PYY, a Therapeutic Option for Type 2 Diabetes?

Claudia Guida and Reshma Ramracheya

Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, UK.

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ABSTRACT: Metabolic surgery leads to rapid and effective diabetes reversal in humans, by weight-independent mechanisms. The crucial improvement in pancreatic islet function observed after surgery is induced by alteration in several factors, including gut hormones. In addition to glucagon-like peptide 1 (GLP-1), increasing lines of evidence show that peptide tyrosine tyrosine (PYY) plays a key role in the metabolic benefits associated with the surgery, ranging from appetite regulation to amelioration of islet secretory properties and survival. Here, we summarize the current knowledge and the latest advancements in the field, which pitch a strong case for the development of novel PYY-based therapy for the treatment of diabetes.

KEYWORDS: PYY, bariatric surgery, pancreatic islets, diabetes

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CORRESPONDING AUTHOR: Claudia Guida, Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford OX37LJ, UK.
Email: claudia.guida@ocdem.ox.ac.uk

Improvement in Islet Function is Crucial for Diabetes Remission After Bariatric Surgery

Spanning from observations made over 30 years ago,[1,2] bariatric surgery remains the most effective procedure leading to early remission of type 2 diabetes (T2D) and metabolic syndrome.[3] According to a common consensus, a combination of factors, rather than a single one can explain such remarkable changes, independently of post-surgery weight loss.[4] This includes alteration in bile acids (BAs) signalling, microbiota products, and gut hormone release, which have been all shown to have a direct effect on islet beta cell functions.

Dysfunctional pancreatic islets are a T2D hallmark, presenting impaired glucose-response and abnormal release of insulin and glucagon hormones. Human and rodent studies have now confirmed that improvements in pancreatic islet secretory function is key in the restoration of normoglycaemia and the resolution of T2D pathogenesis following weight-loss interventions. In humans, measurements of beta cell function through the disposition index have reported post-surgery improvements not only in subjects with diabetes but also with normal glucose tolerance after either intravenous or oral glucose administration.[5-7] Significant changes in insulin secretion have been documented as early as 1 week after Roux-en-Y gastric bypass (RYGB) and further enhanced at 1 year follow-up.[5] Although Dirksen et al[8] have recently pointed out that increased incretin release from the gut is the main driver of the improvement in beta-cell function, several lines of evidence suggest intrinsic changes in islet function and morphology after surgery. Transcriptome analysis in mouse islets isolated 2 weeks after sleeve gastrectomy has indicated intrinsic changes in genes involved in calcium signalling and insulin secretion pathway,[9] which imply that pancreatic islets undergo metabolic adaptation post-surgery via remodelling of their gene expression profile, and which directly affects the function of beta cells and potentially, of other islet cell types. Consistently, islets isolated from diabetic Goto-Kakizaki (GK) rats 10 to 14 days after gastric bypass displayed an improved glucose-stimulated insulin secretion (GSIS) and a better glucose-induced glucagon inhibition compared to islets from sham animals.[10] Circulating factors, altered after the surgery, mainly lead to these improvements, as exposure of islets from diabetic rats to serum collected post-operation can recapitulate *in vitro* both enhanced insulin and glucagon responses to a glucose challenge. Notably, this has been recently proven to be true also in human islets, whose secretory properties are ameliorated by changes in humoral factors maintained at 6 months after bariatric procedures.[11]

In addition to alteration of beta-cell function, bariatric surgery appears to modify some histo-morphometric parameters of islets, such as the number of beta cells per islet.[10,12] In healthy Wistar rats, such effect is exclusively related to increased proliferation and maturation of beta-cells from stem cells, which is consistent with the islet regeneration described in db/db mice after gastric bypass through the PDX-1/Notch-1/Ngn3 signalling.[13] On the other hand, in diabetic GK rats, multiple and bigger effects on islet architecture have been reported, including pancreatic hyperplasia, enlarged beta cell-mass, and increased ratio of beta cells to non-beta endocrine cells.[14] Similar surgery-mediated changes were also described in diet-induced obese (DIO) mice in association with increased islet numbers,[15] implying a direct influence of bariatric surgery on pancreatic cellular turnover and islet structure. Although several factors are likely to cause this, it is now clear that alteration in enterohormone release is one of the major effector.[16]

PYY Plays a Key Role in the Improvement in Islet Function After Bariatric Surgery

The levels of several gut hormones increase after either sleeve gastrectomy or gastric bypass as consequence of structural and functional changes in the gastrointestinal tract, including

accelerated food delivery and absorption.[16] Among these, over the past years, a major role in diabetes remission after surgery, has been attributed to the glucagon-like peptide-1 (GLP-1)[17,18] whose analogues (exenatide, liraglutide, dulaglutide, lixisenatide) are already listed among current anti-diabetic treatments. However, its unique action has been questioned by several knock-out (KO) mouse models[19,20] lacking GLP-1 signalling but still retaining the metabolic benefits of surgery and more recently, by a double KO model in which the combined loss of GLP-1R and NPY2R did not prevent the beneficial effects of RYGB on body weight and glucose homeostasis.[21]

In addition to GLP-1, the role of another gut hormone, namely peptide tyrosine tyrosine (PYY), is now increasingly recognized in the surgical control of diabetes[22] extending beyond its classical effect on appetite regulation. PYY is a 36-amino acid peptide mainly released from specialized enteroendocrine L-cells found in the distal gastrointestinal tract. Two main endogenous forms of PYY have been identified, PYY(1-36) and PYY(3-36), the latter being the predominant circulating form. The ubiquitously expressed proteolytic enzyme dipeptidyl peptidase 4 (DPP-IV) converts PYY(1-36) to PYY(3-36), thus altering its receptor specificity and biological effects.[23] PYY signals through a cluster of receptors belonging to the neuropeptide Y (NPY) family, of which there are four subtypes: NPY1R, NPY2R, NPY4R, and NPY5R. Whereas PYY(1-36) binds to all known subtypes, PYY(3-36) shows high affinity for the Y2-receptor subtype, whose activation mediates anorexic effects in the brain.[24]

The impact of PYY on pancreatic islets was first suggested by genetically modified mouse models either boosting or conditionally deleting the peptide expression. In female mice, ectopic overexpression of PYY in beta cells leads to increased islet number/size and enlarged beta cell mass and improves GSIS.[25] Conversely, the conditional specific ablation of PYY in the gut and in the pancreas reduces beta cell viability, causes insulin loss and induces hyperglycaemia.[26] While pharmacological replacement with a long-acting PYY analogue can reverse these effects, treatment with the short-form PYY(3-36) does not rescue pancreatic insulin loss. This result is not surprising taking into account that PYY(3-36) is a selective agonist for NPY2R, which is expressed at very low levels,[27] if at all[28] in pancreatic islets and a negligible role of this receptor has been demonstrated in glucose homeostasis restoration after bariatric surgery.[21] Proliferative and protective effects of PYY against several cell stressors, have been reported by different laboratories on isolated islets as well as rodent and human immortalized beta-cell lines[27,29] suggesting a crucial role of this peptide in islet function and survival. Studies on isolated rodent islets and cell lines have reported that PYY exertsacute insulinostatic effects.[27] These results remain to be confirmed in human islets, as intravenous 30-minute infusion of PYY in healthy individual does not inhibit the acute insulin response to glucose.[30] On the other hand, chronic application of recombinant PYY improves glucose-responsiveness and hormone release from diabetic rodent and human islets, to an extent that is similar to the one reported after gastric bypass.[10] In men, the role of PYY in the improvement of islet function following bariatric surgery has been recently demonstrated by a means of a translational paradigm combining human islets and serum from patients before and after gastric bypass/sleeve gastrectomy. Exposure of islets to blood-borne factors, altered after operation and conserved in the serum, significantly ameliorates glucose-induced insulin and glucagon response recapitulating the benefits of weight-loss surgery observed *in vivo*. While different factors might contribute to such results, increased levels of PYY are crucial, as immuno-neutralization of this peptide leads to complete reversal of surgery-induced improved insulin secretion and a partial reversal in glucagon response. In addition to potentiated secretory functions, islets treated with post-surgery serum display the same fold increase in insulin content as previously reported following chronic exposure of islets to recombinant PYY,[28] potentially implicating the preservation of insulin content in the functional gain. It is noteworthy that together with an increase in circulation, also intra-islet PYY content is elevated after gastric bypass in GK rat islets, reaching levels even higher than the ones reported in healthy Wistar rats. While this is a possible consequence of islets adaptation post-surgery, it is plausible to speculate that pancreatic PYY is an additional contributor to the islet function improvements following bariatric procedures.[28]

Pancreatic PYY Can Contribute to the Regulation of Insulin Secretion After Bariatric Surgery

In addition to L-cell in the gut, PYY is expressed in the pancreas of rodent and other mammals, including men,[27,31,32] albeit with species-related differences. In rodent islets, PYY-immunoreactivity specifically localizes in PP and delta cells, while in humans it appears to be mainly confined to alpha-cells[28,33] supporting single-cell RNA sequencing data.[34,35] Although conserved, PYY expression in human islets is significantly lower than in rodents as demonstrated by light[33] and electron microscopy imaging, thus suggesting a potential minor role of intra-islet PYY in men. However, we have demonstrated that prolonged action of locally produced full-length form of PYY can modulate insulin secretion even in isolated human islets.

Upon release, PYY (1-36) is cleaved by DPP-IV to form the degradation product, PYY (3-36).[36] As for chronic application of recombinant PYY (1-36), pharmacological inhibition of the intra-islets DPP-IV by sitagliptin potentiates glucose-stimulated insulin release, thus implying that chronic exposure to a local factor normally degraded by DPP-IV mediates such effect. In addition to PYY, several biological substrates exist for DPP-IV action, including active GLP-1(7-36) which is converted into a biologically inactive form as GLP-1(9-36) and is produced in pancreatic islets.[37] Because of its well-known potentiating effect on insulin secretion, the prolonged half-life of active intra-islets GLP-1 was expected to be the main

mediator of the beneficial effects of DPP-IV inhibition.[38] However, while blockade of GLP-1 signalling by either pharmacological or genetic approaches does not reverse the potentiating effect of sitagliptin on GSIS, immunoneutralization of PYY does, thus indicating that the local regulation of pancreatic PYY, rather than GLP-1, mainly modulates insulin response. From a clinical perspective, these results impact on the mechanism of actions of several DPP-IV inhibitors used as therapeutics for type 2 diabetes. While their beneficial effects are thought to be primarily due to the stabilization of active GLP-1, they can actually be ascribed also to a prolonged PYY(1-36) action, as further corroborated by the results of 12-week sitagliptin treatment study showing a significant increase in PYY (1-36) levels in association with improved beta cell secretion.[39]

The fact that application of PYY or DPP-IV inhibitors consistently modifies insulin response to glucose in rodent and human islets, despite their species-specific localization, suggests a common mechanism that may lie in a conserved receptor distribution. Proteomic approaches have not successfully detected NPYRs expression in islets;[40,41] however, mRNA and protein expressions have been reported both in rodent and human islets[27-29,33] for all NPYR subtypes but NPYR2 (which mediates the anorectic effect of PYY and is highly selective for PYY [3-36]). NPY1R expression particularly appears to be conserved and confined to beta cells, suggestive of consistency in PYY signalling and action in rodent and human islets.

In line with this, pharmacologically or genetically mediated suppression of NPY1R pathway negatively impacts islet function and glucose tolerance. In *in vitro* experiments, addition of the NPY1R blocker BIBP3226 abolishes the potentiating effect of sitagliptin on insulin release,[28] while activation of NPY1R (and NPY4R, NPY5R) protects mouse and human islets from cytokine-induced apoptosis and restores their glucose responsiveness.[29] *In vivo* studies have also demonstrated that mice lacking NPY1R either in beta cells[42] or in osteoblasts[43] have impaired glucose tolerance, thus extending the impact of NPY signalling, that could be additionally modulated by NPY and pancreatic polipeptide, on glucose homeostasis beyond pancreatic tissue regulation. On the other hand, injection of lipidated-NPY analogues appears to be able to protect beta cells and reduce hyperglycaemia induced by multiple low doses of streptozotocin[29] thus mimicking the protective effect reported for PYY analogues.

Old and New Regulators of PYY Release After Bariatric Surgery

Bariatric surgery causes major alteration of gut microbiota[44] by changing the abundance of specific bacterial *phila* and the identity of several bacterial metabolites, like short chain fatty acids (SCFAs), which are produced by bacterial fermentation with acetate, propionate, and butyrate being the most abundant. In the past years, several lines of evidence have linked PYY elevation with changes in faecal microbiota[45,46] and proven a direct effect of SCFAs on PYY gene expression and release from L-cells,[47-49] although these effects are more pronounced in human cell line and intestinal primary culture.[50] Likewise, increased levels of systemic BAs after bariatric surgery[51] have been reported to stimulate enterocrine PYY and GLP-1 secretion through the activation of the G protein-coupled bile receptor TGR5.[52] Mechanistically, PYY elevation appears to be dependent on intraluminal intestine delivery of BA and on basolateral intestinal TGR5 expression,[53] although the presence of this receptor has been reported in pancreatic islets too.[54] In search of factors triggering PYY release from islets, we found that, among SCFAs, propionate can induce a modest increase in pancreatic PYY production while also stimulating insulin response to glucose.[55] Unlike the propionate-mediated effect, which is conserved in mouse and human islets, activation of the BA receptor TGR5 in isolated islets results in a prominent induction of islet-derived PYY only in mice,[11] suggesting a possible species-specific impact of BA changes on gut-dependent PYY production. Nevertheless, as for propionate, elevated levels of BA post-surgery are likely to contribute to the restoration of islet secretory function not only through PYY elevation, but also via a direct effect, as application of TGR5 agonist GPBAR-A enhances GSIS in human as well as in mouse islets.[54]

In addition to SCFAs and BAs, other, still unidentified, factors are likely to contribute to the PYY increase from the gut and islets following bariatric surgery, including unexpected molecules. It is now well established that the weight loss achieved after operation reduces the 'low grade' inflammation associated with obesity and metabolic syndrome, as indicated by the reported decrease in circulating inflammatory mediators, such as C-reactive protein and several pro-inflammatory cytokines.[56-58] Surprisingly, we found that the levels of interleukin-22 (IL-22), a small cytokine mainly produced by Th1, Th17, Th22, and ILC3 cells, are indeed elevated in the serum of patients at 6 months after bariatric surgery and this can in turn, stimulate PYY production.[11]

IL-22 is a double-faceted cytokine playing pro-inflammatory and regenerative roles in different tissues.[59] Its effects on the pancreas and pancreatic islet function have been highlighted at cellular levels and in several models of T1D and T2D where it has consistently shown a protective and beneficial impact.[60,61] Unlike other cytokines, IL-22 protects pancreatic islets from oxidative and endoplasmic reticulum (ER) stress[62] and restores glucose tolerance and insulin sensitivity in mice under high fat diet.[63] Due to its unique role in alleviating metabolic disorders and its direct restorative effect on pancreatic beta-cells, increased IL-22 level adds as a potential mediator of the anti-diabetic and beneficial metabolic effects of bariatric surgery. Among its multiple positive influences on metabolic disease, IL-22 injection in obese mice leads to increased serum PYY levels which is thought to contribute to the reduction in food intake and weight.[63] This increase in PYY is likely to be caused by IL-22-mediated stimulation of PYY expression

from enteroendocrine L-cells and, to a small extent, from islets, as major effect of IL-22 on PYY gene expression and release has been demonstrated in colonic primary culture.[11] Thus, it is likely that under physiological conditions, part of the metabolic effects of IL-22 on islet function and survival are achieved through the modulation of PYY secretion.

Collectively, it is now clear that a complex combination of factors orchestrates the metabolic changes that follow bariatric surgery, through direct and indirect mechanisms that in some cases, unveil unprecedented interconnections. Interestingly, gut microbiota, BAs, and IL-22 have been recently been linked in the mechanism of insulin resistance associated with polycystic ovary syndrome (PCOS).[64] It is, therefore, conceivable that similar axes between these and other factors account for PYY and other gut hormone elevation post-surgery and for the long-sought mechanism of diabetes correction after bariatric surgery.

Towards PYY Application in the Clinic

Whereas there is no way to differentiate between the contribution of circulating and intra-islet PYY, rodent and human data suggest that they might both contribute to restore islet function and sustain the benefits of bariatric surgery over the long-term. New mechanistic links between key factors induced by bariatric surgery, restoration of impaired islet function and diabetes correction are constantly emerging and while this review focuses on the regulation of PYY and its effects post-surgery, it is clear that other factors also contribute to achieve the metabolic benefits elicited by surgery, and a combination of therapies may be required to successfully overcome the need for this invasive and irreversible procedure.

As for the additive effect of PYY(3-36) and GLP-1 on food intake reduction[65] the combination of PYY analogues to other incretin mimetics is expected to potentiate and sustain their long-term efficacy as recently proven.[66] Subcutaneous infusion of three hormones: GLP-1, PYY, and oxyntomodulin over a 4-week period improves glucose tolerance in diabetic patients by an effect superior to RYGB and caloric restriction. Despite a smaller reduction in body weight, both fasting and postprandial glucose levels were reported to be better improved with the three peptides infusion in association with a more favourable reduction in glyceamic variability between baseline and last week of intervention. Such results lead the way to surgery-free alternatives which carry not only more (or similar) benefits but also lower risks of adverse effects, such as hypoglycaemic events potentially secondary to RYGB.

In light of PYY involvement in obesity and diabetes, several efforts have been made in the past years to produce stable PYY analogues with particular attention to potent and selective NPY2R analogues which are resistant to DPP-IV-mediated cleavage.[67] Although the incorporation of *N*-methyl amino acids and the combination selective amino acids substitutions have identified stable peptide versions selective for NPYR subsets, finding long-active analogues is still a challenge.[68] Continuous administration is required to achieve durable anti-obesity and anti-diabetic effects even with short-length PYY(3-36) analogues[69] and half-life extending strategies like PEGylation and lipidation.[70] Of note, a recent reported strategy conjugating a functionally silent monoclonal antibody to a cyclized PYY(3-36) analog (mAb-cycPYY) has resulted in a bioactive peptide with unprecedented *in vivo* stability and slow infusion profile.[71] In DIO mice, mAb-cycPYY injection (every 3 days) potently reduced food intake and body weight, and improved parameters of glucose homeostasis (lowering either fasting or postprandial plasma glucose). These benefits are further enhanced by co-administration of the GLP-1 receptor agonist, liraglutide which also leads to a remarkable improvement in insulin sensitivity. Importantly, robust and well-tolerated anorexic effects were also observed in obese macaques in absence of emetic events, thus adding further potential to the GLP-1/PYY-based combination treatment for obese patients.

Concluding Remarks

The early and long-lasting reversal of diabetes after bariatric surgery has attracted a lot of attention and much effort has been made to identify the mechanism behind such remarkable change. A common consensus now posits that several factors, altered after surgery, affect glucose regulation and crucially improve the secretory properties of pancreatic islets. While many have been identified, the role of others is yet to be recognized, including the ones of peptide hormones. The impact of the gut hormone PYY on the post-surgery metabolic benefits is not restricted to food intake reduction and weight loss but extends to the amelioration of islet function and survival. Pancreatic PYY (produced in islet cells) can also contribute to the restoration of insulin response as a result of its post-surgery increase and prolonged action. Because of its known and newly established anti-obesity and anti-diabetic effects, PYY represents a therapeutic tool and significant progresses have been made to create stable and efficacious synthetic analogues. Furthermore, we anticipate that the identification of factors specifically triggering PYY and other incretins, both systemically and within the islets, may pave the way to novel valuable therapeutic strategies, overcoming the stability and pharmacokinetic issues of peptide therapeutics and yet leading to comparable metabolic benefits.

Author Contributions

CG and RR wrote and edit this review.

ORCID iD

Claudia Guida https://orcid.org/0000-0001-9475-1064

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