

MOLECULE PAGE

Pancreatic Polypeptide

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Gene Symbol: [PPY](#)

Abstract

Pancreatic Polypeptide (PP) is a 36 amino acid peptide produced and secreted by PP cells (originally termed F cells) of the pancreas which are primarily located in the Islets of Langerhans. It is part of a family of peptides that also includes Peptide YY (PYY) and Neuropeptide Y (NPY). PP is rapidly released after a meal but remains elevated for 4-6 hours in humans with the Vagus nerve being the major stimulator. PP has effects on GI motility, metabolism and food intake. A potential role as a satiety factor comes from the observation that PP secretion is absent in obese children with Prader-Willi syndrome. Its primary action on the exocrine pancreas is to inhibit secretion in vivo by acting on receptors in the brain leading to inhibition of vagal output to the pancreas.

1. General

Pancreatic polypeptide was discovered as a contaminant in the purification of insulin and then isolated and purified from chicken pancreas (APP) and bovine pancreas (BPP) (45,55). Subsequently it has been purified from a variety of species (46, 57, 82, 92). All PPs except possibly anglerfish possess 36 amino acids with human, bovine, ovine, porcine, and canine species differing by 1-4 amino acids; APP is more different with 17 differences from human PP. The molecular mass of most PP is around 4,200 Da.

Its biological activity resides in the carboxyl hexapeptide and requires the C-terminal amide. Structurally starting at the amino terminal it includes a polyproline helix, a β -turn, and an α -helix followed by the C-terminal hexapeptide. The protein has been crystalized and has a globular shape from which the C-terminal hexapeptide extends out from the globular portion (29). It is synthesized as the amino portion of a larger precursor with Mol Wt of 8-10 kDa (83). The carboxyl end of the precursor gives rise to a conserved icosapeptide of unknown function (84, 86). The structure of the 95 amino acid precursor has also been deduced from the mRNA sequence (14, 53, 91). PP is known to be part of a family of homologous peptides that also includes Peptide YY (PYY) and Neuropeptide Y (NPY) with PP having about a 50% homology to these other family members.

Pancreatic Polypeptide is immunogenic and immunohistochemistry has localized its presence to a specific cell type in the periphery of Islets of Langerhans in a variety of species (**Figure 1**) (26,33,50,57). The secretory granules are generally smaller than for other islet hormones, are electron dense and appear solid with the dense core extending out to the granule membrane in contrast to beta cell granules which have a lucent halo around a dense core.

Originally termed F cells, the cells are now most often referred to as PP cells (24). These cells also occur scattered through the exocrine parenchyma and occasionally in pancreatic duct

epithelium (57). The amount of these extra-islet pancreatic PP cells is more abundant in chicken than most mammals and infrequent in humans (92).

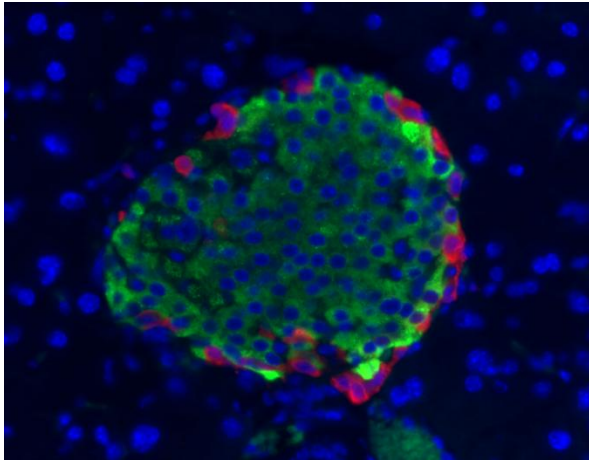


Figure 1. Immunofluorescence staining of a mouse Islet of Langerhans. PP is red, insulin green, and nuclei stained with DAPI blue. Image provided by Ernesto Bernal-Mizrachi of the University of Michigan.

that they are most abundant in the portion of the head of the pancreas that derives from the original ventral pancreatic bud (28, 78) and their relative distribution is opposite to that of glucagon. Small amounts of PP have been measured by RIA in the stomach, intestine and colon (3). Finally, consistent with being a brain-gut peptide, PP occurs in the CNS (35, 36, 60, 73).

Pancreatic Polypeptide Secretion

Pancreatic polypeptide can be measured in plasma by RIA, shows a basal level of 10-30 pM and exhibits a rapid increase after food ingestion peaking at 15-30 min which is followed by a lower sustained phase that lasts 4-5 hours in humans (19, 25, 57, 92). Protein is the most potent stimulus followed by fat with glucose less effective (99). Cephalic, gastric and intestinal components have been demonstrated with the intestinal the largest. The vagal nerve is a major stimulator of PP secretion and this component can be blocked with atropine (23,85). In addition to electrical stimulation of the vagus (13), sham feeding (42,49,93), 2-deoxyglucose (35), and insulin induced hypoglycemia (82) all stimulated PP secretion in a vagal dependent manner. The cephalic vagal phase is relatively short, lasting

about 45 minutes (92). Both intragastric and intrainestinal infusion of nutrients stimulate PP secretion and this is also partly mediated by the vagus. Gastrointestinal hormones, especially CCK and gastrin, appear to take part in stimulating PP secretion (1, 34, 58, 67). Other GI hormones such as GIP, VIP and somatostatin may affect PP secretion. Studies evaluating intrainlet regulation of PP by insulin or glucagon have been inconclusive although somatostatin inhibits PP release in vivo and in the perfused pancreas (17, 43, 47). Ghrelin and obestatin are reported to inhibit PP release from islets in vitro (77). The half-life of PP in plasma is about 6 min with PP being degraded by most capillary beds (92). Renal disease is associated with a prolonged half-life in humans.

Actions of Pancreatic Polypeptide

The reported biologic actions of PP have primarily involved the GI tract although the physiological importance is often not clear (92). In addition to acting on pancreatic secretion as detailed below, exogenous PP has been shown to affect gastric and biliary secretion and motility of the GI tract. PP has been shown to either inhibit or stimulate gastric acid secretion in dogs depending on conditions (56). In contrast, in a study in humans, infusion of PP to reproduce postprandial levels had no effect on gastric acid or pepsinogen secretion (31). Although early reports indicated PP inhibited hepatic bile production, latter studies showed this was due to relaxation of the gallbladder (5). No effect of PP was seen on intestinal secretion or absorption. Reported effects of PP on GI motility include increasing LES pressure and enhancing gastric emptying in the rat but not humans, inhibiting gastric pacemaker activity and reducing gall bladder pressure (92). More recent studies showed that PP also enhanced colonic motility and fecal output (69).

Metabolic effects of PP are modest in rodents including suppression of insulin and somatostatin secretion (6). In birds, APP plays more of a role in metabolism and has been reported to deplete liver glycogen stores. In normal humans PP slightly increased basal insulin concentration in plasma but did not affect glucose- or arginine-stimulated secretion of insulin or glucagon; there was a decrease in plasma motilin (4). Studies in

patients who are PP-deficient due to pancreatic resection or chronic pancreatitis have demonstrated that PP infusion reverses hepatic insulin resistance (16, 87). Similar results were seen in animal models of chronic pancreatitis or pancreas resection (30, 88). These results could explain the isolated hepatic insulin resistance in patients with diabetes associated to chronic pancreatitis, pancreatic neoplasms, pancreatic resection, pancreatic trauma and cystic fibrosis. High affinity PP binding sites have been identified on rat liver membranes (71).

A potential role for PP as a satiety factor arose with the observation that PP secretion is almost abolished in obese children with Prader-Willi syndrome (95,103) and that food intake was reduced by bovine PP infusion both in Prader-Willi syndrome and in normal humans (10,12,38). PP plasma levels and secretion has also been reported to be reduced in morbidly obese individuals (58, 65). An early report suggested that PP could reduce body weight in obese ob/ob mice (64). In normal mice injection of mouse PP ICV increased food intake without affecting anxiety while IV injection reduced food intake (7). Chronic overexpression of PP in transgenic mice resulted in decreased food intake and body weight over a six months lifespan (96). In a latter study by the same research group, PP administration induced negative energy balance by decreasing food intake and increasing energy expenditure (8). These actions of PP involve both brain feeding related peptides and the vagal nerve (48). PP receptors are present in a variety of brain regions (75). Recent studies have shown that the satiety effects of PP involve an action on Y4 receptors in hypothalamic nuclei (54,80) and that this involves a pathway distinct from that mediating the actions of PYY (89).

The actions of PP are mediated by specific receptors. Initially through ligand binding studies and later by molecular cloning, a family of about five receptors were identified that bind NPY, PYY and PP all of which share a common structure, the "PP-fold" (68,81). The various receptors are denoted by a capital Y with a numerical subscript. Y₁ and Y₂ are the primary NPY and PYY receptors. The Y₄ receptor has specificity for PP with a high affinity, <100 pM and a hundred fold

lower affinity for PYY (62,63,101). The Y₄ receptor is present in various tissues including brain, but most abundant in colon. It is a G-protein coupled heptahelical receptor which acts through G_i and G_o to inhibit cyclic AMP formation (68). Recent work suggests that PP is also the primary ligand for Y₆ receptors which also regulate energy homeostasis (102).

2. PP Actions on the Exocrine Pancreas

Purified bovine or porcine PP was shown by Lin et al. in 1977 to reduce pancreatic exocrine secretion in a variety of species (58). In initial studies in dogs, BPP at 10 ug/kg/hour inhibited basal as well as secretin- or CCK-stimulated secretion of protein and bicarbonate. These findings were confirmed by Taylor et al who showed that pancreatic inhibition occurred with doses of PP that raised plasma levels less than seen after a meal (94). Similar actions in dogs have also been reported by others (11,18,21,59). Shiratori et al showed a similar effect of synthetic human PP infused at 1 ug/kg/hour (86). Similar effects of PP infusion to inhibit pancreatic secretion in response to food, CCK or secretin have also been seen in humans (2, 32) and in rats (61,76). Providing further support for a physiological action of PP, Shiatori et al showed that immunoneutralization of endogenous PP enhanced both interdigestive and postprandial pancreatic secretion (90).

Although PP acts to inhibit pancreatic secretion in vivo, this effect appears to be indirect as exogenous PP had no effect on amylase release from isolated rat or mouse pancreatic acini (27,61), the perfused cat pancreas (44), or incubated uncinated pancreas of young rats or pancreatic fragments (44,61). Binding studies with ¹²⁵I-PP also failed to reveal high affinity binding sites on rat pancreatic acini. Although this lack of in-vitro effects is generally accepted (92), there are several differing reports all using isolated rat pancreatic acini showing a small amount of inhibition (38), stimulation by high concentrations of human PP (22), and inhibition of carbachol but not CCK stimulation by bovine PP

(74). Some of these effects could possibly have been due to contaminants.

More recent studies have focused on a neural locus for the action of PP to inhibit pancreatic exocrine secretion. Most studies point to a central site of action in the brain stem. High affinity receptors for PP are present in the rat brain in the area postrema (AP), nucleus tractus solitarius and dorsal motor nucleus of the vagus (97,98) and intravenous PP inhibits pancreatic amylase secretion in vivo stimulated centrally with 2-deoxyglucose in rats (76). More definitively, PP microinjected into the DMV of rats inhibited pancreatic secretion in a site specific manner through an action mediated by the vagal nerve (72). PP directly spritzed on individual DMV neurons revealed a subset where PP reduced postsynaptic currents (15). These findings suggest that PP in the circulation gains access to the brain stem through the AP and reaches the adjacent DMV where it inhibits vagal excitatory output to the pancreas (70). As an alternative neural site for PP inhibition of pancreatic secretion, Jung et al (41) presented data that rat PP or its C-terminal hexapeptide inhibited potassium stimulated amylase release and the presynaptic release of acetylcholine in rat pancreatic slices. It was suggested that PP acts

on postganglionic cholinergic neurons to prevent acetylcholine release. However, this report has not been followed up and has not been supported by demonstration of PP receptors or high affinity PP binding in pancreatic slices.

Finally, there is one report that administration of porcine PP ameliorated experimental pancreatitis induced by feeding a choline deficient diet, ethione supplemented diet to young female mice but no effect was seen in a dog model with ductal retrograde injection of bile salts (20).

3. Molecular Tools for the study of Pancreatic Polypeptide

a. Antibodies. Over 20 antibodies some suitable for immunohistochemistry and a number of ELISA kits are listed in Antibodies-online.com

b. Mouse Models. A transgenic mouse overexpressing PP in multiple organs resulting in increased plasma PP levels has been reported (96). A Ppy gene deleted mouse was reported and stated to show no metabolic phenotype (100). Mice with gene deletion of Y4 (54, 79) and Y6 (102) receptors have also been reported.

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