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The role of pancreatic polypeptide in the regulation of energy homeostasis

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ABSTRACT

Imbalances in normal regulation of food intake can cause obesity and related disorders. Inadequate therapies for such disorders necessitate better understanding of mechanisms that regulate energy homeostasis. Pancreatic polypeptide (PP), a robust anorexigenic hormone, effectively modulates food intake and energy homeostasis, thus potentially aiding anti-obesity therapeutics. Intra-gastric and intra-intestinal infusion of nutrients stimulate PP secretion from the gastrointestinal tract, leading to vagal stimulation that mediates complex actions via the neuropeptide Y4 receptor in arcuate nucleus of the hypothalamus, subsequently activating key hypothalamic nuclei and dorsal vagal complex of the brainstem to influence energy homeostasis and body composition. Novel studies indicate affinity of PP for the relatively underexplored neuropeptide y6 receptor, mediating actions via the suprachiasmatic nucleus and pathways involving vasoactive intestinal polypeptide and insulin like growth factor 1. This review highlights detailed mechanisms by which PP mediates its actions on energy balance through various areas in the brain.

1. Introduction

The increasing threat of obesity has gripped the world as an important health issue. Present studies have estimated that the number of overweight and obese individuals in the world have increased to 2.1 billion in 2013 as against 857 million in 1980 (Ng et al., 2014). Obesity is considered to be a consequence of excessive food intake and/or decreased physical activity and reduced energy expenditure, leading to excessive fat accumulation that often impairs wellbeing. Thus, understanding the regulation of appetite and energy intake or energy expenditure is seen as a potential avenue for the prevention and management of the global obesity epidemic.

Knowledge about appetite regulation has greatly advanced over the last few decades. Studies conducted in this area have unraveled complex pathways involving bidirectional neurohumoral communication systems that allow communication between the gut and the brain. Signals relating to nutritional and energy status are continually relayed between the gut and the central nervous systems to regulate appetite (hunger and satiety). Continued investigations and research into the modulation of appetite have uncovered the complex endocrine and neurological systems that comprise the gut–brain axis. As physiological regulators of appetite, gut hormones offer an attractive therapeutic target for the treatment of obesity. Meal size and overall energy intake are controlled by a series of short- and long-term hormonal and neural signals that are derived from the gastrointestinal tract (Cummings and Overduin, 2007; Perry and Wang, 2012). Besides regulating energy intake, these hormonal and neural signals function together to optimize the processes of digestion and absorption of nutrients from the gut. The most studied gut hormones in this regard are cholecystokinin (CCK), polypeptide YY (PYY), glucagon-like peptide-1 (GLP-1), oxyntomodulin and ghrelin (Chaudhri et al., 2006). With the exception of ghrelin, which functions as a 'hunger hormone' (Inui et al., 2004; Castaneda et al., 2010; Sakata and Sakai, 2010; Al Massadi, Lear et al., 2014), these gut-derived hormones act to suppress hunger, induce satiety and decrease food intake (Malaisse-Lagae et al., 1977; Lieverse et al., 1995; Gutzwiller et al., 1999; Naslund et al., 1999; Keire et al., 2000; Batterham et al.,

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2003; Dakin et al., 2004; Little et al., 2005; Wynne et al., 2005; Lumb et al., 2007).

The mechanisms by which gut hormones modify feeding have been areas of great interest. Local effects such as the inhibition of gastric emptying are thought to contribute to the decrease in energy intake in response to gut satiety factors (Sturm et al., 2004; Xu et al., 2005; Chaudhri et al., 2006). Activation of mechanoreceptors as a result of gastric distension may further inhibit food intake via neural reflex mechanisms that work in conjunction with gut hormones (Valenzuela and Defilippi, 1981; MacIntosh et al., 2001). However, in more recent years our understanding of central neuronal pathways has changed the view that gut hormones mediate effects on satiety predominantly via local effects on the gut, and research efforts in the past decade have focused on the role of the brain in mediating effects of gut hormones on energy intake and energy homeostasis. The importance of the brain–gut axis in the modulation of food intake is suggested by the dual role exhibited by gut peptides, which act as both hormone and neurotransmitter (Chaudhri et al., 2006). Indeed, certain circulating gut hormones have been shown to not only act as endocrine hormones exerting effects over distant target organs via classic hormone pathways, but to also be secreted locally and act directly on neurons in hypothalamic and brainstem centers to control satiety (Lin et al., 2009). Gut hormones have been shown to act on the extensive reciprocal connections that exist between hypothalamic and brainstem areas and the hypothalamic paraventricular nucleus and other centers in the central nervous system that control energy homeostasis (Ter Horst, Luiten et al., 1984; Ter Horst, de Boer et al., 1989). While there is a reasonable level of knowledge about the mechanisms via which CCK, PYY, GLP-1, oxyntomodulin and ghrelin induce their effects, there has been relatively little work on pancreatic polypeptide (PP), another gut-derived hormone that is known to reduce food intake and influence energy balance and body composition. Thus, this review will focus specifically on how PP interacts with central pathways to mediate effects on food intake. Before looking into these mechanisms, it is important to first provide an overview of the biology of PP, from where is it secreted to what effects it mediates.

2. Distribution of PP in the gastrointestinal system

Before describing the role that PP plays in the regulation of energy homeostasis, it is important to note the distribution of PP in the gastrointestinal system. It is also important to provide insight into the group of peptides to which PP belongs, how it interacts with other peptides in that family, and the structural features that contribute to its function.

2.1. The NPY family and the structural significance of PP

PP is a member of the neuropeptide Y (NPY) family that is characterized by three peptides (PP, PYY and NPY) with an amidated carboxyl terminus that results in a hairpin fold referred to as the 'PP-fold' (Cabrele and Beck-Sickinger, 2000; Ekblad and Sundler, 2002). Electromagnetic resonance, X-ray crystallography and other studies have shown that this 'PP-fold' is a tightly organized tertiary structure that is crucial to the physiological functioning and maintenance of biological activities of members of the NPY family (Germain et al., 2013). PP was the first member of this family to be isolated (Kimmel et al., 1975), and is the least evolutionarily conserved of all three members of the NPY family (Blomqvist et al., 1992; Conlon, 2002).

2.2. Relevance of PP and other peptides of NPY family in the gastrointestinal system

The NPY-ergic system has been one of the key targets for research into the prevention and treatment of obesity and related feeding disorders. Studies have shown that while NPY stimulates appetite and reduces energy expenditure, PYY and PP are produced in response to food intake and have opposite effects on appetite or energy expenditure to those induced by NPY. NPY is known as one of the most powerful orexigenic neuropeptides, while PYY and PP act in an antagonistic manner to NPY and are amongst the most effective endogenously-produced satiety hormones known (McLaughlin and Baile, 1981; Taylor and Garcia, 1985; Katsuura et al., 2002; Batterham et al., 2006; le Roux et al., 2006). The peptides in this family induce their effects on energy homeostasis by binding to G-protein coupled receptors, with mammals possessing the subtypes Y1, Y2, Y4, Y5 and y6, as will be outlined in more detail in a subsequent section. While members of the NPY family interact with each other and a common receptor system, these interactions are not limited to the NPY family, as their interactions with other gut hormones (Briggs et al., 2010; Kohno and Yada, 2012; Wang et al., 2013; Chandler-Laney et al., 2014; Schmidt et al., 2014), not discussed in this review, also contribute towards appetite regulation and energy homeostasis.

3. Expression and release of PP from the gastrointestinal tract in response to food

3.1. Location of PP-expressing cells

PP is a 36-amino acid peptide produced by specialized pancreatic islet cells called F cells, which represent approximately 10% (Bommer et al., 1980) of the volume of the pancreatic islets of Langerhans (Larsson et al., 1975; Adrian et al., 1976). Studies have shown that some PP is also produced as an exocrine hormone in the distal gut (Larsson et al., 1975; Adrian et al., 1976; Ekblad and Sundler, 2002). It has been noticed that in humans, the endocrine F cell mass is narrowly restricted to the uncinate process, along with a distinct presence in the duodenal part (the head region) of the pancreas (Orci et al., 1976; Malaisse-Lagae et al., 1977; Rahier et al., 1979; Wang et al., 2013). Observations in the bovine gut revealed relatively large numbers of F cells in the large intestine, while in rats, F cells were also observed in the colon and the rectum (Pyarokhil et al., 2012).

3.2. Release of PP in response to food intake

Evidence demonstrates that the most powerful stimulant for PP release is the intake of food (Simonian et al., 2005), particularly fat-rich food (Kojima et al., 2007; Guyenet and Schwartz, 2012). The post-prandial release of PP is proportional to energy intake, and circulating levels of PP remain elevated for up to 6 h after feeding (Adrian et al., 1976; Adrian et al., 1977). Various phases of PP release have been delineated, and it is known that PP is released into the circulatory system during both the pre-absorptive and the post-prandial phases of nutrient digestion (Schwartz et al., 1978). Thus, taken together it can be seen that the magnitude and time course of the release of PP greatly reflect both the content and size of the meal ingested. (see Fig. 1).

4. The biological effects of PP

In this section we briefly explain the role that PP plays in modulating food intake and energy homeostasis in mammals – namely rodents and humans.

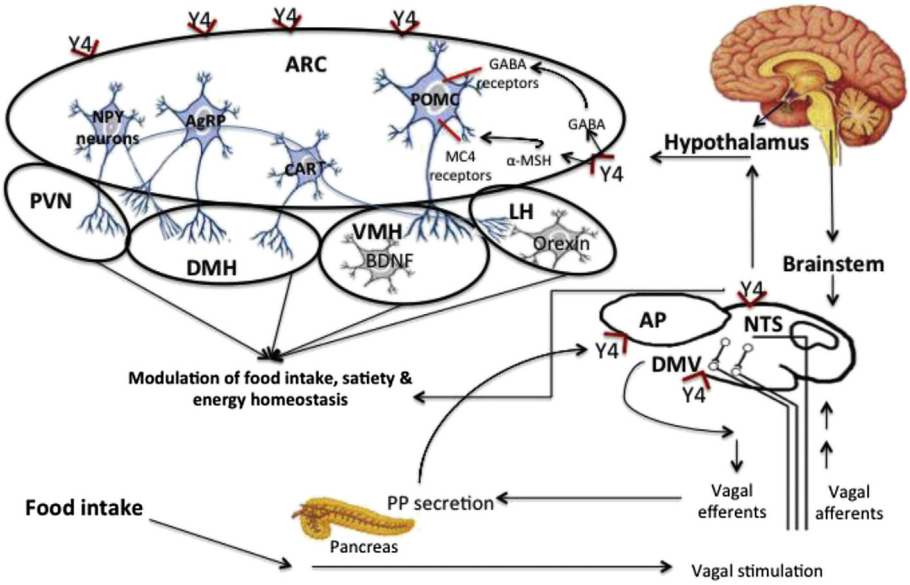

Fig. 1. The figure shows the pathways by which PP exerts its effects via the Y4 receptors in the hypothalamic ARC region and the brainstem areas. PP is secreted by the pancreas in response to food intake. Then via vagal stimulation and activation of the Y4 receptors and neuronal pathways in hypothalmic ARC and brainstem it induces satiety to reduce food intake and thus maintain energy homeostasis.

4.1. The effects of PP in rodents

4.1.1. The effect of PP on food intake and underlying mechanism of gastric emptying contributing to satiety in rodents

Studies aimed at understanding the effects of PP reported that repeated administration of PP to obese mice for six days resulted in a significant reduction in body weight gain (Malaisse-Lagae et al., 1977; Kojima et al., 2007). The reduction in body weight of mice in response to exogenously administered PP is likely due to significant reductions in food intake (Malaisse-Lagae et al., 1977; Katsuura et al., 2002; Sainsbury et al., 2010; Shi et al., 2013). In recent years, it was observed that chronic overexpression of PP in mice lead to postnatal lethality in newborn pups due to an excessive reduction in milk intake (Ueno et al., 1999; Kohno and Yada, 2012), reiterating the potency of PP as a satiety agent. Studies aimed at elucidating the interaction of PP with other members of the NPY family showed that along with its contribution to delaying gastric emptying, PP and the cleaved form of PYY, namely PYY3-36, additively reduced food intake in mice (Shi et al., 2013), showing that PP also interacts with other members of the NPY family to potently reduce food intake.

Investigations into underlying mechanisms for PP-induced satiety and reduced food intake revealed that PP delays gastric emptying. Gastric emptying is a phenomenon wherein neural regulatory mechanisms in the gut–brain axis and hormones act in a cooperative manner to empty the contents of the stomach into the duodenum for absorption in the small intestine, thus vacating the stomach for the further intake of food (Hellstrom et al., 2006). A delay in gastric emptying, as induced by PP, potentially sends feedback signals to the satiety centers of the brain, which then trigger signals that cause an inhibitory effect on food intake (Wang et al., 2008), and further reduce energy intake for over 24 h (Jesudason et al., 2007). It has been proven in rats that PP exerts its effects on satiety in response to food intake at least partially by delaying gastric emptying (Asakawa et al., 2003; Kojima et al., 2007; Verschueren et al., 2014). Similarly, mice showed a decrease in gastric emptying of a solid meal in response to PP administration, while gastric emptying of water remained unaffected, suggesting that PP exerts its effects specifically on solid and not liquid ingestion to induce satiety in rodents (Schmidt et al., 2005), without affecting hydration levels of the body.

4.1.2. Effects of PP on energy expenditure due to changes in the physical activity in rodents

Besides its hypophagic effects, PP may also act to increase energy expenditure. It has previously been demonstrated that PP induced negative energy balance by suppression of gastric emptying and food ingestion while increasing energy expenditure in rodents (Asakawa et al., 2003). Our group later extended these findings to show that PP significantly increased oxygen consumption when administered intraperitoneally to mice, thus implicating an increase in energy expenditure in the mediation of weight loss (Sainsbury et al., 2010; Shi et al., 2013). The effect of PP to increase energy expenditure may be due to effects to stimulate physical activity. A dose-dependent increase in locomotor activity following intracerebroventricular delivery of PP was demonstrated in mice (Nakajima et al., 1994), and it was later shown that this PP-induced increase in physical activity in mice was independent of the concomitant decrease in food intake (Liu et al., 2008).

4.1.3. Effect of PP on feeding when administered centrally in animals

Most studies conducted so far reveal the fact that peripheral administration of PP to rodents significantly decreased food intake by increasing satiety. It also increased energy expenditure, thus proving to be a potent anorexigenic peptide. However, previously studies conducted by Clark and colleagues, revealed that in contrast to being injected peripherally, PP when administered intracerebroventricularly, moderately increased food intake in rats, but significantly increased food intake with a late onset in the light phase of the day (Clark et al., 1984). Further, it has been reported that when administered centrally into the third cerebral ventricle, PP increase food intake in dogs (Inui et al., 1991) and similarly in mice too (Nakajima et al., 1994). It is possible that direct injection of PP into CNS may have an influence on different neural substrates and receptor subtypes, therefore causing an orexigenic effect,

however convincing data for this seems to still be unavailable (Katsuura et al., 2002).

4.2. The effects of PP in humans

4.2.1. The effect of PP on food intake, body weight regulation and energy expenditure in humans

As well as having clear effects on food intake and energy expenditure in rodents, PP is also known to be involved in the regulation of food intake and body weight in humans. However, despite ample information is available on effect of PP administration on energy expenditure in rodents, no data has yet been published on its effect on energy expenditure in humans. PP infusion in humans reduced appetite and food intake by 25%, and this effect was sustained for a minimum 24 h (Batterham et al., 2003). Other studies have shown that obese children have significantly lower levels of circulating PP (Zipf, O'Dorisio et al., 1981; Reinehr et al., 2006; Kanaley et al., 2014), indicating that levels of PP negatively correlate with the body mass index (BMI) and body weight, in keeping with a purported role of PP in energy homeostasis.

Similar to observation in rodents, PP is thought to interact with the other members of the NPY family in the regulation of energy homeostasis in humans. Indeed, it has been shown that circulating PYY and PP levels are reduced in obese humans (Marco et al., 1980; Troke et al., 2014). From studies conducted in rodents, it is known that both PP (Asakawa et al., 2003) and PYY (Batterham et al., 2002; Challis et al., 2003) potently inhibit expression of mRNA for the orexigenic peptide NPY in the hypothalamus, thereby contributing to the reduced food intake induced by PP and PYY. In keeping with these observations, in obese humans it was found that lower circulating levels of PP and PYY are associated with increased secretion of NPY into the cerebrospinal fluid (Mercer et al., 2011; Holzer et al., 2012). Such a change in NPY concentrations in cerebrospinal fluid, if it reflects an increase in NPY-ergic activity in the hypothalmus, would be expected to lead to effects such as hyperphagia, reduced energy expenditure, reduced physical activity and increased fat accumulation (Luo et al., 2011; Zheng et al., 2013), thereby providing a potential mechanism by which low circulating PP and PYY levels could contribute to the development of obesity.

4.2.2. The role of PP in human pathophysiology

Understanding the role of PP in human pathophysiology and its importance in the regulation of body weight, obesity-related disorders and feeding disorders has been examined by studying the effects of external administration of PP to human beings. It has been observed that repeated doses of PP reduced hyperphagia in Prader–Willi syndrome (Tan et al., 2012; Tauber et al., 2014), a syndrome characterized by excessive hunger that leads to morbid obesity if food intake is not vehemently controlled. In cases of Prader–Willi, decreased levels of PP have been associated to increased ghrelin levels, the fact which explains the conditions of uncontrolled hyperphagia in such patients (Cummings et al., 2002) PP administration to such individuals could thus aid in reducing hunger, by reducing the ghrelin hormone levels and controlling obesity symptoms, thus restoring energy balance. Further, the role of PP has also been investigated in other feeding-related disorders, namely bulimia nervosa and anorexia nervosa. Bulimia nervosa is characterized by binge eating and purging. It was observed that people with bulimia nervosa exhibited attenuated post-prandial circulating levels of gastrointestinally-derived hormones including reduced levels of PP, in response to food ingestion (Naessen et al., 2011). These reduced levels of PP are thought to contribute to the intake of larger portions of food intake in patients with bulimia nervosa. While the contributions of this difference to post-binge purging behavior remain to be elucidated, external administration of PP to patients with bulimia nervosa could potentially ameliorate the binge eating aspects of this disorder. On the contrary, anorexia nervosa is characterized by immoderate food restriction. Patients with anorexia nervosa exhibit abnormally elevated levels of PP (Kinzig et al., 2007), suggesting that this change may contribute to the anorexia observed, and that deploying orexigenic hormones to increase appetite and food intake could help in balancing the abnormally elevated levels of PP.

Taken together, the observations in rodents as well as humans clearly suggest a role of PP in reducing food intake and potentially also increasing energy expenditure via effects on other regulators of energy homeostasis, thus contributing to changes in BMI and body weight. Further sections of this review will now elaborate on the mechanisms of action of PP at the neurological level.

5. Neurological mechanisms by which PP induces effects on food intake and energy balance

5.1. Actions of PP in the hypothalamus

5.1.1. Actions of PP via G-protein coupled Y receptors in the hypothalamus

Extensive studies have been conducted to localize central binding sites for PP, as such knowledge provides insights into mechanisms of action. It is known that while PP binds to all members of the G-protein coupled Y receptor superfamily (Y1, Y2, Y4, Y5 and y6), it exhibits greatest affinity for the Y4 receptor (Parker and Herzog, 1999). PP works as an agonist to Y4 and activates hypothalamic nuclei that are known to be critical in the regulation of appetite and satiety in association with activation of c-Fos, a protein whose expression is induced by stimulation by a neurotransmitter or via the activity-dependent phosphorylated form of extracellular signal-regulated kinases (p-ERKs), which translocates into the nucleus of the cell to activate downstream transcriptional factors (Lin et al., 2009). These pathways will be explained in more detail below.

Y4 receptor mRNA has been localized to brainstem areas and also the hypothalamus, with a particularly high density in the hypothalamic arcuate nucleus (ARC) (Gustafson et al., 1997; Parker and Herzog, 1999). The ARC is an aggregation of neurons in the mediobasal region of the hypothalamus that innervates virtually the entire hypothalamus and provides first and the second order neurons that are involved in the regulation of food intake and energy balance.

In case of appetite regulation via the NPY system, it is important to note that at least two populations of first-order neurons are present in the ARC region. These are (1) neurons that co-express NPY and agouti-related protein (AgRP) and which stimulate food intake (Shutter et al., 1997; Broberger et al., 1998; Hahn et al., 1998) and (2) neurons co-expressing pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART), which are known to repress appetite (Elias et al., 1998; Kristensen et al., 1998). These first order neurons of the ARC are in direct contact with peripherally circulating hormones in the blood stream, including PP. Studies showing the presence of Y4 receptors on these first order neurons of the ARC indicate that PP agonism of Y4 receptors leads to effects on the POMC pathways to regulate food intake (Lin et al., 2009), which will be discussed in detail in the following section.

First order neurons in the ARC synapse with second order neurons in the regulation of appetite and energy balance. Such second order neurons are located in several hypothalamic nuclei, notably the paraventricular nucleus (PVN), dorsomedial hypothalamic nucleus (DMH), ventromedial nucleus (VMH) and lateral hypothalamus (LHA) (Chronwall, 1985; Chronwall et al., 1985).

Unlike the first order neurons in the ARC, these second order neurons are not readily accessible to circulating blood-borne hormones (Schwartz and Porte, 2005; Heijboer et al., 2006), including PP. As such, they depend upon neuronal relays to mediate responses to PP. Y4 receptors are known to be important in activation of these second order neurons in response to PP, because agonism of Y4 receptors by PP causes the activation of these regions, thereby potentially contributing to the effects of PP on food intake, energy expenditure and adiposity (Ueno et al., 1999; Asakawa et al., 2003).

Apart from action on Y4 receptors, PP is thought to act on and possibly also mediate effects via other Y receptors, namely Y5 and y6. In some species, including humans although not in rats (Cabrele et al., 2001), PP is known to bind with moderate affinity to Y5 receptors. Y5 receptors are primarily expressed in the PVN of the hypothalamus and interact synergistically with the Y1 receptor in regulating energy homeostasis (Gerald et al., 1996; Kanatani et al., 2000; Mashiko et al., 2009). Thus it is possible that PP mediates its actions in the PVN via Y5 receptors in addition to its high affinity to Y4 receptors. Very limited information is available about the potential role of y6 in mediating actions of PP. *In situ* hybridization has revealed the presence of y6 in the hypothalamus (Yulyaningsih et al., 2014). This Y receptor type is less conserved than other Y-receptors, and only exists as a truncated version in humans, primates and rats, hence the lower case y, but it is present as a fully functional receptor in mice and rabbits (Gregor et al., 1996; Matsumoto et al., 1996; Rose et al., 1997; Burkhoff et al., 1998). Recently published data suggests that PP is an endogenous high affinity ligand for the y6 receptor, and that PP may induce effects on energy homeostasis or body composition via y6 receptors and effects on circadian rhythms (Yulyaningsih et al., 2014). The circadian clock in mammals is located in the suprachiasmatic nucleus (SCN), and is primarily responsible for maintaining important biological processes via a key regulator called vasoactive intestinal peptide (VIP) (Harmar et al., 2002; Aton and Herzog, 2005; Hannibal et al., 2011). Disruptions in the SCN lead to metabolic dysfunctions and hormonal imbalances (Huang et al., 2011). Furthermore, VIP plays a role in maintaining the growth hormone/insulin-like growth factor-1 (GH/IGF-1) axis that is responsible for maintenance of circulating levels of IGF-1 (Asnicar et al., 2002; Niewiadomski et al., 2008), which plays a key role in the regulation of body mass, size and lean tissue content. In keeping with a role of y6 in regulating this pathway, it was observed that knockdown of y6 receptors in mice led to a reduction in hypothalamic VIP expression. This disruption in VIP expression was associated with impaired SCN functioning, as indicated by reduced circulating IGF-1 levels, which presumably played a causative role in the observed reduction in lean mass in y6 receptor-deficient mice. These mice additionally exhibited reductions in energy expenditure and aberrant glucose metabolism and obesity. Interestingly, intracerebroventricular injection of PP reversed some of these effects in y6 deficient mice (Yulyaningsih et al., 2014), suggesting not only the affinity of PP towards y6 receptors but also implicating y6 in mediating some effects of PP. Studies indicating that PP was the only ligand that could trigger significant expression of c-Fos protein via y6 receptors confirmed PP-mediated actions via the functional form of the Y6 receptor in mice.

5.1.2. Critical role of the melanocortin system in mediating hypophagic effects of PP

The melanocortin system, located in the ARC region of the hypothalamus, is involved in a diverse range of functions, one of which includes the regulation of energy homeostasis. Past investigations have demonstrated a critical role of the melanocortin system in mediating the effects of PP on food intake (Barsh et al., 2000; Gantz and Fong, 2003). This system comprises several melanocortin peptides derived from the POMC gene, including α-, β-, and γ-melanocyte-stimulating hormone (α-, β-, γ-MSH) (Catania, 2007). The melanocortin system additionally comprises five G protein-coupled melanocortin receptors (MC1, MC2, MC3, MC4 and MC5) (Mountjoy et al., 1992), two endogenous antagonists called agouti and agouti-related peptide (AgRP), and two ancillary proteins termed mahogany and syndecan-3 (He et al., 2001; Gantz and Fong, 2003).

Our studies have shown that in the ARC of the hypothalamus, peripheral PP injection increases the expression of Fos, the protein product of the immediate early gene c-Fos, and an index of neuronal activation (Lin et al., 2009). This activation was particularly notable in neurons containing the anorexigenic α-MSH, and was abolished by conditional knockdown of Y4 receptors in the hypothalamus, indicating that PP acted on Y4 receptors to induce c-Fos activation in α-MSH-expressing neurons. It is noteworthy that POMC neurons in the ARC are known to be negatively regulated by cells producing gamma-aminobutyric acid (GABA) (Dicken et al., 2012). Our study further showed that peripheral PP administration reduced mRNA expression of glutamic acid decarboxylase 65 (GAD65), a key enzyme involved in the synthesis of GABA (Lin et al., 2009), thus providing further evidence that PP could have mediated its anorectic actions via increases in activity of POMC neurons andα-MSH actions in the ARC region. These observations extended earlier findings (Huszar et al., 1997) which first suggested that POMC may be involved in mediating the effects of PP, by demonstrating that POMC mRNA expression in the ARC is upregulated by PP administration, and that the reduction in food intake associated with peripheral PP delivery is absent in mice lacking the MC4 receptor, presumably contributing to the hyperphagia and obesity that characterises MC4 receptor deficient mice (Huszar et al., 1997).

Further evidence that the melanocortin system is involved in mediating PP effects via effects on GABA-ergic neurons is a study using manganese-enhanced magnetic resonance imaging in mice (Hankir et al., 2011). That study revealed decreased signal intensity (indicating decreased activation) of GABA-ergic cells in the ARC of fasted mice following subcutaneous delivery of PP, which would be expected to contribute to increased activation of POMC neurons. This change was accompanied by a reduction in food intake for up to 8 h after PP administration (Hankir et al., 2011). This finding is consistent with electrophysiological studies in slice preparations from brains of wild type mice demonstrating reduced activity of GABA-ergic cells in the ARC following *ex vivo* PP application (Acuna-Goycolea et al., 2005). Taken together, these findings collectively suggest that Y4 agonism with PP could induce PP-induced hypophagia via reduced GABA-ergic inputs to POMC neurons, with subsequent increase in α-MSH transmission (Lin et al., 2009).

Having outlined the role of PP in modulating the melanocortin system, likely via changes in GABA-ergic activity in the repression of appetite and inhibition of food intake, the following sub-sections will elaborate on the role of PP in the activation of second order neurons of the hypothalamus to affect feeding and satiety.

5.1.3. Role of brain-derived neurotrophic factor (BDNF) in mediating hypophagic effects of PP

The VMH has long been considered to be a satiety center. Emerging evidence suggests that BDNF, which is abundantly expressed in the VMH, plays widespread roles in energy homeostasis by exerting hypophagic and weight-reducing effects (Xu et al., 2003; Lebrun et al., 2006). Central or peripheral administration of BDNF has been shown to reduce food intake and increase energy expenditure in obese mice (Ono et al., 1997; Nakagawa et al., 2000; Nonomura et al., 2001). Reciprocally, fasting reduced the levels of BDNF mRNA in the VMH, indicating an adaptive measure

to counteract energy loss (Xu et al., 2003; Komori et al., 2005; Komori et al., 2006). Interestingly, new research suggests that BNDF may play a role in mediating the effects of PP. IP administration of PP to mice increased BDNF mRNA expression in the VMH (Sainsbury et al., 2010). As VMH is not readily accessible to blood-borne PP, it is unlikely that PP regulation of BDNF occurs via a direct effect. Thus it was expected that an indirect mechanism of action exists that plays a role in mediation of PP signals for the regulation of BDNF. Therefore it was shown that PP influences the expression of BDNF by acting on the ARC, thus influencing the expression of POMC and transmission of α-MSH to the VMH (Sainsbury et al., 2010). This was also found to be in agreement with a similar study showing that BDNF expression is stimulated by α-MSH produced by POMC neurons in the ARC via MC4 receptors (Xu et al., 2003). Further, it was shown that α-MSH signaling in the ARC in response to PP is initiated via the changes in GABA-ergic neurons. PP administration decreased GABA neuronal activity in the ARC (Acuna-Goycolea et al., 2005). This decrease in the GABA activity in turn leads to decreased mRNA expression in POMC, thus inhibiting the release of α-MSH (Jegou et al., 1989; Vergoni and Bertolini, 2000). As it has been established that BDNF expression is stimulated by α-MSH as outlined above, these observations collectively indicate that PP-dependent expression of BDNF in VMH is mediated via the GABA-ergic neuronal function. This expression of GABA in the POMC neurons affects the release of α-MSH and its activity on MC4 receptors. All these signals are then collectively transmitted in the VMH area, thus affecting BDNF mRNA expression and together leading to reductions in food intake (Xu et al., 2003; Sainsbury et al., 2010).

5.1.4. Role of orexin neurons in mediating hypophagic effects of PP

Orexins are important neuropeptides involved in the regulation of appetite. Orexins are located in the LHA of the hypothalamus (King, 2006; Sainsbury et al., 2010). Orexins (particularly orexin A and orexin B) powerfully stimulated food intake after intracerebroventricular administration, and fasting in rats is known to show markedly up-regulated orexin mRNA expression in the LHA region of the hypothalamus (Sakurai et al., 1998; Haynes et al., 1999), in keeping with a role in opposing negative energy balance. A role for orexins in mediating effects of PP has been suggested from the observation that repeated administration of PP to mice over 24 h significantly down-regulated mRNA expression of orexin in the LHA (Asakawa et al., 2003), suggesting that orexin-expressing neurons in the LHA may be important mediators of the effects of PP on energy balance and food intake. Furthering these observations, it was recently demonstrated that PP injection induced c-Fos activation in orexin-expressing neurons of the LHA, in association with down-regulation of orexin mRNA expression in this region and thus conceivably contributing to a reduction in the orexigenic drive in response to PP administration (Sainsbury et al., 2010).

5.2. The actions of PP in the brainstem and effects on vago-sympathetic pathways

Besides actions in the hypothalamus to induce effects on food intake, PP likely also induces effects via actions in the brainstem. In order to describe the actions of PP in the brainstem areas and the resultant vagal pathways, it is important to first outline the general structure and components of the brainstem. The following sections will give a brief insight into the structure of the brainstem, and will then explain the mechanisms of actions of PP via vagal pathways emanating from the brainstem.

5.2.1. General structure of the brainstem with reference to its involvement in the gut–brain axis

The brainstem includes the dorsal vagal complex (DVC), which plays a critical role in relaying information about energy homeostasis to and from the gut. The DVC is composed of the area prostema (AP), the nucleus tractus of the solitary tract (NTS), and the dorsal motor nucleus of the vagus nerve (DMV). The DMV is considered to be the primary source of vagal innervation of various organs, including the stomach and pancreas. In addition to providing efferent outputs, the DMV also receives vagal afferent inputs from the periphery as well as from areas of the hypothalamus such as the PVN and LHA. The efferent projections of the DMV largely serve the parasympathetic vagal functions of the gastrointestinal tract, and contain the neurons that control gastric motility and secretion (Feng et al., 1990; Rogers et al., 1996; Rogers et al., 1999). The AP is situated outside of the blood brain barrier and sends rich projections to feeding-related nuclei, including the NTS (Schwartz et al., 1999; Schwartz, 2000). The information from the NTS is relayed to various regions of the brain, including the PVN in the hypothalamus as well as other nuclei in the brainstem.

5.2.2. Actions of PP via vago-sympathetic pathways

It has been long established that PP release is dependent on function of the vagus nerve (Schwartz, 1983), and that following vagotomy, PP no longer exerts its anorectic effects (Asakawa et al., 2003). PP responses to meal ingestion, as well as its actions on energy homeostasis, are collectively dependent on several pathways that are under the control of vagal cholinergic reflex circuits involving changes in expression of hypothalamic feeding-regulatory peptides and activity of the vago-vagal and vago-sympathetic reflex axis. It is also known that the inhibitory actions of PP on food intake are indirectly regulated via vagal nerves, while PP acting on the central nervous system involves a specific receptor system, which as we now know includes the G protein coupled Y receptors, particularly Y4.

Peripheral injection of radiolabeled PP has revealed strong binding of PP in the AP, NTS and DMV (Larsen and Kristensen, 1997). Both NTS and DMV are essential components of the gastrointestinal vago-vagal reflexes, and participate in modulation of PP-driven gastrointestinal functions. The vagal afferents carrying information from the gastrointestinal tract conveys information to neurons of the NTS and AP. The information is processed by the NTS and transferred to the DMV. The vagal efferents that originate from the DMV send their axonal projections to the gastrointestinal tract and pancreas. Thus, when the vago-vagal reflex gets activated due to the vagal afferents, the vagal efferents send signals to the gut regions to release PP (and/or other gut hormones) from the pancreas.

Peripheral delivery of PP increases c-Fos expression in cells of the AP and NTS (Lin et al., 2009), indicating PP responses in the AP and NTS. As PP is known to act at least partially via Y4 receptors, and high levels of Y4 receptors are present in the brainstem areas of the NTS, AP and DMV (Larsen and Kristensen, 1997; Parker and Herzog, 1999), it is clear that blood-borne PP can bind to Y4 receptors in the AP and NTS, which in turn modulate vagal responses to control appetite. This vagovagal stimulation after food ingestion involves the peripheral neuron activation of the nicotine receptors (Schwartz, 1983), while the final mediation of the signals is achieved via acetylcholine leading to muscarinic activation that further activates the anorectic process via the G-protein coupled Y receptors in the hypothalamus (Adrian et al., 1976; McTigue et al., 1997).

6. Clinical applications

PP represents a promising target for the pharmacological

treatment of obesity and other disorders characterized by excess energy intake. In contrast to centrally produced anorexigenic ligands, PP exerts its hypophagic effects upon peripheral administration, making it more amenable as a target for drug development. The key potential advantage of pharmacologically targeting the PP system is the ability to manipulate food intake with minimal side effects. For instance, PP administration to humans is well tolerated and does not induce nausea (Batterham et al., 2003; Jesudason et al., 2007). However, a major outstanding challenge to potentially using this or other peptides for therapeutic applications is to determine effective routes of administration while also enabling the compound to function effectively without rapid degradation or unpleasant secondary effects such as nausea and vomiting. The half-life of PP in the circulation is relatively short, at approximately 6–7 min (Adrian et al, 1978). Thus, to obtain long-lasting effects of PP we need longer-lasting PP analogs. Indeed, PP-based compounds are currently under development for clinical use (Batterham et al., 2003; Jesudason et al., 2007; Tan et al., 2012). One of the drugs in phase II clinical trial is Obinepitide from 7TM Pharma, which is a dual analog of PYY3-36 and PP. This drug has been shown in one study to improve glucose metabolism and reduce obesity (Zac-Varghese et al., 2011). In recent years, Bloom and colleagues have established an analog of PP named PP1420 and have published phase 1 studies (Tan et al., 2012), wherein they modified the amino acid sequence of PP to increase resistance against rapid degradation. This change increased the half-life of the peptide to approximately 2.5 h, and the compound had no tolerability issues, such as nausea or other adverse side effects, while also reducing food intake over several hours (Tan et al., 2012). Another group developed a 'lipidated' analog of PP, which proved to be more stable than native PP (Bellmann-Sickert et al., 2011). Also, *in vitro*, the micellar formulation of PP increased the half-life of PP to 2.5 h (Banerjee and Onyuksel, 2012). However, the only successful clinical trial with regards to PP-based therapy so far is from Bloom and colleagues as mentioned above (Tan et al., 2012). All other analogs of PP, mentioned above, await additional studies before proceeding to clinical trails. Additionally, further trials with PP1420 would be necessary to study the efficacy of this analog and explore its potency in case of multiple doses.

7. Directions for future research into PP

Considerable research has been conducted and progress has been made in understanding the importance of PP in the modulation of food intake and the underlying hypothalamic mechanisms of action and possible therapeutics using PP-based compounds. However, certain pathophysiological aspects still remain unanswered. As a hormone influencing many areas in the brain, it would be of interest to better understand the involvement of PP in aspects other than feeding and energy expenditure, for example its effect on stress and emotional modulation, since earlier studies showed that peripherally-administered PP induced Y4-dependent c-Fos expressions in areas with higher expression of Y4 receptors, resulting in reduction of anxiety- and depression-like behavior via the GABA-ergic signals along with increased physical locomotor activity (Asakawa et al., 2003; Tasan et al., 2009). The relationship between PP concentrations and age is interesting and yet remains unexplained, as does its relation with reference to age-related obesity occurring due to changes in sex hormones and particularly its potential involvement in weight gain occurring in the post-menopausal state of women. Recent observations have indicated that estrogen levels in women positively correlate with serum BDNF levels (Firozan et al., 2014), and as mentioned earlier in this review, PP induces BDNF expression in the VMH. Therefore, it is possible that lower levels of estrogen in post-menopausal women could cause reduction in serum BDNF thus causing impairment in the mediation of the signals by PP via BDNF in the VMH, and therefore contributing to the common observation of post-menopausal obesity.

Development of PP-analogs to increase the half-life of this peptide has indeed been an important breakthrough in the potential use of PP-based anti-obesity drugs. Thorough *in vivo* studies in humans in this regard would be necessary to evaluate the potency of such analogs in terms of efficacy and secondary effects. Despite promising results suggesting that these analogs could be used as monotherapies, research is increasingly inclined towards using combination therapies for the treatment of obesity. To this end, it has been established that two peptides of the same family, PYY3-36 and PP, reduce food intake in mice in an additive manner (Shi et al., 2013). There has been some study in this direction using hormones other than PP to show that combination of hormones such as PYY and OXM (Field et al., 2010), and also dual agonism of GLP-1 and glucagon to reduce obesity (Day et al., 2009; Patel et al., 2013). More understanding of the central mechanisms of PP would enable development of better strategies to utilize PP as a drug for obesity by itself, or in combination with other compounds.

8. Summary and conclusion

In summary, we have reviewed here some of the central pathways via which PP exerts its actions on feeding, energy homeostasis and body composition regulation. The integration of these observations along with understanding of the interactions of PP with other gut hormones, into a unified model could help to explain the complex regulation of feeding and energy balance and would thus enable better insights into potential new ways to treat the obesity pandemic.

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