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Review

The role of peptide YY in regulating glucose homeostasis

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ABSTRACT

The gut-derived hormone peptide YY (PYY) is most commonly known for its effect on satiety, decreasing food intake and body weight in animals and humans. However, PYY is also involved in a wide range of digestive functions including regulating insulin secretion and glucose homeostasis. Over the last few years, there have been several interesting clinical and animal studies investigating the role of PYY in glucose homeostasis. This review aims to present an updated summary of findings over the last few decades highlighting the role of PYY in regulating insulin output and insulin sensitivity, and the potential mechanisms involved.

Contents

1. Introduction

Peptide YY (PYY) was originally named in light of two tyrosine residues at the N- and C-terminus of the protein [46]. PYY belongs to a family of peptides that includes neuropeptide Y (NPY) and pancreatic polypeptide (PP). These peptides are comprised of 36 amino acids and share extensive sequence homology [43]. PYY is expressed in both neurons and

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endocrine cells, notably endocrine L cells in the colon epithelium, whereas NPY and PP are preferentially expressed in neurons and endocrine cells, respectively. These peptides have various functions based on their receptor binding affinity to G-coupled protein Y receptors (Y1, Y2, Y4, Y5, Y6) that are widely expressed on different cells and organs.

There are two endogenous forms of PYY: PYY1-36 and PYY3-36. PYY3-36 is produced by the removal of two N terminal amino acids from the full-length form via dipeptidyl peptidase-IV (DPPIV) [43]. DPPIV is a cell surface enzyme ubiquitously expressed on endothelial and epithelial cells [35]. This enzyme most likely cleaves PYY3-36 from the full-length form as it is secreted from L cells in the colon. In removing the two N terminal amino acids, DPPIV changes the receptor specificity of PYY3-36 [35]. In contrast to PYY1-36, which binds to the Y1, Y2 and Y5 receptor and with lesser affinity to the Y4 receptor, PYY3-36 predominantly binds to the Y2 and Y5 receptor [9].

1.1. *Distribution of PYY*

PYY is mainly produced by endocrine L cells of the colon and rectum and appears to be the earliest hormone released by colonic endocrine cells, suggesting that this hormone is important in the development of the gastrointestinal tract [49]. PYY is also produced by endocrine cells of the lower intestine, stomach and pancreas and is present in neurons of the central nervous system (hypothalamus, pons, medulla, brainstem and spinal cord) and peripheral nervous system (enteric neurons) [16,41].

Within the pancreas, PYY is primarily co-expressed with glucagon in alpha cells of the islets of Langerhans, but is also found in pancreatic polypeptide-expressing islet cells as well as the exocrine pancreas [12]. The expression of PYY in early pancreatic islet cell precursors, particularly in the lineage-specific glucagon producing alpha cells, suggests that PYY may have a vital role in the differentiation, growth and development of the pancreas [16]. Considering that PYY is co-expressed in all islet cell types, albeit in lower quantities than in alpha cells, it appears that that all islet cell types are derived from a common PYY-expressing progenitor cell [48]. Interestingly, pancreatic alpha cells and intestinal cells that express PYY also co-express glucagon or glucagon-like peptides (GLP-1 and GLP-II), respectively [16].

1.2. *Factors influencing the release of PYY*

In humans, PYY3-36 is the main form produced postprandially, contributing to approximately 63% of circulating PYY in the fed state and only 37% in the fasted state [18]. PYY levels increase within 15 min of ingesting a meal, peak at approximately 60 min after ingestion and remain elevated for up to 6 h [1]. The initial rise in circulating PYY levels occurs before nutrients have reached the L cells of the colon, suggesting that an indirect neural and/or hormonal response regulates the immediate release of PYY after ingestion of a meal [43]. The sustained production of PYY after a meal appears to be a direct effect of intraluminal contents acting on the endocrine L cells of the colon [40]. Interestingly, dietary fat is the most potent stimulant of PYY release [3].

1.3. *Functions of PYY*

PYY regulates a broad range of gut functions that are mainly inhibitory. These include inhibiting glucose-stimulated insulin secretion [12], inhibiting gastric secretion and emptying [3], decreasing gastrointestinal motility [29], reducing gallbladder emptying [23], inhibiting pancreatic and intestinal secretion [46], promoting vasoconstriction to the gastrointestinal tract and pancreas [30,46] and enhancing salt and water absorption in the colon [39]. All of these PYY-mediated effects are induced via actions on the brainstem, and could affect digestion, absorption, satiety and energy balance [37,40]. Indeed, it has been shown that both forms of PYY reduce food intake when peripherally administered [15]. Other functions of PYY include inhibiting lipolysis [14] and stimulating the proliferation of the gastrointestinal mucosa [28]. More recently, it has been demonstrated that PYY exhibits a mitogenic effect on pancreatic acinar and ductal cells in vitro [26].

2. Effect of PYY1-36 on glucose homeostasis

Initial studies revealed that PYY administered intravenously to mice has no effect on basal plasma levels of insulin, glucagon or glucose [12]. However, in the dog, it was shown that PYY administered intravenously at postprandial concentrations inhibits basal insulin secretion [19,21]. In contrast, there have been more consistent findings to confirm that PYY has an important role in glucose-stimulated rather than basal insulin secretion. Intravenously administered PYY inhibits glucose-stimulated insulin secretion as well as carbachol- and arginine-induced glucagon secretion in mice [12,45]. In vitro studies also demonstrate that PYY dose-dependently inhibits glucose-stimulated but not basal insulin secretion [38]. This is supported by work on isolated mouse islets where PYY antiserum potentiates glucose-induced insulin secretion in culture [25]. Indeed, studies using perfused islets isolated from rats suggest that this is a direct action of PYY on islets [7].

Studies from our laboratory suggest that PYY has an important regulatory role in insulin secretion in vivo. PYY knockout mice generated by us that do not produce PYY1-36 or PYY3-36 are equally glucose tolerant as control mice. However, they have significantly higher insulin levels for the duration of a glucose tolerance test [11]. Islets of Langerhans from PYY knockout mice were found to hyper-secrete insulin in response to high glucose concentrations [10]. Together, these data suggest that PYY importantly modulates glucose-stimulated insulin secretion from the islets of Langerhans.

2.1. *Effect of PYY3-36 on glucose homeostasis*

Recent studies have investigated whether PYY3-36, like PYY1-36, also has a role in regulating glucose homeostasis in vivo, in light of the new findings that PYY3-36 reduces food intake. In a study by Pittner et al. [42], a single intraperitoneal injection of PYY3-36 administered to fasted *ob/ob* and *db/db* mice did not affect plasma glucose concentrations. Furthermore, a 4-week infusion of PYY3-36 by osmotic pump to *ob/ob* mice and *fa/fa* rats did not influence fasting plasma glucose levels [42]. In contrast, circulating HbA1c and fructosamine levels are

lowered in genetically obese rodents and in diet-induced obese mice also given a 4-week infusion of PYY3-36 by osmotic pump, consistent with a possible hyperglycemic-lowering effect of PYY3-36 [36]. However, the effect of PYY3-36 on fasting insulin and glucose-stimulated insulin levels were not reported in either of these two studies. Separate experiments have also shown that PYY3-36 had no effect on glucose-stimulated insulin secretion or arginine-stimulated glucagon secretion in anesthetized Sprague–Dawley rats [8].

It is important to address the fact that PYY3-36 is predominantly produced after a meal and may therefore be less potent in affecting fasting glucose and insulin levels when compared to PYY1-36. Interestingly, one study has compared these two forms of PYY in inhibiting 2-deoxy-D-glucose (2-DG)-stimulated insulin release, demonstrating that PYY3-36, the main form produced postprandially, inhibits D-glucose-stimulated insulin release, a glucose analogue and vagal stimulant of insulin release, albeit to a lesser degree than PYY1-36 [52]. It may be worthwhile to explore and compare the effects of PYY1-36 or PYY3-36 or both forms together on basal and glucose-stimulated insulin secretion in vivo and in vitro, and in acute and long-term studies to determine how these peptides function in fasting and postprandial conditions and whether these peptides have a synergistic action.

2.2. *Mechanisms for PYY-mediated inhibition of insulin secretion*

The mechanism by which PYY inhibits insulin secretion is still unclear. However, several studies have led to an understanding that PYY acts on Y1 receptors to influence insulin secretion. A study in conscious dogs suggests that Y2 and Y5 receptors are not involved in the inhibitory effect of PYY on 2DG-induced insulin secretion, and that the effect is likely to be mediated by Y1 receptors [52]. This is because PYY3-36, a selective Y2 and Y5 agonist, was less potent than PYY1-36, an agonist for all known Y receptors, in inhibiting insulin secretion. Moreover, the Y1 receptor requires the amino acid terminal of PYY for full biological activity [52]. The finding that PYY3-36 had no effect on glucose-stimulated insulin secretion in rats also suggests that insulin secretion is not mediated by Y2 or Y5 receptors [8]. One study has suggested that PYY inhibits insulin secretion by inhibiting the accumulation and action of cyclic AMP [38]. However, as adenylate cyclase inhibition is a feature of all Y receptor subtypes, it was not determined which Y receptor subtype was involved in the PYY-mediated inhibition of insulin secretion [38].

It is likely that PYY acts directly on Y1 receptors in the pancreas to inhibit insulin secretion. Of all the known Y receptors, only the Y1 receptor subtype has been detected on pancreatic islets [13]. Within the islet of Langerhans, it has been demonstrated that these Y1 receptors are found on beta cells that produce insulin [54] and delta cells that produce somatostatin, a hormone that potently inhibits insulin and glucagon secretion [33]. However, the possible mechanisms by which PYY secreted by alpha cells acts via the Y1 receptor on beta or D cells to influence insulin secretion requires further investigation.

PYY may also act on and influence other cells in pancreatic islets to inhibit insulin release by beta cells. Indeed, it has been shown that PYY inhibits arginine-induced secretion of glucagon in anesthetized rats [33]. Moreover, PYY decreases the insulin-stimulating effect of glucagon in perfused isolated mouse islets at glucose concentrations where PYY alone does not affect insulin secretion [25]. This suggests that PYY may indirectly attenuate the stimulatory effect of glucagon on insulin secretion [25]. Considering PYY and glucagon are co-localized in the secretory granules of islet alpha cells, it is possible that PYY acts as a paracrine regulator of insulin secretion [38]. However, it is still unclear whether PYY is co-released with glucagon [25]. Another study from the same laboratory also revealed that PYY inhibits gastric inhibitory polypeptide (GIP)-stimulated insulin secretion in dogs [21]. Both of these studies imply that PYY may be part of an integral negative feedback loop, which regulates insulin secretion.

PYY may also exert its effects on the central nervous system to inhibit insulin secretion. It is likely that PYY binds to the Y1 and Y2 receptors located in the brainstem to modulate vagal output and influence digestive functions that include regulating insulin secretion [22,31]. Studies have demonstrated that PYY inhibits neurally-stimulated insulin release mediated by 2-DG in dogs and mice [19,20]. In particular, it was shown that PYY blocks β-adrenergic-stimulated insulin secretion in dogs [19]. However, PYY also inhibits neuropeptide-stimulated insulin release mediated by gastrin-releasing peptide (GRP) and tetragastrin (G4) [20].

2.3. *Effect of PYY3-36 on insulin sensitivity*

Although it appears that PYY3-36 has less of a role on basal and glucose-stimulated insulin secretion, recent studies suggest a role for PYY3-36 in regulating insulin sensitivity. From the same study by Pittner et al. [42], a 4-week infusion of PYY3-36 by osmotic pump to diabetic fatty Zucker rats not only improves glycemic indices of HbA1c and fructosamine, but also results in a trend to improved insulin sensitivity during hyperinsulinemic–euglycemic clamps [42]. A later study also showed that an intravenous infusion of PYY3-36 for several hours under hyperinsulinemic–euglycemic clamp conditions in diet-induced insulin resistant mice enhanced insulin sensitivity and improved glucose disposal [50]. However, PYY3-36 had no affect under either basal or hyperinsulinemic conditions to reduce endogenous glucose production [42].

Together, these two studies highlight that endogenous PYY3-36 may influence insulin sensitivity and glucose uptake. A possible mechanism by which PYY3-36 could influence insulin sensitivity is via the hypothalamic Y2 receptor. This is likely, considering previous reports have demonstrated that PYY3-36 acts on the Y2 receptor to inhibit NPY neurons and activate proopiomelanocortin (POMC) neurons in the hypothalamus [6]. Moreover, NPY over-expression in the hypothalamus results in obesity and insulin resistance in rodents [32,53], whereas activation of melanocortin receptors 3 and 4 enhance insulin sensitivity and inhibition of these receptors diminish insulin sensitivity [32,53]. However, the downstream pathways by which PYY3-36 leads to changes in glucose uptake by muscle and adipose tissue are not well characterized [50]. It is

still to be determined whether PYY1-36 has a role in regulating insulin sensitivity.

3. Clinical studies

PYY was not found to inhibit basal insulin secretion in humans after acute intravenous administration [2]. A more in depth study has also revealed that PYY administered acutely does not influence glucose-stimulated insulin secretion or the glucose elimination rate in a population of healthy female subjects [4]. There has been only one study investigating circulating PYY profiles after an oral glucose tolerance test in obese and lean people. This study showed that the PYY was comparable between lean and obese people, despite the fact that the obese people were more insulin resistant and produced significantly more insulin in response to glucose [27]. Another study found no correlation between circulating PYY or insulin levels in normal, obese and anorexic subjects [44].

There have also been several studies investigating the effect of PYY3-36 on glucose homeostasis in humans. One study showed that PYY3-36 infusion did not affect circulating insulin levels in either obese or lean subjects [5]. It has also been reported that fasting PYY3-36 levels are significantly higher in type 2 diabetic subjects than controls, although this difference did not correlate to insulin or glucose levels [17]. Also, this study demonstrated that postprandial PYY levels were blunted when compared to controls [17].

Although these studies suggest that PYY1-36 or PYY3-36 do not have a role in glucose homeostasis, it is important to highlight that PYY levels were measured in obese people that already have high fasting insulin [5], in diabetic subjects that were already insulin resistant [17] or in anorexic subjects who had an eating disorder and were likely to have an altered PYY response in addition to having decreased baseline insulin levels [44]. Indeed it is feasible that these obese, diabetic and anorexic subjects may have decreased sensitivity to PYY1-36 and PYY3-36, which normally function to influence glucose-stimulated insulin secretion or insulin sensitivity, respectively. There have not been any studies to date investigating the effects of PYY3-36 on insulin sensitivity in humans. However, more recent findings demonstrating that there is a modest association between the Arg72Thr mutation in the PYY gene and a decrease in glucose tolerance and lower glucose-stimulated insulin release in type 2 diabetes [47] highlights that the effect of PYY and glucose homeostasis is worth investigating further.

In contrast to previous studies investigating PYY levels in people with metabolic disorders, we recently investigated PYY levels in a group of females who were first-degree relatives of people with type 2 diabetes [10]. Our aims were to determine whether PYY deficiencies play a causative role in the development of obesity and type 2 diabetes. We found that women with a genetic propensity to type 2 diabetes and the development of excess adiposity had significantly lower fasting serum PYY levels than controls without any family history of type 2 diabetes. Fasting serum PYY levels were positively correlated with insulin sensitivity, and negatively correlated with fasting serum adiponectin levels, which predicts both adiposity and insulin sensitivity [24,51]. There was also a negative correlation between fasting serum PYY levels and HOMA-B, an estimation of insulin secretion using the homeostasis model assessment, which approximates the steady state beta cell function for the duration of the euglycaemic–hyperinsulinemic clamp, using the fasting serum glucose and insulin levels [34]. These data together with our in vitro work suggests that low circulating levels of PYY could contribute to the development of insulin hypersecretion and insulin resistance. Moreover, low PYY levels may predispose to the subsequent development of excess adiposity and type 2 diabetes that occurs with high frequency in people with a family history of type 2 diabetes.

Currently, DPPIV inhibitors are being used in clinical trials for the treatment of type 2 diabetes. This is because DPPIV is the major enzyme that degrades incretins such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which are important in reducing glucose levels and stimulating insulin secretion [35]. However, DPPIV inhibitors would conceivably block the production of PYY3-36. It has not been established whether DPPIV inhibitors promote the action of PYY1-36 to influence insulin secretion. Moreover, it is unclear whether DPPIV inhibitors attenuate the effect of PYY3-36 to enhance insulin sensitivity. Indeed, DPPIV is also required for the anorectic effect of PYY3-36 and therefore DPPIV inhibitors may down regulate the function of incretins and negatively influence food intake in type 2 diabetic subjects. Nonetheless, it is important to determine whether these incretins, which are produced by the same endocrine L cells that produce PYY, co-regulate insulin secretion or food intake.

4. Conclusions

From the studies performed so far, it appears that PYY1-36 has a more potent role in inhibiting glucose-stimulated insulin secretion than PYY3-36, whereas PYY3-36 acts to improve insulin sensitivity. Future experiments need to address whether PYY1-36 affects insulin sensitivity as well as to clarify the combined effect of both PYY1-36 and PYY3-36 in influencing glucose-stimulated insulin secretion. It is likely that these two forms of PYY have different functions due to variations in receptor binding, and because they are differentially produced under fasting and postprandial conditions. To gain a better understanding into how these two forms of PYY influence glucose homeostasis, future experiments examining and comparing the short- and long-term effects of PYY1-36 and PYY3-36 on basal and glucose-stimulated insulin secretion and insulin sensitivity in vivo and in vitro would be useful. This would also clarify whether these two forms of PYY have a synergistic or counter-regulatory function on insulin secretion and insulin sensitivity. These findings would contribute significantly towards understanding how these hormones might be altered in type 2 diabetes as well as understanding how DPPIV inhibitors may be acting on hormones other than incretins as a means for treating type 2 diabetes.

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