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PEPTIDE YY

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Gene Symbol: PYY
Other Names: **PYY, Peptide tyrosine**

1. General Information

Peptide YY (PYY) is a 36-amino acid peptide structurally related to two other gastrointestinal (GI) peptides, neuropeptide Y (NPY) and pancreatic polypeptide (PP) by a common structural feature, the PP-fold. PYY was isolated from a porcine intestinal homogenate by means of a unique chemical assay that identified the C-terminal amide structure, a characteristic structure of many biologically active peptides (61, 62). Peptide YY was named PYY since there are tyrosine residues at the amino and carboxy terminals, "Y" is the chemists' shorthand for the tyrosine amino acid. PYY occurs as two variants in the bloodstream and at the tissue level in the GI tract, PYY (1-36) and PYY (3-36). PYY is synthesized in enteroendocrine "L" cells of the distal ileal, colonic, and rectal mucosa (Figures 1, 2) (1, 13, 23). In the pancreas, PYY is co-produced with pancreatic glucagon and PP (20), and in the lower intestine, PYY is co-produced with proglucagon (13). In the proximal gut, PYY is observed in neuronal structures. PYY is the first major gut hormone to be expressed during development in the mouse colon (63) on embryonic day 15.5. This early developmental pattern of intestinal PYY expression implies a possible role for PYY in regulation of intestinal development and in the control of epithelial cell proliferation or differentiation. In this context, PYY administration has been shown to stimulate intestinal growth in mice and rats (21). In the fetal mouse pancreas (embryonic day 9.5), PYY is detected in the four islet cell types (63). These studies speculated that this early developmental appearance of PYY is linked to regulation of pancreatic and GI function during development by endocrine and paracrine pathways. PYY is also detected in the adult dog pancreas and in vivo experiments show PYY is secreted into the systemic circulation upon vagal stimulation (70).

PYY, NPY and PP bind to G-protein-linked receptors called Y receptors (7, 22). Five distinct Y receptor subtypes are described for mammals (Y1, Y2, Y4, Y5, and y6). The y6 receptor is shown in the lower case because it encodes a truncated receptor. All Y receptor subtypes are expressed in the small or large intestine with specific distribution profiles (22). PYY (1-36) binds to all known Y receptors with differing affinities, PYY (3-36) preferentially binds to the Y2 receptor and to a lesser extent the Y5 receptor. The Y1 receptor is linked to inhibition of fluid secretion in

the intestine. The Y4 receptor is expressed in the pancreas and is involved in PYY-induced blockade of pancreatic exocrine secretion.

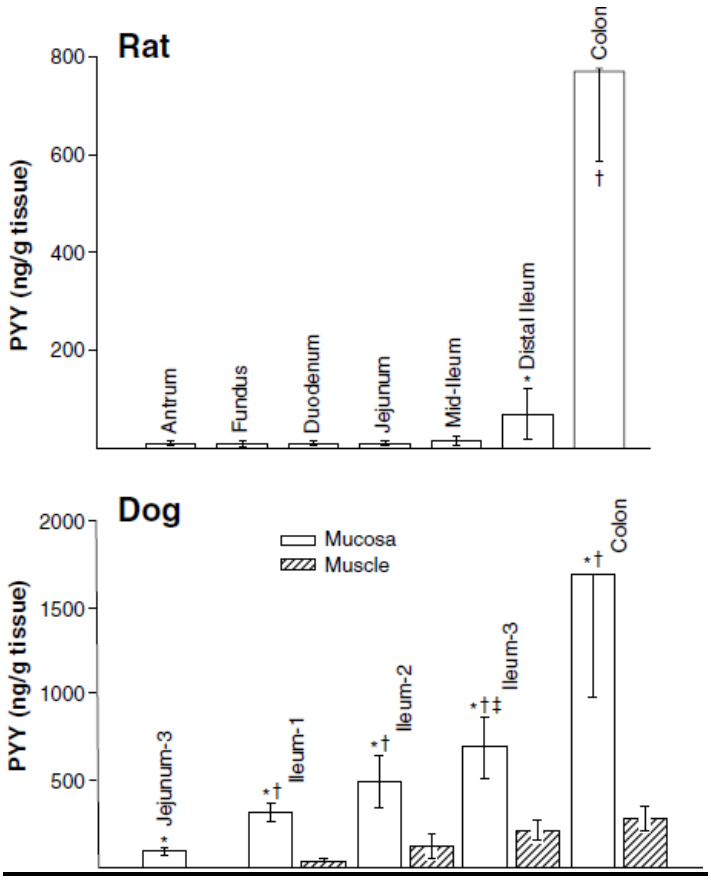

Figure 1. Distribution of PYY in the digestive tract of the rat and dog (mucosal and muscle layers). In the dog, the duodenum, jejunum and ileum were divided into three segments of equal length. The colon was divided into two segments. Top panel: * = p<0.05 vs. antrum, fundus, duodenum, jejunum and mid ileum. † = p < 0.05 vs. distal ileum. Bottom panel: * = p<0.05 vs. antrum, fundus, duodenum, proximal and distal jejunum; † = p<0.05 vs. muscle layer of respective region; ‡ = p<0.05 vs. distal jejunum, proximal and mid-ileal mucosal layers. (Modified with permission from [23]).

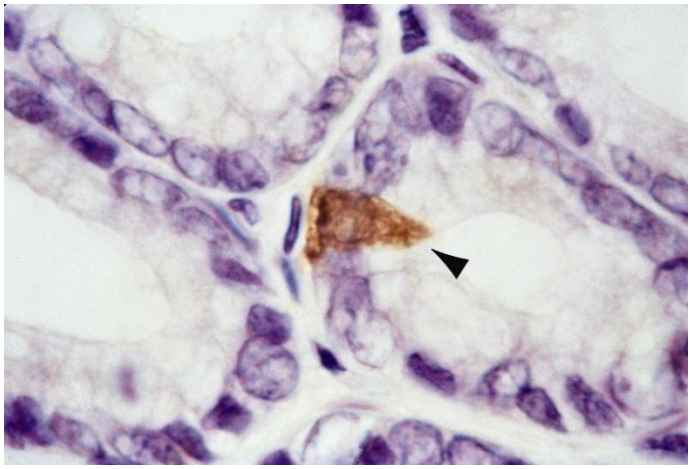

Figure 2. Flask-shaped PYY cell of the open type in the rat colonic mucosa (magnification x360). (With permission from [33].

2. PYY and Gastrointestinal Function

Numerous physiological studies in rodents, dogs and humans demonstrate that PYY exerts several inhibitory actions on the GI tract (2, 35, 38, 44-46, 49). PYY can inhibit stomach acid secretion, stomach emptying, pancreatic exocrine secretion and intestinal transit. Based upon these multiple inhibitory activities on the gut and its primary expression in the distal gut, physiologists refer to PYY as an “ileal brake”. Additionally, because PYY is a strong inhibitor of acid secretion, PYY is called an “enterogastrone”. The finding that PYY can inhibit gastric (and pancreatic secretion) implies that PYY is the original gastric and pancreatic inhibitor isolated as an impure extract decades earlier from the ileocolonic mucosa that is released into the general circulation by intestinal perfusion with oleic acid (27, 28, 42, 55).

PYY also influences stomach emptying and intestinal motility. It is well known that the presence of unabsorbed nutrients in the distal small intestine suppresses upper gut motility (32, 59, 65). This negative-feedback influence of the distal intestine is a key control mechanism of upper gut motility and may be a key mechanism involved in the ileal brake. The distinct distribution of PYY production in the GI tract and PYY’s suppressive activities on gastric emptying and intestinal motility (47, 56, 60) support PYY’s role as an ileal brake factor. PYY also exerts a potent antisecretory action resulting in calling PYY an endogenous inhibitor of diarrhea (52). In support of this idea, PYY receptors are detected in intestinal crypt cells where chloride secretion occurs (67).

Dietary fat is a strong secretagogue for stimulation of PYY secretion into the blood stream from intestinal PYY cells (1, 19). Interestingly, blood PYY levels increase significantly within 15-30 minutes after nutrient ingestion implying that an upper gut signal (i.e., hormone, neural trigger) activates this immediate PYY secretion (24). In this context, CCK administration has been shown to stimulate PYY secretion in dogs and humans (24, 29).

PYY can influence glucose and insulin homeostasis, food intake and overall energy utilization and balance (10, 26, 66, 68). Interest has developed in PYY (3-36) and in Y2 receptor agonists as a strategy to treat obesity (11, 36). Administration of PYY (3-36) can reduce appetite and weight gain in rodents (5, 51) and in obese humans (4). In humans, Roux-en-Y gastric bypass (RYGB) surgery is frequently done to foster long-term weight loss. RYGB is thought to induce anorexia and weight loss by inducing changes in gut hormones that regulate food intake, including PYY (6, 53). RYGB surgery has been shown to elevate circulating PYY levels (3, 12, 16, 43, 48), suggesting a role for endogenous PYY in the post-surgical reduction of food intake.

3. PYY and Pancreatic Function

Exogenous PYY has been shown to reduce pancreatic exocrine secretion in several species including rats, dogs and humans (2, 30, 34, 44, 50). PYY can inhibit the stimulatory effects of exogenous pancreatic secretagogues (i.e., cholecystokinin [CCK], secretin) as well as the stimulatory effects of endogenous secretagogues released after nutrient ingestion (45) (Figure 3). PYY inhibits pancreatic secretion of enzymes, fluid and bicarbonate. PYY (1-36), PYY (3-36) and PYY (4-36) are equally potent in their reductions of pancreatic secretion (69). In vitro, PYY exposure can inhibit VIP and forskolin-induced amylase secretion from guinea pig acini (31). A rodent study showed that PYY, as well as PP and NPY, could not inhibit CCK-stimulated amylase secretion from isolated pancreatic acini or lobules (46). Additionally, binding of PP to pancreatic acini was not evident. Together, these findings implied that PP-related peptides block pancreatic secretion by indirect mechanisms. An autoradiographic study utilizing frozen sections of rat pancreas showed localization of radio-labeled

PYY primarily over vascular smooth muscle cells and less localization over endothelial cells (57).

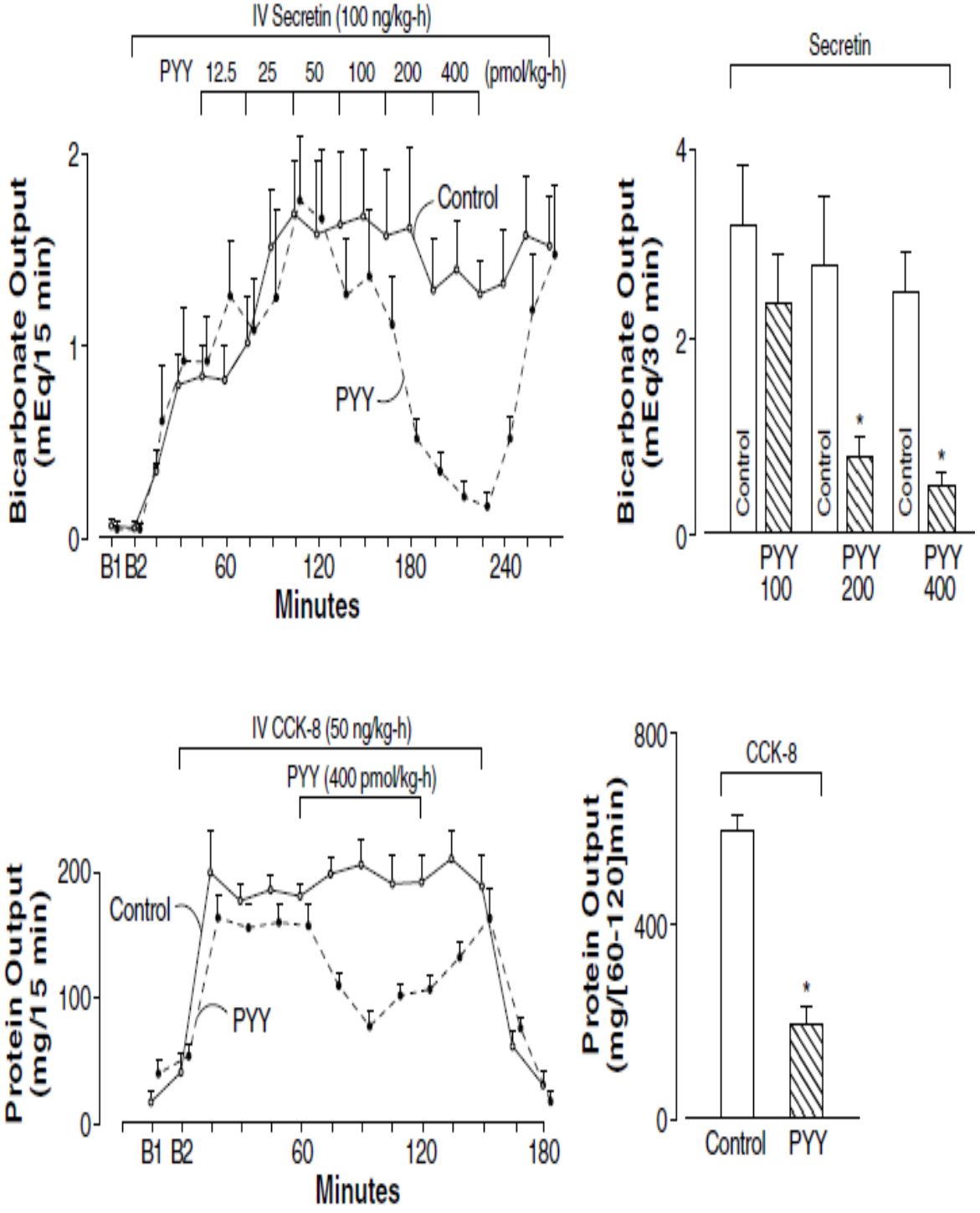

Figure 3. Pancreatic bicarbonate output (top) in response to a submaximal dose of secretin (100 ng/kg/h-IV) alone (control) or in combination with graded doses of PYY (12.5, 25, 50, 100, 200, 400 pmol/kg/h) given each for 30 minutes in conscious dogs. PYY at 200 and 400 pmol/kg/h inhibited secretin stimulated pancreatic bicarbonate output significantly. Pancreatic protein output (bottom) in response to a submaximal dose of CCK-8 (50 ng/kg/h, IV) alone or in combination with PYY (400 pmol/kg/h, IV). PYY inhibited CCK stimulated pancreatic protein secretion significantly † = P <0.05 vs. control; n = 6 dogs. (With permission from [33]).

This study concluded that pancreatic Y1 receptors are located principally on vascular smooth muscle cells. Other studies have shown that PYY can inhibit pancreatic secretion by adrenergic pathways (38) as well as intrapancreatic neural pathways (35). In conscious rats given a combination of CCK and secretin, PYY administration has been shown to inhibit pancreatic secretion by an area postrema-dependent mechanism (17). Further work (18) confirmed that PYY inhibited CCK-stimulated pancreatic secretion, however PYY failed to completely inhibit 2-deoxyglucose (2-DG)-stimulated pancreatic secretion. The authors concluded that PYY's inhibitory activity on pancreatic secretion appears to be primarily on the CCK-stimulated pathway at a site proximal to the convergence of CCK and 2-DG pathways in the rat. Interestingly, the same group of investigators reported that PYY 1-36 may stimulate pancreatic secretion by a PYY receptor subtype different from Y1, Y2, Y3, Y4 or Y5 (25).

Administration of PYY will also block intestinal CCK secretion in dogs (30, 44) and in humans (64), implying another inhibitory mechanism for PYY on pancreatic secretion.

Summary

Peptide YY (PYY) is a 36-amino acid peptide hormone structurally related to two other gut peptide hormones, pancreatic polypeptide and neuropeptide Y. Together, they are called the pancreatic polypeptide-peptide YY-neuropeptide Y (PP-PYY-NPY) family of peptides or the PP-fold family of peptides. PYY is produced in enteroendocrine “L” cells in the ileum-colon. PYY is found in “L” cells in the cat, human, rat, dog, monkey, and rabbit mucosal epithelium of the terminal ileum, colon, and rectum. Marginal amounts of PYY are found in the stomach antrum, proximal small intestine and in endocrine cells of the pancreas. In the lower intestine, PYY is co-produced with proglucagon and in the pancreas, PYY can co-reside with glucagon or PP. PYY is also detected in neuronal elements of the proximal GI digestive tract of the rat, cat, ferret, and pig. PYY is found in nerve cell bodies and nerve fibers of the canine stomach and intestinal myenteric plexus, and in the intestinal submucosal plexus. Since PYY is secreted into the general circulation after fat ingestion and blocks stomach gastric acid secretion PYY is a candidate enterogastrone. PYY also reduces pancreatic exocrine secretion, gastric emptying and intestinal transit. PYY is called an “ileal brake” based on these inhibitory actions on the GI tract. Much data also support a role for PYY in regulation of food intake and overall metabolism. Together, enterogastrone, ileal brake and satiety activities of PYY may be important physiological functions of intestinal PYY.

4. Tools for Study

a. cDNA clones.

The PYY gene has been cloned from several species including the rat and human (8, 14, 15, 37, 39, 40, 58).

b. Antibodies

PYY antibodies are available commercially from Bachem Americas Inc. (Torrance, CA) and Phoenix Pharmaceuticals (San Carlos, CA) which are suitable for immunohistochemistry and immunoassay studies.

c. Viral Vectors-none published.

d. Mouse Models

There are several publications describing PYY-Tag transgenic mice (9, 41, 54).

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