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Pancreatic polypeptide revisited: Potential therapeutic effects in obesity-diabetes

Wuyun Zhu, Neil Tanday, Peter R. Flatt, Nigel Irwin *

Diabetes Research Centre, Biomedical Sciences Research Institute, Ulster University, Coleraine, Northern Ireland, BT52 1SA, UK

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ABSTRACT

Pancreatic polypeptide (PP), a member of the neuropeptide Y (NPY) family of peptides, is a hormone secreted from the endocrine pancreas with established actions on appetite regulation. Thus, through activation of hypothalamic neuropeptide Y4 (NPY4R or Y4) receptors PP induces satiety in animals and humans, suggesting potential anti-obesity actions. In addition, despite being actively secreted from pancreatic islets and evidence of local Y4 receptor expression, PP mediated effects on the endocrine pancreas have not been fully elucidated. To date, it appears that PP possesses an acute insulinostatic effect, similar to the impact of other peptides from the NPY family. However, it is interesting that prolonged activation of pancreatic Y1 receptors leads to established benefits on beta-cell turnover, preservation of beta-cell identity and improved insulin secretory responsiveness. This may hint towards possible similar anti-diabetic actions of sustained Y4 receptor modulation, since the Y1 and Y4 receptors trigger comparable cell signalling pathways. In terms of exploiting the prospective therapeutic promise of PP, this is severely restricted by a short circulating half-life as is the case for many regulatory peptide hormones. It follows that long-acting, enzyme resistant, forms of PP will be required to determine viability of the Y4 receptor as an anti-obesity and -diabetes drug target. The current review aims to refocus interest on the biology of PP and highlight opportunities for therapeutic development.

1. Introduction

In recent times incretin-based drugs have emerged as notable effective therapeutic agents for the management of Type 2 diabetes mellitus (T2DM) and obesity [51]. These drugs focused on mimicking and extending the biological action profile of glucagon-like pepitide-1 (GLP-1) [3]. However, recent FDA approval of a hybrid peptide with dual GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptor modulating actions for T2DM, namely tirzepatide [39], demonstrates the antidiabetic efficacy of peptide therapies beyond GLP-1 alone. As such, a related family of gut-derived peptide hormones, namely the neuropeptide Y (NPY), have generated interest in terms of exploitable therapeutic potential for obesity-diabetes in this regard.

The NPY family consists of three structurally similar peptides, neuropeptide Y (NPY), pancreatic polypeptide (PP) and peptide tyrosine tyrosine (PYY), that all possess an amidated tyrosine residue at their C-terminus and a common tertiary PP-fold [12,95]. All NPY peptides are natural ligands of neuropeptide Y receptors (NPYR), a group of rhodopsin-like G_i-protein-coupled receptors (GPCR) linked to inhibition of cAMP production ([64]; Fig. 1A). To date, four NPYR subtypes (Y1, Y2, Y4 and Y5) have been characterised in humans [71], with receptor distribution evidenced both within the central nervous system (CNS) as well as peripheral organs [105,5]. NPYR6 (Y6) has also recently been observed in rodents with some postulated involvement in the regulation of energy homeostasis, but this receptor appears to exist as a pseudogene and is of no obvious physiological importance in the human setting [63]. Native PYY and NPY are known to bind to Y1, Y2 and Y5 receptor subtypes, whilst PP is a selective agonist for the Y4 receptor [71].

In terms of biological function, modulation of Y1 receptor activity is known to affect appetite [68] as well as pancreatic islet cell function [50]. Similar to Y1, the Y5 receptor is also associated with stimulation of appetite leading to increased energy intake [38]. Conversely, much attention has been directed towards activation of the Y2 receptor as an anti-obesity therapeutic target, given its ability to suppress appetite and reduce body weight [74]. However, Y4 receptor activity has also been implicated in the induction of satiety and regulation of energy metabolism, especially within the area postrema (AP) and nucleus tractus solitarius (NTS) [28] that are accessible to peripherally released PP.

* Correspondence to: Ulster University, School of Pharmacy and Pharmaceutical Sciences, Coleraine, Northern Ireland, BT52 1SA, UK.
E-mail address: n.irwin@ulster.ac.uk (N. Irwin).

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Further to this, clear expression of Y4 receptors in the endocrine pancreas would also suggest a role for this receptor in islet function [45]. Nonetheless, the majority of literature deliberating therapeutic potential of the NPY family of peptides has concentrated on the Y2 receptor and anti-obesity actions [51,8]. Therefore, the current review will focus on PP and the Y4 receptor that has been somewhat neglected to date.

2. PP discovery and evolution

PP producing cells are located within the pancreas of most tetrapod vertebrates, including humans [23]. Accordingly, PP was first documented in 1968 as an impurity during the isolation of insulin from avian pancreatic tissues [46], being later separated and fully characterised in 1975 [47]. Indeed, early work attempting to decipher the immunogenicity of porcine insulin preparations documented production of insulin antibodies in humans that was ultimately shown to be a combination of antibodies against various islet hormones including PP [11,21]. PP was the first peptide to be identified among the NPY family, despite emerging later in evolution [55]. In this regard, evidence suggests that the PP gene appeared as a duplication of the PYY gene during the evolution of tetrapods [55]. However, the peptide was also recognised in early amphioxus (protochordate), a primitive form of fish, where endocrine pancreatic cells were located within the gut, of which PP was a significant constituent [75]. In contrast to the other members of the NPY family, sequence homology of PP is less well preserved among species [55] with only seven residues remaining conserved during evolution that are speculated to be important for protection of the essential PP-fold tertiary structure [23]. Thus, PP was present in evolution at a very early stage, but the amino acid sequence is somewhat different to that found in humans today.

3. PP structure

As the name suggests, the classic structural feature of the NPY family of peptides, namely the PP-fold, relates to its first demonstration in avian PP using X-ray crystallography [12]. The PP-fold contains a polyproline helix (residues 2–8) and an α-helix (residues 14–32) connected by a β-turn, forming a hairpin-like structure and small hydrophobic pocket within the molecule [12]. This structure is critically important for receptor binding and bioactivity of the NPY peptides [34]. In that respect, it should be noted that evolutionary conservation of the Pro^5 and Pro^8 residues, with Pro^2 being present in most, but not all species, highlights the likely critical involvement of these amino acid residues for the polyproline helix of PP [23]. Furthermore, Gly^9 is highly conserved across species, as is a Pro^{13} or Pro^{14} residue, suggesting their importance for preservation of the classic PP fold [24]. The α-helical region of PP is more variable across species, but hydrophobic residues are consistently found at positions 20, 24 and 28, again highlighting likely involvement in maintenance of the PP structural motif [24]. A further conformational aspect that has been shown to influential for PP biological activity relates to the C-terminus, since removal of the Tyr^{36} residue that is highly conserved in mammals, precludes physiological effects of PP [58]. Moreover, there is a suggestion that the key biological actions of PP reside predominantly within its C-terminal hexapeptide fragment [22], although further studies are required to confirm this.

Importantly, PP is recognised by two regions of the Y4 receptor, with the PP-fold inserted into the hydrophobic receptor region at the top of transmembrane helix 2 (TM2), where Tyr^{27} is docked by $Tyr^{2.64}$, and the C-terminal region of PP attached to transmembrane helices 6 and 7 (TM6–7) with Arg^{33} and Tyr^{36} binding to $Phe^{7.35}$ [72]. The most recognised cell signaling cascade linked to Y4 receptor activation is inhibition of adenyl cyclase activity and cAMP formation, decreasing activity of downstream targets such as protein kinase A (Fig. 1A). However, the Y4 receptor has also been described to couple to a G_q protein in certain tissues, such as smooth muscle cells, that promotes generation of inositol 1,4,5-phosphate (IP_3) ([66]; Fig. 1B), a typical downstream signaling molecule of G_q-protein-coupled receptors. Although, the overall impact of this lesser described Y4 intracellular pathway on the physiological action profile of PP, as described below, is relatively unknown.

4. PP metabolism

PP has a short biological half-life in human circulation of around 7 min [1], being chiefly degraded by the proteolytic enzymes DPP-4 and neprilysin (NEP) (Fig. 2). While DPP-4 classically cleaves X-Pro dipeptides from the N-terminus of polypeptides, NEP tends to digest the molecule into smaller sequences consisting of 5–10 residues ([37,76]; Fig. 2). Similar to other regulatory peptides [26,100], N-terminal dipeptide cleavage of PP by DPP-4 severely impedes biological activity [25]. Equally, NEP-mediated proteolysis is also believed to exert an important impact on the bioactivity of PP [25], but the identity and

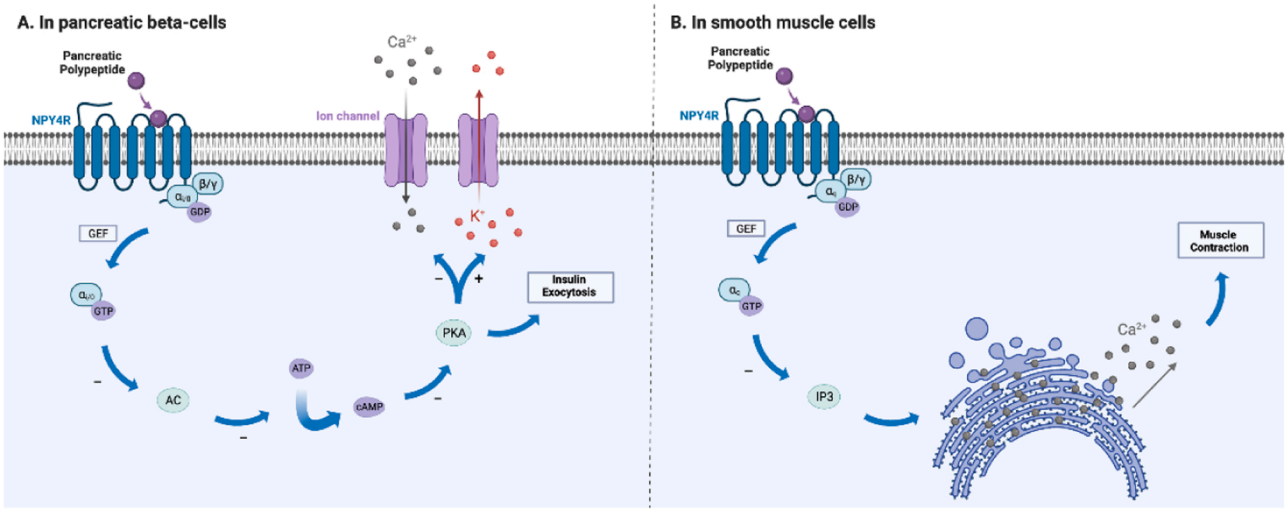

Fig. 1. Proposed intracellular signalling pathways for PP in (A) pancreatic islet beta-cells and (B) smooth muscle cells. (A) The most described action of PP related to G_i-protein coupling linked to inhibition of cAMP production and decrease in activity of downstream activity such as PKA within islet cells. (B) There is also a suggestion that PP can couple with a G_q protein in certain tissues including smooth muscle, that promotes generation of IP_3 through PLC activity. *Abbreviations*: AC, adenylyl cyclase; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; GDP, guanosine diphosphate; GEF, guanine nucleotide exchange factors; GTP, guanosine triphosphate; IP_3, inositol 1,4,5-phosphate (IP_3); PKA, protein kinase A; PP, pancreatic polypeptide.

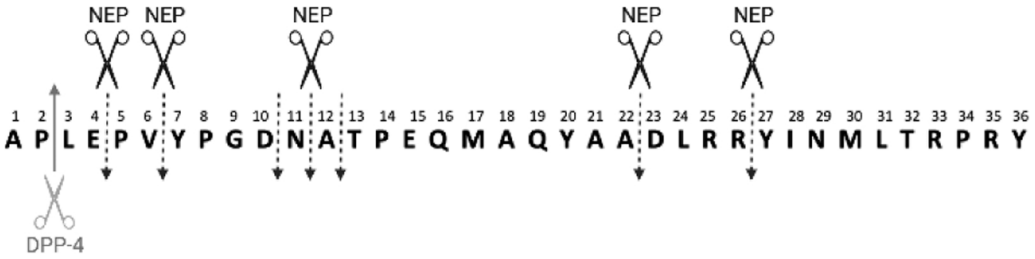

Fig. 2. Amino acid sequence of PP highlighting potential cleavage sites for DPP-4 and NEP, as described by [25]. One letter amino acid abbreviations and the residue number within the sequence is provided. Dashed arrow shows DPP-4 cleavage site between amino acid residue numbers 2 and 3, with solid arrows denoting the various NEP cleavage sites.

biological profile of NEP-derived PP degradation products has not yet been fully established. Although, NEP has been suggested to cleave PP between Glu^4 and Pro^5, Val^6 and Tyr^7, Asp^{10} and Asp^{11}, Asp^{11} and Ala^{12}, Ala^{12} and Thr^{13}, Ala^{22} and Asp^{23} as well as Arg^{26} and Arg^{27} (Fig. 2). Thus, fully enzymatic resistant forms of PP will likely be required to fully uncover both its overall physiological action profile as well as any related therapeutic benefits.

5. PP distribution

PP is principally expressed by a particular group of cells originating from islet cells of the endocrine pancreas named PP-cells (also known as γ-cells or F-cells). It follows that PP is predominantly produced from the pancreas in humans, but extrapancreatic secretion has been evidenced in some species including rats, dogs and possums [29]. Although PP-cells account for less than 5% of total pancreatic islet cell mass [14], PP-cell rich regions are found in the uncinate process with some slight extension to the surrounding pancreatic head [101]. In these specific islet areas PP-cells can account for over 50% of the islet cell count [101], advocating a possible functional role for PP in such regions. Interestingly, the development of T2DM has been linked to a preferential loss of insulin secreting beta-cells within the head of the pancreas [102]. Given pancreatic islet cells are known to utilise important paracrine signalling pathways [17], this could imply a role for PP in the pathogenesis of T2DM, but confirmation of such is still required. There was an initial suggestion that the PP-cell population increases in type 1 diabetes mellitus [33], but that has been challenged by others [78]. However, such inconsistencies could also be related to the part of the pancreas analysed, given PP cells are located predominantly in the uncinate process. There are also well characterised alterations of PP secretion in patients with chronic pancreatitis [87], that may be linked to early observations of PP cell hyperplasia in this condition [48]. Interestingly, PP has been demonstrated to improve abnormal glucose metabolism in patients with chronic pancreatitis [16], further highlighting a potentially important role for PP in this inflammatory disease. Of note, there are two types of PP-cells present in human pancreatic islets, either cells with electron-dense large secretory granules or those with electron-lucent, smaller secretory granules [90], but the significance of this in terms of normal physiology and disease is still unknown.

6. PP secretion

PP levels are elevated following nutrient ingestion, characterised by two distinct phases. In the initial cephalic phase, PP secretion significantly increases within a few minutes postprandially [60]. Such an effect that can be partially recapitulated by sham-feeding [85], but is abolished by vagotomy [83,86], highlighting a critical role of vagal transmission for PP hormone release. Indeed, this cholinergic pathway is considered to be the primary regulator of PP secretion [84]. The second phase is linked to the GIT and triggered by various enteric stimulus, including protein [104], lipid [1] and carbohydrates [62]. In addition, two other hormones appear to play a crucial role in the postprandial release of PP, namely cholecystokinin (CCK) and somatostatin (SST), the former being a stimulant and the latter a suppressant [59]. In addition, GIP has also been demonstrated to stimulate PP secretion [98], but the implication of this is not yet confirmed. Although, the GIP stimulatory effect, that appears to be dependent on calcium channel activity, has recently been confirmed following development of a new sandwich enzyme-linked immunosorbent assay for assessing mouse islet PP secretion [82]. Interestingly, there is a suggested link between glucagon and PP secretion [4], with GIP also known to directly modulate glucagon secretion [19], that could represent an as yet unexplored link between the complementary islet effects of PP and GIP. In addition, in a certain population of humans with T2DM, it has been proposed that PP could represent a biomarker for GIP receptor activation [97], further highlighting a relationship between these peptide hormones. Circulating blood glucose concentrations can also regulate PP release, with hypoglycaemia acting as a strong secretory stimulus [30] and a hyperglycaemic environment suppressing hormone release [62]. In that respect, blockade of cholinergic signalling diminishes PP secretion in response to hypoglycaemia [83], in keeping with the idea that cholinergic, vagal stimulation is the overall most important factor regulating PP secretion [84].

7. PP physiological effects and therapeutic potential

In terms of pancreatic effects, PP exerts insulinostatic actions [44,6] and has also been reported to inhibit both glucagon [4] and somatostatin [45] release. More recently, despite an inhibitory effect on insulin secretion, native PP has been shown to protect against beta-cell apoptosis [44], that could suggest possible benefits in diabetes. Interestingly, sustained activation of Y1 receptors also results in a similar positive effect on pancreatic beta-cell function [94]. In addition, PP is a recognised key player within the gut-brain axis, interacting with many other gut and pancreatic factors to help control overall metabolism [36]. As such, the primary physiological actions of PP uncovered to date are suppression of gastric emptying and appetite [40], as well as increasing energy expenditure [49]. In this regard, it has been demonstrated that PP gains access to the CNS via the dorsal vagal complex (DVC) that has a leaky blood-brain-barrier (BBB) [49], binding to abundant Y4 receptors located in this region to control energy balance [103]. However, the possibility that local PP secretion activates vagal afferents to modulate central energy homeostasis should not be discounted. Either way, PP appears to exert a negative effect on energy balance, raising the suggestion of therapeutic potential for obesity as an endogenous satiety signal.

Accordingly, peripheral administration of PP results in reduced energy intake in rodents [61] and healthy humans [7]. Indeed, a blunted PP secretion was first observed in obese hyperphagic Prader-Willi patients [108] with exogenous PP application able to reduce food intake in these patients [9]. Furthermore, in people with bulimia nervosa, reduced circulating levels of PP in response to food ingestion are observed [69], whilst in anorexia nervosa plasma PP concentrations are

elevated [25], which likely contributes to the pathophysiology of these disorders in humans. Nonetheless, to date there is little direct evidence that PP, or activation of Y4 receptors, can reduce body weight in humans. However, in agreement with an effect of PP to reduce appetite, rodent models overexpressing PP present with significant decreases in food consumption and suppression of gastric emptying [96]. Somewhat surprisingly, in contrast to the energy-negative characteristics of peripherally infused PP, direct CNS administration of PP exerts quite opposite effects. As such, PP injection into the Y4-rich region of the hypothalamus leads to increased food intake [18]. In a similar manner, Y4 receptor knock-out mice exhibit signs of reduced appetite and body weight [80,89]. These differences are intriguing and suggest the actions of PP in the periphery and CNS work in concert to exert an overall inhibitory effect on energy intake. Taken together, it is clear that the gut-brain axis has a significant impact on the biological action profile of PP, and this merits genuine consideration in terms of attempts to exploit PP therapeutically (Fig. 3), as discussed below.

8. Pharmacotherapy

8.1. PP as anti-obesity agent

Obesity is generally linked to long-term excessive calorie intake leading to an energy imbalance [107], and is also an independent risk factor for the development of T2DM. In this regard, Y4 receptors represent an important aspect of negative energy balance [42] to directly regulate circadian food ingestion [28]. Specifically, the Y4 receptor is known to operate in conjunction with Y2 receptors, as well as vagal afferents, to control energy intake and expenditure [28]. In the brain, PP activates Y4 receptors of the postrema region to trigger anorexic signals within the hypothalamus through modulation of the vago-vagal reflex arc, a system that conveys messages from the stomach to the brain, and then back to the stomach [57]. In this respect, activation of α-melanocyte-stimulating hormone (α-MSH) signaling is considered a potential mechanism for the anorexic effect of hypothalamic Y4 receptor activation [57,79]. In addition, PP has also been shown to suppress appetite by inhibiting hypothalamic orexigenic pathways through down-regulation of the hunger-stimulating hormone orexin, while simultaneously increasing anorexigenic pathways through up-regulating brain-derived neurotrophic factor (BDNF) signaling [81]. This collective knowledge relating to the mechanisms of how PP modulates energy intake is derived exclusively from rodent systems.

It follows that although the satiety-inducing effects of PP have been established for some 40 years [10], clinical application in obesity has yet to be fully realised [99]. As suggested above, this could be related in part to the short biological half-life of native PP [25], as well as a more intense research focus on other satiety inducing peptide hormones such as GLP-1 and PYY [92]. In addition, whilst the mechanisms involved in PP-induced reductions of appetite have been investigated in rodents, related mechanistic pathways in humans remain to be fully elucidated, although inhibition of food intake is undoubtedly observed in both settings [7]. Moreover, recent evidence of pronounced appetite suppression and body weight lowering actions of combined regulatory peptide hormone receptor modulation, such as GLP-1 and Y2 [27], may see a rekindling of interest in Y4 receptor activating compounds as anti-obesity agents ([13,27]; Fig. 3). This combined therapy approach can often lead to milder adverse effect profiles due to decreased individual drug doses, alongside improvements in long-term weight-control ([2,56]). Indeed, following initial positive outcomes of GLP-1 and PYY (3−36) combination therapy [27], a dual GLP-1/Y2 receptor agonist has been characterised with prominent benefits on glucose regulation and body weight control [65]. In this regard, the possibility of Y4 receptor activation to augment generation of IP_3 (Fig. 1B), a cell signaling pathway also employed by incretins [70], highlights potential complementary GLP-1/Y4 receptor actions. This could suggest as yet untapped anti-obesity potential for GLP-1/Y4 receptor combination therapies that merits further detailed investigation (Fig. 3).

8.2. PP as anti-diabetic agent

A therapeutic role for PP in diabetes would initially seem unlikely given its general insulinostatic properties [44]. However, it has recently been documented that prolonged activation of specific pancreatic Y receptors can yield positive effects on islet cell function, including a marked upregulation of beta-cell proliferation/apoptosis ratios [106,50]. Accordingly, acute activation of Y1 receptors also evokes an inhibitory effect on insulin secretion [43], but more interestingly sustained stimulation of Y1 receptors in rodent models of diabetes leads to notable enhancements of pancreatic islet morphology and insulin secretion possibly due to induction of beta-cell rest, resulting in significantly improved metabolic state [52,53,94]. We recognise that the islet effects of Y1 and Y4 receptor modulation may not be directly transferable, but consider this probable given that both receptor subtypes activate almost identical cell signalling pathways [15]. Interestingly, these Y1 receptor agonists were derived from phylogenetically ancient fish PYY amino acid sequences, since enzyme-resistant peptides originating from the human PYY sequence lacked bioactivity [52], highlighting the challenges in synthesising enzymatically stable, bioactive, peptides of

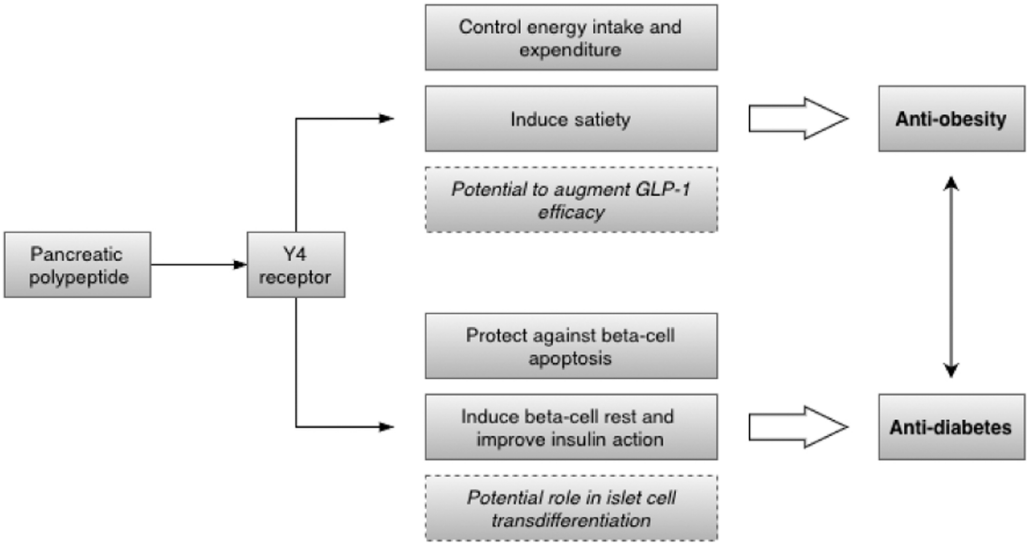

Fig. 3. A schematic summarising the potential anti-obesity and anti-diabetic actions of PP. Through activation of hypothalamic Y4 receptors PP can induce satiety and regulate energy expenditure to reduce body weight, and potentially augment centrally-mediated GLP-1 actions. In addition, modulation of pancreatic Y4 receptors can improve beta-cell turnover and preserve identity, alongside a complementary effect of augmentation of peripheral insulin action, to exert anti-diabetic actions. There is also a suggestion that PP can positively affect islet cell transdifferentiation events. Actions noted in *italicised text* are still hypothetical and require confirmation.

the NPY family. Some small molecular weight Y4 agonists have been characterised [41,88], but specificity and safety of such compounds for activation of peptide hormone receptors has long been of concern. Importantly, in good accord with observations utilising Y1 receptor modulation, PP-induced activation of pancreatic Y4 receptors has been demonstrated to possess beta-cell benefits such as protection against apoptosis [44], although full translation of such effects to the human setting is still required. Furthermore, PP has been reported to improve insulin sensitivity through enhancing the availability of haptic insulin receptors [77], an action conceivably linked to the 'resting' effect of PP on beta-cells and prevention of hyperinsulinaemia induced insulin receptor downregulation [20]. Although still in its infancy, these observations could suggest an important beta-cell protective effect of PP with obvious therapeutic benefits in T2DM (Fig. 3).

Furthermore, the role of beta-cell dedifferentiation and alterations in islet cell lineage have recently emerged as significant events in the development and progression of T2DM [91]. In this regard, lineaging tracing of the *Ppy* gene, that encodes for PP, has uncovered important beta-cell heterogeneity that is dependent on *Ppy* gene activation [31]. Indeed, *Ppy*-positive cells have long been identified as essential for normal islet differentiation during development [35]. Moreover, it is now suggested that in the initial stages of diabetes development, where total beta-cell mass remains unchanged, an increase in the transdifferentaition of *Ppy*-positive cells towards insulin-positive beta-cells is a likely protective mechanism to preserve islet structure and function [31]. In full agreement, it has also been revealed that up to 40% of *Ppy*-positive islet cells can be reprogrammed to produce secretable insulin [73], demonstrating important plasticity of these cells for beta-cell regeneration. This concurs with the observed initial expansion of PP islet cell population in STZ-induced diabetic rodent models [44]. That said, as noted above, the majority of work relating to the impact of PP on islet cell function is restricted to observations from rodent cell lines and related in vivo models, with transferability to the humans setting still required. However, PP-producing islet cells obtained from deceased human donors can be reprogrammed to produce and secrete insulin in a glucose-dependent manner [32], highlighting potential translatability of these findings. Moreover, whilst alterations of islet cell lineage have been evidenced predominantly in rodent systems where cellular plasticity is believed to be more apparent [93], it is clear that fully mature human islet cells also possess capability to alter their identity in situ [67], that could be positively exploited by PP.

In good agreement with these observations, activation of pancreatic Y1 receptors, that signal in an identical fashion to Y4 receptors [15], is linked to positive islet cell lineage alterations in diabetic rodents including transdifferentiation of alpha- to beta-cells that helps to retain overall beta-cell mass [54]. These more recent discoveries suggest genuine potential for PP in the treatment of T2DM related to numerous direct mechanisms that safeguard against loss of beta-cell mass (Fig. 3).

9. Conclusion

PP has established effects on appetite suppression providing potential promise as an anti-obesity agent [7]. Although PP was discovered some 45 years ago [47] and is known to be largely secreted from the endocrine pancreas, a putative role for the hormone in islet cell function has been largely overlooked. However, recent knowledge that PP can protect against beta-cell destruction [44], as well as exerting probable important beneficial effects on islet cell transdifferentiation [31] and beta-cell rest [44], should bring about a resurgence of interest in the anti-diabetic properties of PP compounds and Y4 receptor activation. Future advances in our understanding of PP biology, coupled with appropriate therapeutic application likely linked to the development of enzyme-resistant, long-acting bioactive PP analogues, may well lead to the generation new and effective therapeutic agents for obesity and diabetes.

CRediT authorship contribution statement

All authors contributed equally to conception and design, analysis and interpretation of data. WZ drafted the manuscript, with NT, PRF and NI revising it critically for important intellectual content. All authors approved the final version of the manuscript.

Data Availability

No data was used for the research described in the article.

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Conflict of interest

PRF and NI are named on patents filed by Ulster University for exploitation of incretin-based drugs and other peptide therapeutics. WZ and NT declare no conflict of interest.

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