Peptide YY, appetite and food intake

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Obesity is taking on pandemic proportions. The laws of thermodynamics, however, remain unchanged, as energy will be stored if less energy is expended than consumed; the storage is usually in the form of adipose tissue. Several neural, humeral and psychological factors control the complex process known as appetite. Recently, a close evolutionary relationship between the gut and brain has become apparent. The gut hormones regulate important gastrointestinal functions such as motility, secretion, absorption, provide feedback to the central nervous system on availability of nutrients and may play a part in regulating food intake. Peptide YY (PYY) is a thirty-six amino acid peptide related to neuropeptide Y (NPY) and is co-secreted with glucagon-like peptide 1. Produced by the intestinal L-cells, the highest tissue concentrations of PYY are found in distal segments of the gastrointestinal tract, although it is present throughout the gut. Following food intake PYY is released into the circulation. PYY concentrations are proportional to meal energy content and peak plasma levels appear postprandially after 1 h. PYY_{3-36} is a major form of PYY in both the gut mucosal endocrine cells and the circulation. Peripheral administration of PYY_{3-36} inhibits food intake for several hours in both rodents and man. The binding of PYY_{3-36} to the Y2 receptor leads to an inhibition of the NPY neurones and a possible reciprocal stimulation of the pro-opiomelanocortin neurones. Thus, PYY_{3-36} appears to control food intake by providing a powerful feedback on the hypothalamic circuits. The effect on food intake has been demonstrated at physiological concentrations and, therefore, PYY_{3-36} may be important in the everyday regulation of food intake.

Peptide YY: Obesity: Appetite regulation: Food intake

Obesity is taking on pandemic proportions. An estimated 30·5 % of the US population were obese and 64·5 % were overweight in 2000 (Flegal *et al*. 2002), while 21 % of men and 20 % of women were found to be obese in the Health Survey for England and Wales (Finer, 2003). Energy will be stored if less energy is expended than consumed, usually in the form of adipose tissue, according to the laws of thermodynamics. In support of these phenomena, it has been calculated that the average man living in the USA increases his weight by >9·1 kg between the ages of 25 and 35 years (Rosenbaum *et al*. 1997), as a result of only a 0·3 % imbalance between energy consumed and expended during this period.

Several neural, humeral and psychological factors control the complex process known as appetite (Schwartz *et al*. 2000). The homeostatic system regulating energy balance powerfully drives the desire to eat, especially after weight loss. There may never have been an evolutionary advantage in weight loss, and as such man may have evolved to consume as much food as possible whenever possible (Rosenbaum *et al*. 1997). As far back as 1912 stomach contractions were proposed to be involved in up regulating appetite (Cannon & Washburn, 1912), and later the duodenum was postulated to act as the 'pituitary of the gastrointestinal tract' as it exerts control over gut hormones (Ugolev, 1975). A close evolutionary relationship between the gut and brain seems apparent as gut peptides have also been discovered in the hypothalamus (Cowley *et al*. 2003), and hypothalamic peptides have been found in the gut (Kirchgessner & Liu, 1999; Wren *et al*. 2001). Gut hormones also seem to have important functions in the central nervous system (Jin *et al*. 1988; Geiselman, 1996; Tang-Christensen *et al*. 2000).

Diffuse populations of endocrine cells are scattered throughout the mucosa, thus ensuring that the endocrinological capacity of the gut is diverse and important

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(Buchan, 1999). Nutrient contact with the mucosa releases gut hormones that regulate important gastrointestinal functions such as motility, secretion and absorption, and provide feedback to the central nervous system on the availability of nutrients. These factors may all play a part in regulating food intake. The first gut hormone found to act as a satiety signal in this way was cholecystokinin (Gibbs *et al*. 1973).

The most abundant endocrine cell type in the ileum and colon is the L-cell. The apical microvilli of these cells are in contact with the intestinal lumen, allowing the L-cells to sense the nutrients and other substances presented in the lumen. The bases of the L-cells are rich in endocrine granules that allow secretion of hormones from the basal granules into the circulation. L-cells release peptide YY (PYY; Pedersen-Bjergaard *et al*. 1996; Anini *et al*. 1999) and the proglucagon-derived peptides glucagon-like peptide 1, glicentin and oxyntomodulin after nutrient ingestion (Kervran *et al*. 1987; Adrian *et al*. 1993). Plasma concentrations of these hormones increase almost immediately postprandially, and well before food can reach the ileum. This process suggests the possible involvement of other mechanisms that could lead to the release of these hormones. A neuroendocrine reflex, whereby nutrient entry into the upper gastrointestinal tract could lead to a neural stimulation of L-cells in the distal gut is possible. The neuroendocrine reflex theory is supported by experiments involving the strategic placement of fistulas in canine models, which allows perfusion of different parts of the bowel with nutrients (Lin *et al*. 2000; Lin & Chey, 2003). Nutrients, nerves and possibly other factors most probably act in concert, as blocking one of these factors may reduce, but does not abolish, gut hormone release (Lin *et al*. 2000).

PYY is a thirty-six amino acid peptide related to neuropeptide Y (NPY) and is co-secreted with glucagon-like peptide 1. PYY is produced by the intestinal L-cells and the highest tissue concentrations are found in distal segments of the gastrointestinal tract, although it is present throughout the gut (Adrian *et al*. 1985; Pedersen-Bjergaard *et al*. 1996). Following food intake PYY is released into the circulation (Adrian *et al*. 1985), and PYY concentrations are proportional to meal energy content (Adrian *et al*. 1985), with peak plasma levels occurring postprandially after 1 h (Batterham *et al*. 2002, 2003). PYY_{3-36} is a major form of PYY in both the gut mucosal endocrine cells and the circulation (Eberlein *et al*. 1989; Grandt *et al*. 1994). Both PYY_{1-36} and PYY_{3-36} may have local effects on gut motility (Hagan, 2002) and they inhibit gallbladder emptying and secretion of gastric acid and pancreatic enzymes (Pittner *et al*. 2004).

In several gastrointestinal diseases associated with loss of appetite chronically-elevated fasting levels of PYY have been described (Adrian *et al*. 1986, 1987). Known actions of PYY include: reduced gastric emptying and delayed gastrointestinal transit (Imamura, 2002). In situations of acute small intestinal disease the actions of PYY might be considered an appropriate response, as they would increase absorption time and decrease the nutrient load. In obese subjects lower fasting plasma levels of PYY have been reported (Batterham *et al*. 2003). The same study has also shown that even though the obese subjects consume more

energy than normal-weight controls their PYY levels are still lower (Batterham *et al*. 2003). The balance between preprandial hunger and postprandial satiety determines the end of a meal (Nicolaidis & Even, 1985; Geiselman, 1996), and overweight and obese individuals require more energy (approximately 940 kJ (225 kcal)) to reach maximum satiety than normal-weight individuals (Delgado-Aros *et al*. 2004). However, to gain weight as little as 420 kJ (100 kcal) in excess of daily requirements is sufficient (Hill *et al*. 2003). In obese subjects the delayed onset of satiety after consuming a meal may be related to the hormones involved in signalling satiety (Delgado-Aros *et al*. 2004). Thus, obese subjects may be left with a functional deficiency in PYY-induced satiety, which may reinforce obesity.

Gut motility is affected by both PYY_{1-36} and PYY_{3-36} (Adrian *et al*. 1985; Hagan, 2002). Administration of PYY into the cerebrospinal fluid of rats causes increased food intake (Hagan, 2002), while peripheral administration of PYY_{3-36} inhibits food intake for several hours in both rodents and man (Batterham *et al*. 2002; Challis *et al*. 2003, 2004; Cox & Randich, 2004; Halatchev *et al*. 2004; Riediger *et al*. 2004). In rodents food reduction by peripheral injection of PYY_{3-36} has been reported to be difficult (Tschop *et al*. 2004), with particular care needed to acclimatise rodents and so minimise the stress of intraperitoneal injections and handling (Halatchev *et al*. 2004). When conditions are optimal, however, a dose–response reduction in food intake following peripheral PYY_{3-36} has been reported for fasted and freely-feeding rodents (Batterham *et al*. 2002; Challis *et al*. 2003, 2004; Cox & Randich, 2004; Halatchev *et al*. 2004; Riediger *et al*. 2004).

PYY_{3-36} have been reported to be associated with a dose-dependent weight loss in a number of obese models, including *ob/ob* mice, diet-induced obese mice and non-diabetic fatty Zucker rats (Batterham *et al*. 2002; Pittner *et al*. 2004). Plasma glucose levels are unaffected by PYY_{3-36} in the short term, but indices of hyperglycaemia such as HbA_{1c} and fructosamine show a dose-dependent reduction after 4 weeks of peripheral administration of PYY_{3-36} in ZDF rats (Pittner *et al*. 2004).

Increased c-fos expression (an early gene product) in the hypothalamic arcuate nucleus is observed following intraperitoneal injections of PYY_{3-36} in rats (Batterham *et al*. 2002; Halatchev *et al*. 2004), whereas the brainstem does not show any such activity (Halatchev *et al*. 2004), suggesting that the action of PYY_{3-36} may be associated with the hypothalamus. Circulating substances have access to the hypothalamic arcuate nucleus (Merchenthaler, 1991) and there appears to be non-saturable transport of PYY_{3-36} across the blood–brain barrier (Nonaka *et al*. 2003). Moreover, food intake is inhibited if PYY_{3-36} is injected directly into the arcuate nucleus (Batterham *et al*. 2002). PYY_{3-36} has a high affinity for the Y2 receptor, a member of the NPY receptor family. A Y2 receptor-specific agonist inhibits appetite (Potter *et al*. 1994), while PYY_{3-36} is rendered ineffective in the Y2 receptor knock-out mouse (Batterham *et al*. 2002). After a meal PYY_{3-36} is released into the circulation, and it is proposed that appetite is inhibited by PYY_{3-36} acting directly on the arcuate nucleus via the Y2 receptor, a pre-synaptic inhibitory autoreceptor.

Pro-opiomelanocortin (POMC) neurons are under a tonic γ-aminobutyric acid-mediated inhibition by NPY neurons, and thus decreased γ-aminobutyric acid-mediated tone, as effected by leptin, may lead to disinhibition of POMC neurons (Cowley *et al*. 2001; Batterham *et al*. 2002). The binding of PYY_{3-36} to the Y2 receptor leads to an inhibition of the NPY neurons and a possible reciprocal stimulation of the POMC neurons (Batterham *et al*. 2002). Reduced NPY mRNA expression levels and increased POMC mRNA levels are observed after peripheral PYY_{3-36} administration (Challis *et al*. 2003).

The actions of another important peripheral signal of energy homeostasis, leptin, are also mediated through the activation of arcuate POMC neurons (Cowley *et al*. 2001). Mice lacking all melanocortin ligands, such as POMC-null mice and melanocortin 4 receptor-knock-out mice, remain sensitive to the anorexic effect of PYY_{3-36} (Challis *et al*. 2004; Halatchev *et al*. 2004). This outcome in these two independent models, one lacking the melanocortin 4 receptor and the other lacking the α-melanocyte-stimulating hormone ligand, implies that PYY_{3-36} does not require the central melanocortin system to acutely reduce food intake in rodents. However, for both models the administration of chronic saline (9 g NaCl/l) or PYY_{3-36} does not affect the cumulative food intake, suggesting that POMC may have some permissive role in PYY_{3-36}-mediated food intake regulation. Ghrelin has been described as the 'hunger hormone', as it rises preprandially. In food-deprived rats c-fos expression within the arcuate nucleus is also strongly induced (Riediger *et al*. 2004). After a meal few c-fos-containing nuclei are observed, while c-fos activation of fasting-induced arcuate nuclei is also reversed by peripheral PYY_{3-36} (Riediger *et al*. 2004). In arcuate nucleus neurons electrophysiological studies have shown ghrelin excitation and PYY_{3-36} inhibition of neurons (Riediger *et al*. 2004). Neurons of the arcuate nucleus are post-synaptically inhibited by PYY_{3-36}, suggesting that direct action of PYY_{3-36} on receptive neurons may cause the suppressive effects on c-fos expression and food intake. In man infusion of PYY_{3-36} markedly decreases circulating ghrelin levels and attenuates the preprandial rise (Batterham *et al*. 2003). The action of PYY_{3-36} on ghrelin may thus be twofold: first, a reduction in the direct inhibitory effect on ghrelin-stimulated neurons; second, attenuation of circulating levels. In the brainstem the area postrema is devoid of a blood–brain barrier and has been implicated in the regulation of food intake. NPY Y_2 receptors are also densely expressed in the area postrema (Cox & Randich, 2004) and circulating PYY_{3-36} has been shown to bind there (Dumont *et al*. 1996). The effect of PYY_{3-36} is attenuated by lesions of the area postrema, especially in relation to secretions of the stomach, basal pancreatic secretion and cholecystokinin-stimulated secretion (Deng *et al*. 2001). PYY_{1-36} binds to the area postrema and increases c-fos expression (Leslie *et al*. 1988; Bonaz *et al*. 1993), but PYY_{3-36} has not been shown to increase c-fos expression in the brainstem (Halatchev *et al*. 2004). Ablation of the area postrema in rats still allows PYY_{3-36} to suppress food intake in a dose-dependent manner. This suppression is, however, five to eight times greater than that achieved in sham-operated rats (Cox & Randich,

2004). The effect of PYY_{3-36} acting directly on the area postrema may be to increase food intake, or the enhanced suppression of food intake in the area postrema-ablated group may be a result of different populations of Y receptors. Thus, the strong anorectic effect of PYY_{3-36} may be unmasked by eliminating the area postrema, and thus any opposing NPY Y_5 influence.

PYY_{3-36} appears to control food intake by providing a powerful feedback on the hypothalamic circuits. The effect on food intake has been demonstrated at physiological concentrations, and therefore PYY_{3-36} may be important in the everyday regulation of food intake.

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