What is Pancreatic Polypeptide and what does it do?

This document aims to evaluate current understanding of pancreatic polypeptide (PP), a gut hormone with several functions contributing towards the maintenance of energy balance. Successful regulation of energy homeostasis requires sophisticated bidirectional communication between the gastrointestinal tract and central nervous system (CNS; Williams et al. 2000). The coordinated release of numerous gastrointestinal hormones promotes optimal digestion and nutrient absorption (Chaudhri et al., 2008) whilst modulating appetite, meal termination, energy expenditure and metabolism (Suzuki, Jayasena & Bloom, 2011).

The Discovery of a Peptide

Kimmel et al. (1968) discovered PP whilst purifying insulin from chicken pancreas (Adrian et al., 1976). Subsequent to extraction of avian pancreatic polypeptide (aPP), mammalian homologues bovine (bPP), porcine (pPP), ovine (oPP) and human (hPP), were isolated by Lin and Chance (Kimmel, Hayden & Pollock, 1975). Following extensive observation, various features of this novel peptide witnessed its eventual classification as a hormone (Schwartz, 1983).

Molecular Structure

PP is a member of the NPY family including neuropeptide Y (NPY) and peptide YY (PYY; Holzer, Reichmann & Farzi, 2012). These biologically active peptides are characterized by a single chain of 36-amino acids and exhibit the same ‘PP-fold’ structure; a hair-pin U-shaped molecule (Suzuki et al., 2011). PP has a molecular weight of 4,240 Da and an isoelectric point between pH 6 and 7 (Kimmel et al., 1975), thus carries no electrical charge at neutral pH.

Synthesis

Like many peptide hormones, PP is derived from a larger precursor of 10,432 Da (Leiter, Keutmann & Goodman, 1984). Isolation of a cDNA construct, synthesized from hPP mRNA, proposed that this precursor, pre-propancreatic polypeptide, comprised 95 residues (Boel et al., 1984) and is processed to produce three products (Leiter et al., 1985); PP, an icosapeptide containing 20-amino acids and a signal peptide (Boel et al., 1984). PP is derived from the amino-terminus and the icosapeptide from the carboxy-terminus (Fig. 1) (Schwartz, 1983).

![Figure 1](image.png)

Figure 1. A schematic diagram illustrating the primary structure of pancreatic polypeptide (PP) and the icosapeptide synthesized within the common precursor hormone, pre-propancreatic polypeptide. The table (lower right) indicates differences in amino acid sequence found in five mammalian PP homologues (Schwartz, 1983).
Secretion

PP is predominantly secreted by the PP cells, also known as ‘F cells’ (Koska et al., 2004), dominating the duodenal pancreas (Schwartz, 1983). Minor amounts are also secreted by colonic and rectal cells of the distal gut (Adamska et al., 1994). Most PP cells are located at the periphery of the endocrine islets of Langerhans (Fig. 2) with fewer present within the exocrine acinar cells (Wynne et al., 2005).

Stimulatory Mechanisms

The principal stimulus for PP secretion is parasympathetic vagal cholinergic innervation (Dembinski et al., 2004). Vagotomy reaffirms this as ablation of the vagal nerves attenuates PP secretion. Administration of atropine, a competitive muscarinic acetylcholine antagonist (Kumari, Sreetama & Mohanakumar, 2007), also eliminates PP response (Schwartz, 1983), demonstrating that release is governed by cholinergic mechanisms (Fig. 3). Consequently, basal PP levels correspond to parasympathetic activity, measuring lowest in the morning and peaking during the evening (Wynne et al., 2005). Also, secretion increases with age, quadrupling between 30 and 70 years old, reflecting heightened vagal tone (Schwartz, 1983).

PP is mainly released in response to food intake (Batterham et al., 2003) proportional to caloric consumption (Adamska et al., 1994). Secretion is biphasic (Wynne et al., 2005) with a cephalic and gastrointestinal phase (Schwartz, 1983). The initial cephalic phase is represented by a rapid postprandial rise in plasma PP shortly after eating, the rate of which surely depends on neural mechanisms. Sham-feeding, a process whereby food ingested does not reach the stomach, triggers this cephalic phase (Schwartz, 1983). Gustatory and olfactory sensations are responsible for transmission of neural afferent signals to the CNS with vagal efferent neurones subsequently stimulating PP release (Fig. 3). The secondary gastrointestinal phase is stimulated by various enteric stimuli, primarily protein and lipid consumption (Schwartz, 1983) and is prolonged with plasma PP concentrations remaining elevated for up to 6 hours post-satiation (Jesudason et al., 2007). Food entering the stomach causes gastric distension which mediates food intake (Wang et al., 2008). Activation of gut epithelial mechanoreceptors induces vagal afferent stimulation of PP cells thus PP release (Fig. 3) (Troke, Tan & Bloom, 2014).
Duodenal entry of pancreaticobiliary juice also stimulates secretion (Dembiński et al., 2004). Other secretagogues include bioactive peptides; gastrin, gastrin releasing peptide (GRP), secretin (Dembiński et al., 2004), ghrelin, motilin (Wynne et al., 2005) vasoactive intestinal polypeptide (VIP) and cholecystokinin (CKK; Fig. 3; Schwartz, 1983). Hypoglycaemia, which can be induced by insulin infusion, is another powerful stimulus. The extent of secretion is proportional to the decrement in blood glucose (Schwartz, 1983). During exercise, endogenous sympathetic adrenergic mechanisms provoke mild PP secretion. This is markedly lower than observed following meal consumption (Schwartz, 1983). Conversely, hyperglycaemia; which can be induced by glucose infusion, inhibits PP secretion. Peptide hormones; somatostatin and bombesin, glucocorticoids, elevated plasma fatty acids and morphine are examples of PP inhibitors (Schwartz, 1983).

**Receptor Interactions**

PP-fold peptides elicit their effects through interaction with G-protein-coupled receptors; Y1 to Y6 (Sliwińska-Mossoń, Borowiecka & Milnerowicz, 2012). These seven-transmembrane-domain receptors are distributed within central tissues; the hypothalamus and brainstem (Troke et al., 2014). PP, unable to diffuse across the blood-brain barrier, interacts with Y4 and Y5 receptors (Adamska et al., 1994) but is the most potent agonist for Y4 receptors (Cabrele & Beck-sickinger, 2000) located within the hypothalamic arcuate nucleus (ARC) or dorsal vagal complex (DVC) of the brainstem. The brainstem, a principal region for PP activity, comprises neuronal populations crucial for appetite regulation (Troke et al., 2014); the dorsal motor nucleus of vagus (DVN), area postrema (AP) and nucleus of the tractus solitarius (NTS; Fig. 4; Suzuki et al., 2011). Circulating PP can access the DVN and bind its respective receptor to modulate energy balance (Asakawa et al., 2003).

![Figure 4. Pancreatic peptide (PP) and other gut hormones interact with complementary receptors, within specific regions of the hypothalamus and brainstem, to modulate appetite. PP interacts with Y4 receptors of the hypothalamic arcuate nucleus (ARC) and neuronal populations within the dorsal vagal complex (DVC) of the brainstem; the dorsal motor nucleus of vagus (DVN), area postrema (AP) and nucleus of the tractus solitarius (NTS) (Suzuki et al., 2011).](image-url)
Mechanisms of Action

PP, an anorectic peptide, promotes satiety by reducing food intake, the rate of gastric emptying, gall bladder contraction and pancreatic exocrine secretion (Sam et al., 2015).

Appetite Regulation

Interestingly, PP causes both orexigenic and anorexigenic effects according to the route of administration (Katsuura, Asawaka & Inui, 2002). Intracerebroventricular PP infusion in rodents increases appetite and food intake, whilst peripheral administration induces negative energy balance by reducing food intake (Tong et al., 2007). Human subjects of normal weight show a 25% reduction in food intake when infused with PP over 24 hours (Wynne et al., 2005). Asawaka et al. (2003) found that intraperitoneal PP administration modifies neuropeptide expression. Hypothalamic anorexigenic peptide, urocortin, gene expression was increased whilst orexigenic peptide, gastric ghrelin, mRNA expression simultaneously decreased (Fig. 5). Ghrelin, the only recognised orexigenic peptide (Troke et al., 2014), is elevated in sufferers of Prader-Willi Syndrome (PWS), a disorder distinguished by morbid obesity and hyperphagia (Cummings et al., 2002). PP infusion may improve symptoms of PWS by decreasing ghrelin expression (Asawaka et al., 2003).

Anxiety

PP administration also significantly decreases corticotrophin-releasing factor (CRF), a hormone activating the hypothalamo-hypophyseal-adrenal axis involved in the pathogenesis of stress-related eating disorders (Fig. 6) (Asawaka et al., 2003).

Weight Management

Repeated peripheral PP administration decreases...
body weight gain in obese mice (Fig. 7). Adiposity and adipokines, such as leptin, decrease (Asawaka et al., 2003), potentially preventing hyperleptinaemia and leptin resistance, key contributors to obesity (Sinha & Caro, 1998). PP also improves states of dyslipidemia, reducing plasma free fatty acids, cholesterol and triglyceride levels, as well as ameliorating glycaemic control and insulin resistance (Asakawa et al., 2003).

Sam et al. (2015) postulates PP an effective biomarker for ectopic fat deposition as fasting PP concentrations significantly correlate to visceral abdominal and hepatic adiposity. Both pose major risks to cardiometabolic health and contribute to type II diabetes (Tong et al., 2007).

**Gastrointestinal Motility**

Elevated levels of PP reduce gut motility (Batterham et al., 2003). According to Asawaka et al. (2003), transgenic mice, overexpressing PP, show delayed gastric emptying, a classic symptom of anorexia nervosa and cachexia (muscle wasting) in humans. In contrast, obese individuals, expressing low PP, tend to experience increased gastric emptying (Asawaka et al., 2003).

**Energy Expenditure**

PP influences energy expenditure. Studies show that peripheral PP administration, in obese rodents, increases spontaneous locomotor activity for up to 5 hours (Liu et al., 2008) and increases oxygen consumption for up to 2 hours post-treatment (Fig. 8) (Asawaka et al., 2003).

**Exocrine and Endocrine Interactions**

PP is believed to moderate pancreatic exocrine secretions indirectly through prohibition of insulin activity. Diabetics typically possess elevated PP levels and thus impaired exocrine secretion (Park, Lee & Kwon, 1993). Endocrine secretions, such as delta-cell somatostatin secretion, are also suppressed by PP (Kim et al., 2014).

**Pharmacological Therapy**

Obesity is one of the most prevalent non-communicable diseases posing a phenomenal challenge to medical professionals globally. Currently, bariatric surgery is the most successful treatment option; post-surgical alterations in gut hormone concentrations have a major influence on sustained weight loss (Troke et al., 2014).

Evidence that PP induces satiety and increases energy expenditure renders it an appealing option for use as an anti-obesity agent; however, pharmacological interventions are unsuccessful long-term (Suzuki et al., 2011). Orally administered peptide pharmaceuticals are rapidly degraded by gastric enzymes (Troke et al., 2014), easily excreted and have a limited shelf-life.
(Bellmann-Sickert et al., 2011). PP analogues, designed with pharmacokinetic modifications such as fatty acid or polyethylene glycol acylation (Bellmann-Sickert et al., 2011), enhance efficacy in modulation of appetite and extend PP's short half-life of 7 minutes, eliminating necessity for prolonged infusion (Troke et al., 2014).

It must be appreciated that gut-hormone therapies may not suffice as a single solution for obesity treatment (Chaudhri et al., 2008). The gut-brain axis does not operate in isolation but in conjunction with complex cortical centers and reward-related corticolimbic pathways of the brain, responsible for hedonistic control (Suzuki et al., 2011). Social, environmental and emotional factors also influence food intake in humans, overriding homeostatic requirements. Furthermore, as most research discussed utilises rodent models, one may question whether PP exerts identical physiological effects in humans.

References


