein coupled receptors, exclusively via the $G\beta\gamma$ subunit. This isoform is present in insulinoma cells, and mouse and human islets. Studies in knockout mice demonstrate that PI3Ky is a positive regulator of insulin secretion irrespective of changes in beta-cell mass. Despite normal plasma glucose and insulin levels, islets isolated from PI3Ky deficient mice display impaired GSIS, associated with a paradoxical elevation in insulin content and beta-cell mass[63, 64]. It has been argued that the increase in beta-cell growth observed in these mice could be a compensatory mechanism towards a potential impairment in secretory function and that it is

actually reversed by treatment with a GLP-1 agonist. Insight from additional studies has indicated that PI3Ky can coordinate the proper localization of insulin granules to the plasma membrane via a negative regulation of F-actin polymerization, thus facilitating insulin granule recruitment to the membrane[65]. In support for a similar mechanism for PYY action, PI3Kinase has been identified in the NPY receptor signalling cascade ~~in cultured adult cardiomyocytes~~[66] ~~and in human placental syncytiotrophoblast~~[67] although connected with ERK1/2 activation ~~in HEK293 cell lines~~[68]. It is therefore plausible to speculate that PI3Ky activation by PYY in the pancreatic beta-cells could lead to improved insulin secretion. Less specific inhibition of PI3Kinases by wortmannin also abrogates the protective effects of the GLP-1 receptor agonist liraglutide against cytokine or free fatty acids-induced apoptosis, although the importance of PI3Ky in insulinotropic effects mediated by GLP-1 has ~~also~~ been questioned[69].

- PYY and glucagon regulation

In health, blood glucose levels are tightly regulated by the joint actions of insulin and glucagon secreted from the pancreatic beta- and alpha-cells, respectively. Likewise, hyperglycaemia or diabetes is not a disease of insulin deficiency alone. Thus, dysregulation of glucagon secretion has been shown to occur in all forms of diabetes and elevated glucagon levels are known to aggravate hyperglycaemia[70]. The importance of glucagon in diabetes is illustrated by the finding that mice lacking glucagon receptors remain normoglycemic even after complete destruction of the insulin-producing beta-cells [71]. However, in contrast to insulin secretion, the role of gut hormones on glucose-mediated glucagon release remains insufficiently characterised. GLP-1 inhibits glucagon secretion in the presence of extracellular glucose levels of above 4 mmol/L[72]. Nevertheless, it is still unclear whether this is a direct or indirect effect as controversial data have been reported on the expression levels of the GLP-1 receptor in the alpha-cells[73]'[74]. Likewise, we have shown that PYY is capable of inhibiting glucagon release from isolated islets although NPY receptors appear to be restricted to beta-cells, thus suggesting that PYY modulates glucagon release via indirect pathways which may involve insulin or somatostatin secretion. It is thought that impairment of glucagon regulation constitutes a major fifty percent of the pathogenesis of diabetes[75]. Therefore, addressing both the insulin and glucagon defects would effectively 'cure' the disease. To date, very few anti-diabetic drug therapies target both hormonal derangements. This is well illustrated by the remarkable success rate of GLP-1-based therapies for T2D. However, the unpleasant side-effects associated with these therapies have hampered their suitability for many patients. Thus, the fact that PYY is also capable of restoring both deranged insulin and glucagon release seen in T2D, is of significant clinical relevance and merits further investigation

Changes in PYY levels ~~in humans~~ post-surgery

Although restricted mostly to obese, non-diabetic individuals, data on PYY levels after bariatric surgery are currently expanding. While controversial post-operative results have been described for fasting levels of PYY at short-term, clear elevations in postprandial levels have been well documented at both short- and long-term, along with progressive improvement in insulin secretory response and sensitivity [13, 76].

~~Similar results have been reported 18 months post surgery, implying a major role of PYY in appetite reduction and prolonged efficacy of the surgery in sustained weight loss~~[77]. ~~Some~~ insights on PYY

regulation post-operation can also be derived from comparative post-analysis of different bariatric procedures. In particular, a number of publications have addressed the superior efficacy of gastric bypass over sleeve gastrectomy in diabetes remission presenting opposite results [78, 79]. Enhanced PYY levels after glucose or mixed meal tests have been consistently described after both surgical procedures in obese non-diabetic patients following 3 months to 2 years of surgery [26, 80, 81] and associated with significant reductions in glucose levels. On the other hand, there is a lack of consensus regarding changes in PYY levels in postoperative diabetic patients. Nannipieri et al. have compared changes in gut hormones following RYGB and sleeve gastrectomy at two different time-points; consistent elevations in PYY levels (under both fasting and postprandial conditions) were observed only after one year of both types of surgical procedures. In contrast, postprandial PYY increase over the short-term (15 days) was only documented in the gastric bypass group. Interestingly, changes in GLP-1 levels following the two surgeries appear to display an opposite trend with clear elevations noted only at short-term. Nevertheless, the rate of diabetes remission was similar in both procedures. ~~Thus, there was an improvement in beta-cell glucose sensitivity at both time-points.~~ Likewise, similar to sleeve gastrectomy, biliopancreatic diversion results in diabetes correction after one year of the procedure, although different levels of improvement in insulin sensitivity have been reported. Yet, GLP-1 and PYY responses during OGTT were dramatically enhanced after either procedure at 1, 3, and 12-month time-points, implying that post-surgery changes in incretin levels at the early time-points, are not sufficient to cause diabetes remission[82].

In an attempt to explain gut hormone alteration and improvement in glucose tolerance following bariatric surgery, several mechanisms have been proposed to date. According to the “foregut hypothesis”, the exclusion of the proximal bowel in biliopancreatic diversion or gastric bypass may prevent the release of inhibitory factors which physiologically counteract the effect of incretins. However, the afore-mentioned similarities between the two procedures and sleeve gastrectomy in terms of diabetes remission, excludes such a possibility. Instead, accelerated gastric emptying common to different types of surgeries, may account for the hyperstimulation of gut hormone release in the distal intestine as stated in the “hindgut hypothesis”. In addition, alteration in other factors such as bile acids and bacterial metabolite, are also likely to affect PYY levels[83]. Emerging evidence supports an association between PYY elevation and changes in fecal microbiota[84, 85] after 6 months of surgery in humans. It is possible that these modifications may qualitatively and quantitatively influence bacterial derivatives from fibre digestions that may in turn differentially regulate PYY expression levels as previously reported for GLP-1 and the bacterial metabolite indole[86]. It has also been proposed that short chain fatty acids can directly influence L-cells via G-protein coupled receptors to release GLP-1 and PYY, which can subsequently modulate glucose metabolism[87]. Furthermore, Toll-like receptor ligands and the short chain fatty acid butyrate, can synergistically stimulate PYY expression in L-cells via NFκB signalling [88] suggesting a unique sensitivity of the microbiota for PYY synthesis.

Concluding remarks and future perspectives

There is no doubt that gut hormones are crucial factors in the improvement of glucose tolerance post bariatric surgery. Data obtained from rodent and human studies support GLP-1 as a master regulator because of its neogenic, mitogenic and protective effects on the beta-cells. However, additional findings from several transgenic animal models have questioned its pivotal role, strongly suggesting that other factors may be involved. It has recently been demonstrated that the gut

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hormone PYY can restore secretory islet function in diabetic rats after RYGB and ~~potentiate-improve~~ both insulin and glucagon release from cultured human islets *in vitro*, highlighting a critical role of PYY in the regulation of glucose homeostasis and diabetes.

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GLP-1 and PYY are both produced by the intestinal L-cells in response to nutrient intake. Whilst GLP-1 is a well-characterised incretin with insulinotropic effect, PYY has been limited mainly as an appetite regulator with anorexigenic effect. However, accumulating data from independent studies clearly indicate additional roles of PYY extending beyond food intake. Thus, the local expression of PYY and its receptors in the pancreas, coupled with evidence of drastic disruption of islet structure arising from the loss of pancreatic PYY, along with its ability to modulate glucose-stimulated insulin secretion, collectively point to a pivotal function of PYY in the pancreatic islet. Moreover, PYY exerts proliferative and anti-apoptotic effects on the beta-cells, strongly suggesting that this hormone can enhance insulin production by increasing beta-cell mass. Similar findings have been reported for GLP-1 and its agonist exenatide and their actions on insulin release have been extensively characterized. In contrast, PYY is increasingly being recognised as the 'new kid on the block', but the mechanism by which it affects pancreatic islet function, remains unclear.

The accredited dominance of GLP-1 has somewhat ~~whattimes~~ overshadowed the importance of PYY in glucose homeostasis (**Text Box 2**) ~~and as in the case of~~ in dipeptidyl peptidase-IV (DPP-IV) inhibition studies. The inhibition of DPP-IV, the proteolytic enzyme responsible for the degradation of GLP-1 and PYY, constitutes an effective therapy for T2D, but the benefits have so far been attributed to the prolongation of active GLP-1 alone. However, the documented expression ~~existence~~ of a DPP-IV system within the islets[89] is likely to influence the local regulation of pancreatic PYY, which could subsequently alter the ratio of [PYY₁₋₃₆]/[PYY₃₋₃₆], with a significant impact on islet secretory function. Potential synergistic effects of GLP-1 and PYY on islet activity require additional studies.

Although it is being recognized that PYY has a major impact on beta-cell recovery and maintenance, other unidentified factors are also likely to play a role. Thus, the administration of a stable PYY analogue does not completely rescue pancreatic insulin levels following beta-cell apoptosis induced by PYY ablation or streptozotocin[45]. Likewise, immunoneutralization of PYY does not completely reverse the potentiating effects of RYGB rat serum on insulin secretion, suggesting that other blood-borne factors affected by the surgery, may also be involved[16]. It should be noted that co-administration of GLP-1 and PYY analogues has no additive effects on insulin content following pancreatic PYY ablation and fails to entirely rescue impaired insulin secretion[45]. Future studies should aim to define the missing factors contributing to the restoration of impaired insulin secretion and resolution of diabetes.

Of key importance is the finding demonstrating that in addition to enhancing insulin release, PYY can also significantly improve glucagon secretion. Dysregulation of glucagon secretion represents fifty percent of the pathogenesis of diabetes. Whilst most studies have exclusively focused on insulin secretion, only a handful of studies have evaluated the effect of bariatric surgery on circulating glucagon levels. Expression of PYY in pancreatic alpha-cells suggests a possible paracrine effect on glucagon release. However, NPY receptors are not present on glucagon-secreting alpha-cells, and therefore whether PYY affects glucagon release by a direct or indirect mechanism, remains unknown.

Bariatric surgery in man leads to significant improvements in several metabolic disorders associated with obesity and diabetes and for which, PYY may be critical beyond its established function on

weight loss. A positive association between an elevation in plasma PYY levels and improved glucose tolerance has been demonstrated in obese individuals shortly after surgery. On the other hand, additional studies in diabetic patients are necessary to establish a more causative relationship. Accelerated nutrient delivery to the intestine is likely to stimulate PYY expression after surgery together with newly identified factors, such as altered intestinal microbiota and their metabolic products. Although new, this area of investigation holds promises for identifying novel regulators of PYY that may represent effective therapeutic targets.

Lower PYY levels have been reported in people with T2D[90, 91]. We have previously reported that circulating PYY levels are drastically increased post RYGB in GK rats[16] and are associated with the restoration of impaired islet secretory function. However, it remains unknown whether RYGB can also affect PYY levels in the pancreatic islets which may have a direct impact on diabetes correction. This hypothesis will require future investigation.

Taken together, studies from recent years provide compelling evidence for a role of PYY in the maintenance of pancreatic islet integrity and the regulation of its secretory function. Much is yet to be learnt about the role of PYY in metabolic improvements following bariatric surgery but accumulating evidence points towards the possibility of novel PYY-based therapies for T2D.

Text box 1: Role of PYY in food intake and weight loss

PYY (1-36) is the intact form of PYY, which belongs to the neuropeptide Y (NPY) system and acts as a master regulator of appetite, energy expenditure and eating behaviour [92]. It is mainly released from neuroendocrine L-cell in the ileum in response to nutrient intake and acts via G-coupled protein receptors called NPY receptors. Five NPY receptors are currently known; NPY1R, NPY2R, NPY4R, NPY5R and NPY6R. Although the distribution of these receptors is not confined to the brain, they remain less characterized in the periphery. PYY (1-36) has similar affinity for all its receptors, unlike its truncated version PYY (3-36) which only binds to NPY2 receptor with high affinity. Upon release, PYY (1-36) is converted by dipeptidyl peptidase-IV-4 (DPP-IV) to generate PYY (3-36). This shorter PYY peptide constitutes the main circulating form which acts via NPY2R to modulate the activity of neurons of the hypothalamic arcuate nucleus and reduce food intake in mice and in man[93, 94] by modulating the activity of neurons of the hypothalamic arcuate nucleus[95](Figure 1).

It has been suggested that obesity is a state of PYY deficiency as endogenous levels of PYY are significantly lower in obese patients and body mass index negatively correlates with fasting PYY levels [90]. However, in obesity PYY (3-36) maintains its anorectic action because since its infusion inhibits food intake and leads to the reduction levels of the appetite-stimulating hormone, ghrelin in lean as well as in obese individuals. This indicates that the potential therapeutic effect of PYY administration may not be limited by a progressive resistance, as for the “satiety hormone” leptin.

The importance of PYY in weight loss after bariatric surgery is demonstrated by PYY-deficient mice which do not lose weight after gastric bypass unlike their control littermates[96]. In addition, sustained increased levels of PYY are necessary to avoid weight regain, a complication observed in 20% of patients three years after surgery[97].

Text box 2: Misattribution of credits: is PYY overshadowed by GLP-1?

Until now, GLP-1 has been recognised as the holy grail of the beneficial effects of bariatric surgery on glucose homeostasis and associated metabolic parameters. The significance of PYY in this process has been largely overshadowed by GLP-1. Such hypothesis originates from the evidence that PYY-deficient mice do not show improvement in glucose tolerance after bariatric surgery, an effect attributed to a lack of increase in plasma GLP-1 levels. According to this study, activation of peripheral NPY2R by PYY (3-36) administration increases the plasma concentrations of active GLP-1 in the hepatic portal vein while inclusion of exendin (9-39) prior to PYY (3-36) administration abolishes the effects on glucose tolerance, thus demonstrating a hierarchy of GLP-1 over PYY[98]. However, it should be borne in mind that these results only address specific activation of peripheral Y2R, which is not expressed in pancreatic islets. Moreover, there is now emerging evidence from several independent human and rodent studies that GLP-1 may not be the critical factor as previously assumed. The assumption of a dominant role of GLP-1 in glucose homeostasis also arises from studies with DPP-IV inhibitors, which ~~DPP-IV inhibitors~~ are currently used as anti-diabetes drug therapies [99, 100]. Although several biological substrates exist for DPP-IV action, according to a common model, DPP-IV inhibitors work by preventing the rapid degradation of GLP-1 into its biologically-inactive form GLP-1 (9-36) and prolonging ~~theirs~~ half-life of active GLP-1 [101]. Thus, injection of rats with the DPP-IV inhibitor P32/98, ameliorates glucose tolerance and increases islets and beta-cell number following depletion induced by streptozotocin[102]. These effects were ascribed to enhanced plasma activity of GLP-1 since similar protective effects had been observed in rat insulinoma cells following stimulation with GLP-1. However, it is noteworthy that changes in plasma levels and potential beneficial effects of other DPP-IV substrates were not analysed. More recently, protective effects of the DPP-IV inhibitor linagliptin, has been described against oxidative stress, cytokine secretion and apoptosis induction in human islets under diabetogenic conditions. These findings were complemented by the restoration of GLP-1 receptor expression and increased levels of GLP-1 in the supernatant samples. Co-treatment with exendin (9-39) abrogated the stimulatory effects of linagliptin on insulin secretion, thus indicating that this DPP-IV inhibitor acts via the stabilization of GLP-1[103]. On the other hand, a major role of GLP-1 in DPP-IV inhibition therapy has been questioned whilst taking into consideration that the metabolic beneficial effects that are trademarks of GLP-1 therapy, are either delayed or absent in patients on long-term DPP-IV treatments [104]. Thus, patients on DPP-IV inhibitors do not exhibit decreased appetite, reduction in food intake and increased weight loss as with GLP-1 analogues, questioning the involvement of GLP-1 in DPP-IV inhibition therapy.

In agreement with these arguments, we have found that chronic stimulation of mouse and human islets with sitagliptin results in improved GSIS independently of GLP-1 as it is preserved in islets isolated from the GLP-1 receptor knockout mice (McCulloch et al., unpublished). Conversely, blockade of the NPY1R significantly blunts the improved insulin responses induced by the DPP-IV inhibitor, implying a PYY-dependent effect (unpublished data). Furthermore, data from clinical studies have shown that the administration of sitagliptin for 12 weeks in diabetic patients improves both glucose and non-glucose stimulated insulin secretion, in parallel with an increase in PYY (1-36) levels and other incretin hormones[105], supporting the idea that beneficial effects of DPP-IV inhibition therapy on glycaemic control may be actually triggered by a major or at least concomitant action of PYY.

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