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PYY transgenic mice are protected against diet-induced and genetic obesity

Dana Boey [a], Shu Lin [a], Ronaldo F. Enriquez [b], Nicola J. Lee [a], Katy Slack [a], Michelle Couzens [a], Paul A. Baldock [b], Herbert Herzog [a,1], Amanda Sainsbury [a,*,1]

[a] *Neuroscience Research Program, Garvan Institute of Medical Research, St. Vincent's Hospital, 384 Victoria Street, Darlinghurst, Sydney NSW 2010, Australia*
[b] *Bone and Mineral Research Program, Garvan Institute of Medical Research, St. Vincent's Hospital, 384 Victoria Street, Darlinghurst, Sydney NSW 2010, Australia*

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Abstract

The gut-derived hormone, peptide YY (PYY) reduces food intake and enhances satiety in both humans and animals. Obese individuals also have a deficiency in circulating peptide YY, although whether this is a cause or a consequence of obesity is unclear. Our aims were to determine whether peptide YY (PYY) over-expression may have therapeutic effects for the treatment of obesity by altering energy balance and glucose homeostasis. We generated PYY transgenic mice and measured body weight, food intake, temperature, adiposity, glucose tolerance, circulating hormone and lipid concentrations and hypothalamic neuropeptide levels (neuropeptide Y; proopiomelanocortin, and thyrotropin-releasing hormone) under chow and high-fat feeding and after crossing these mice onto the genetically obese leptin-deficient *ob*/*ob* mouse background. PYY transgenic mice were protected against diet-induced obesity in association with increased body temperature (indicative of increased thermogenesis) and sustained expression of thyrotropin-releasing hormone in the paraventricular nucleus of the hypothalamus. Moreover, PYY transgenic mice crossed onto the genetically obese *ob*/*ob* background had significantly decreased weight gain and adiposity, reduced serum triglyceride levels and improved glucose tolerance compared to *ob*/*ob* controls. There was no effect of PYY transgenic over expression on basal or fasting-induced food intake measured at 11–12 weeks of age. Together, these findings suggest that long-term administration of PYY, PYY-like compounds or agents that stimulate PYY synthesis *in vivo* can reduce excess adiposity and improve glucose tolerance, possibly via effects on the hypothalamo–pituitary–thyroid axis and thermogenesis.

Keywords: Peptide YY; Transgenic mouse; Adiposity; Thermogenesis

1. Introduction

Type 2-diabetes mellitus and its complications are affecting increasing numbers of people at alarmingly younger ages. This is exacerbated by the current epidemic of obesity, a major risk factor for type 2-diabetes. Although weight loss in overweight or obese individuals significantly reduces the risk or severity of type 2 diabetes, currently the most effective treatments for obesity involve surgical interventions that not only pose medical risks and complications, but are also expensive and unfeasible for many, considering these procedures are generally performed on subjects with a body mass index over 35. Investigating the predisposing and protective factors in the etiology of obesity is vital for finding

* Corresponding author. Tel.: +61 2 9295 8294; fax: +61 2 9295 8281.
E-mail address: a.sainsbury-salis@garvan.org.au (A. Sainsbury).
[1] These authors contributed equally to this work.

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long-term treatments for obesity and reducing the incidence of type 2 diabetes.

Gut-derived hormones have been of major interest as possible targets for the treatment of obesity in light of their marked effects on satiety and food intake. One of these hormones is peptide YY (PYY), which belongs to a family of peptides including neuropeptide Y (NPY) and pancreatic polypeptide (PP), all of which are known to have potent effects on feeding and energy balance via their unique interactions with G-protein-coupled Y receptors (Y1, Y2, Y4, Y5, y6) (Blomqvist and Herzog, 1997; Stanley et al., 1986; Ueno et al., 1999).

PYY is predominantly produced by endocrine L cells of the lower gastrointestinal tract and is also expressed in alpha cells of the islets of Langerhans as well as in the stomach and brainstem (Pieribone et al., 1992). Two forms of PYY exist in the circulation: the full length PYY1-36, and the shortened form PYY3-36, cleaved from secreted PYY1-36 by the cell surface enzyme dipeptidyl peptidase IV (Lundberg et al., 1982). PYY1-36 binds to all known Y receptors, albeit to each with differing affinities, whereas PYY3-36 preferentially binds the Y2 receptor and to a lesser extent the Y5 receptor (Blomqvist and Herzog, 1997). Obese subjects have significantly reduced circulating levels of PYY (Batterham et al., 2003). Moreover, it has been suggested that this is due to a deficiency in PYY release from the colon (Le Roux et al., 2005). In light of these observations, and considering that low fasting serum PYY levels are seen in non-obese subjects with a high genetic predisposition towards subsequent development of obesity on account of a family history of type 2 diabetes mellitus (Boey et al., 2006a), it is likely that low levels of circulating PYY may not simply be a consequence of obesity but a predisposing factor to the development of obesity.

Recent studies have demonstrated acute affects of PYY1-36 and PYY3-36 in inhibiting food intake in animals and in man (Adams et al., 2004; Batterham et al., 2002; Challis et al., 2003; Chelikani et al., 2004, 2005; Halatchev et al., 2004; Riediger et al., 2004). It is thought that after a meal, PYY3-36, the main form of PYY circulating postprandially, acts on the arcuate nucleus of the hypothalamus. Specifically, PYY3-36 binds to Y2 receptors on NPY neurones, thereby inhibiting the orexigenic effect of these neurons and indirectly stimulating the action of anorexigenic neurons producing POMC (proopiomelanocortin, the precursor to the anorexigenic alpha melanocyte stimulating hormone) (Batterham et al., 2002). In contrast, other work has suggested that PYY3-36 not only acts via Y2 receptors to inhibit NPY neurones but also directly inhibits POMC neurones via Y2 receptors (Acuna-Goycolea and van den Pol, 2005; Fetissov et al., 2004). In light of these findings, it has been proposed that the PYY3-36-mediated inhibition of food intake occurs primarily through the inhibition of NPY neurones. Other studies also show that intraperitoneally injected PYY3-36 activates neurones in the area postrema and nucleus tractus solitarius in rodents, which may be another mechanism by which PYY3-36 influences food intake (Bonaz et al., 1993; Halatchev and Cone, 2005).

PYY appears to play a long-term role in regulating food intake, body weight and body composition. A four-week continuous infusion of PYY3-36 in diet-induced obese mice reduced cumulative food intake, weight gain and adiposity (Pittner et al., 2004). In *ob/ob* mice and *fa/fa* rats, on the other hand, four-week continuous infusion of PYY3-36 decreased body weight gain in association with a transient reduction in food intake observed during the first 4 days of infusion only (Pittner et al., 2004). These findings suggest that PYY may also influence body weight and body composition via effects independent of changes in food intake. Indeed, seven day subcutaneous administration of PYY3-36 to diet-induced obese mice transiently reduced food intake and also led to maintenance of mass-specific energy expenditure despite concurrent anorexia, reduced respiratory quotient (indicating increased fat oxidation) and led to significantly decreased adiposity (Adams et al., 2006). Moreover, we and others have previously shown that PYY ablation results in obesity in mice (Batterham et al., 2006; Boey et al., 2006b).

Collectively, these studies suggest that PYY plays a major role in influencing long-term energy balance via effects on food intake and possibly also on metabolic processes, and that long-term elevation of PYY levels may attenuate obesity. However, studies investigating the effects of PYY administration have been limited to a maximum of 4-week duration, which is also not representative of PYY secretion *in vivo*. Furthermore, the mechanisms underlying PYY-induced effects on food intake, metabolic rate, body weight and adiposity have not yet been elucidated. Answers to these caveats are of relevance to human health since pharmacological treatments for obesity are administered for months, not weeks, and because new obesity treatments may involve enhancing endogenous PYY release with meals or episodic dosing strategies.

In order to test the hypothesis that elevated PYY might result in long-term reductions in food intake, body weight and adiposity, we generated PYY transgenic mice to over-express murine PYY. These mice were studied under chow fed conditions as well as under diet- and genetically induced obesogenic conditions to determine whether long-term endogenous PYY over-expression may have an anti-obesity effect. Moreover, we aimed to elucidate mechanisms for any possible effects of PYY over-expression on energy homeostasis by investigating thermogenesis, the hypothalamo–pituitary–thyroid axis as well as glucose homeostasis.