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Effects of Glycine-Extended and Serine¹³-Phosphorylated Forms of Peptide YY on Food Intake in Rats

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Abstract

The gut hormone peptide YY(3–36)-amide [PYY(3–36)-NH₂] is significantly more potent than PYY(1–36)-NH₂ in reducing food intake in rats and humans. Other Gly-extended and Ser¹³-phosphorylated PYY forms have been detected or predicted based upon known cellular processes of PYY synthesis and modification. Here we compared the effects of 3-h IV infusion of PYY(1–36)-NH₂, PYY(3–36)-NH₂, PYY(1–36)-Gly-OH, PYY(3–36)-Gly-OH, Ser¹³(PO₃)-PYY(1–36)-NH₂, Ser¹³(PO₃)-PYY(3–36)-NH₂, Ser¹³(PO₃)-PYY(1–36)-Gly-OH, and Ser¹³(PO₃)-PYY(3–36)-Gly-OH during the early dark period on food intake in freely-feeding rats. PYY(3–36)-NH₂ and Ser¹³(PO₃)-PYY(3–36)-NH₂ reduced food intake similarly at 50 pmol/kg/min, while only PYY(3–36)-NH₂ reduced food intake at 15 pmol/kg/min. PYY(1–36)-NH₂ and Ser¹³(PO₃)-PYY(1–36)-NH₂ reduced food intake similarly at 50 and 150 pmol/kg/min. In contrast, PYY(1–36)-Gly-OH, PYY(3–36)-Gly-OH, Ser¹³(PO₃)-PYY(3–36)-Gly-OH, and Ser¹³(PO₃)-PYY(1–36)-Gly-OH had no effect on food intake at doses of 50 or 150 pmol/kg/min. Taken together, these results indicate that i) PYY(3–36)-NH₂ is significantly more potent than PYY(1–36)-NH₂ in reducing food intake, ii) Gly-extended forms of PYY are significantly less potent than non-extended forms, and iii) Ser¹³-phosphorylation of PYY(3–36)-NH₂ decreases the anorexigenic potency PYY(3–36)-NH₂, but not PYY(1–36)-NH₂. Thus, PYY(3–36)-NH₂ appears to be the most potent PYY form for reducing food intake in rats.

Keywords

peptide YY(3-36); molecular forms; satiety

1.1 INTRODUCTION

The 36 amino acid gut hormone peptide YY(1–36)-amide [PYY(1–36)-NH₂] was first discovered using an assay to detect peptides with carboxyl-terminal amides in porcine

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intestinal extracts [16,17]. In 1989, Eberlein et al. [4] discovered a new molecular form of PYY, PYY(3–36)-NH₂. In 2002, Batterham et al. [1] reported that PYY(3–36)-NH₂ inhibits food intake in humans and rodents. Numerous groups have since confirmed that PYY(3–36)-NH₂ reduces food intake in several species including rodents, monkeys, and humans [2,11,13]. We and others have demonstrated that PYY(3–36)-NH₂ is significantly more potent than PYY(1–36)-NH₂ in reducing food intake in rats [2] and humans [13].

The proposed processing of proPYY to PYY(3–36)-NH₂ is as follows: i) the amino terminus of PYY is formed as it enters the endoplasmic reticulum by the action of signal peptidase; ii) the carboxyl terminus of PYY(1–36)-Gly-OH and PYY(1–36)-NH₂ is formed in sequential steps in the golgi and secretory vesicle by the actions of prohormone convertase [14], carboxypeptidase E [12], and peptidylglycine- α -amidating monooxygenase (PAM) [5], and iii) dipeptidyl peptidase-4 (DPP-4) converts PYY(1–36)-Gly-OH to PYY(3–36)-Gly-OH and PYY(1–36)-NH₂ to PYY(3–36)-NH₂ [10]. While the relative proportions of the various intermediate forms of proPYY processing have been determined in intestinal tissue in dog [7] and rat [8], the relative bioactivities of the forms to reduce food intake have not been determined.

We recently developed the RAPID (**R**educed temperature, **A**cidified, **P**eptidase inhibited, **I**sotopically-enriched mass spectrometry standards and **D**iluted) method for extracting and purifying peptides from tissue [7,15]. This method minimizes enzymatic breakdown of peptides and uses internal standards to monitor their recovery during extraction and purification. Using this method and high-resolution mass spectrometry to quantify PYY forms, we determined that PYY(1–36)-NH₂, PYY(3–36)-NH₂, and PYY(1–36)-Gly-OH comprise about 79, 5, and 16%, respectively, of total PYY in canine ileum [7], and 64, 6, and 1%, respectively, of total PYY in rat ileum [8].

Chen et al. [3] used HPLC and MALDI-TOF and electrospray tandem mass spectrometry to discover a post-translationally modified form of PYY(1–36)-NH₂ from porcine intestine that was phosphorylated at Ser¹³. These investigators also demonstrated that Ser¹³(PO₃)-PYY(1–36)-NH₂ exhibits high affinity for binding to neuropeptide Y receptors Y1, Y2 and Y5, and inhibits forskolin-stimulated cAMP accumulation in SK-N-MC cells.

Here we compared the effects of 3-h intravenous (IV) infusions of the various detected and predicted forms of PYY [PYY(1–36)-NH₂, PYY(3–36)-NH₂, PYY(1–36)-Gly-OH, PYY(3–36)-Gly-OH, Ser¹³(PO₃)-PYY(1–36)-NH₂, Ser¹³(PO₃)-PYY(3–36)-NH₂, Ser¹³(PO₃)-PYY(1–36)-Gly-OH, Ser¹³(PO₃)-PYY(3–36)-Gly-OH] at dark onset on food intake in rats with free access to food.

2.1 METHODS AND PROCEDURES

2.1.1 Peptides synthesis and purification

PYY(1–36)-NH₂ was purchased from Phoenix Pharmaceuticals (Burlingame, CA). PYY(1–36)-Gly-OH, PYY(3–36)-Gly-OH, Ser¹³(PO₃)-PYY(1–36)-NH₂, Ser¹³(PO₃)-PYY(3–36)-NH₂, Ser¹³(PO₃)-PYY(1–36)-Gly-OH, and Ser¹³(PO₃)-PYY(3–36)-Gly-OH were synthesized and delivered to us as desalted crude material by GL Biochem (Shanghai) Ltd. (Shanghai, China). PYY(3–36)-NH₂ was synthesized in our laboratory by Fmoc solid-phase methodology. Purification of the crude material from GL Biochem (Shanghai) L.t.d. (Shanghai, China) and the PYY(3–36) synthesized in our laboratory was accomplished by reverse phase high performance liquid chromatography. Purity of each peptide was greater than 98%. Proof of structure for each peptide was verified by electro-spray mass spectrometry. Stock solutions were prepared by dissolving each peptide in 0.15 M NaCl, 0.1% BSA. Single-use aliquots were stored at –70°C. Effects of thawing of peptide aliquots

and incubation of peptides in infusate (0.15 M NaCl, 0.1% BSA) for 6 h at room temperature on peptide stability were assessed using reverse phase HPLC. Analysis was performed on a C18 Vydac (0.46×15 cm) analytical column using a Waters 600 HPLC system. Elution gradient was from 94% Buffer A/6% Buffer B to 40% Buffer A/60% Buffer B over 30 min. Buffer A was 0.1% trifluoroacetic acid (TFA)/H₂O and Buffer B was 0.095% TFA/acetonitrile. Flow rate was 1 ml/min and detection was with UV at 214 nm. Single peaks were observed for each peptide after both thawing and incubation in infusate. HPLC results for PYY(3–36)-Gly-OH are shown in Fig. 1. Thus, freeze-thawing and incubation of peptides in infusate at room temperature for 6 h appear not to affect the stability of the peptides.

2.1.2 Animals

Male Sprague-Dawley rats (Charles River, Kingston, NY) weighing 350–500 g (12 to 20 weeks of age) were housed individually in hanging wire-mesh cages in a room with controlled temperature (19–21°C) and a 12:12-h light-dark cycle (time of onset of light cycle varied across experiments). Rats were provided pelleted or powdered rat chow (Labdiet®, 5001 Rodent diet, PMI® Nutrition International, Brentwood, MO) and water ad libitum. The Animal Studies Subcommittee of the Omaha Veterans Affairs Medical Center approved the experimental protocol.

2.1.3 Surgical procedures

The procedure for implantation of a jugular vein catheter for peptide infusions has been described previously [18]. Catheters were kept patent by flushing with 0.2 ml of heparinised saline (20 U/ml) on alternate days, and plugged with stainless steel wire. The animals were allowed at least 1 week to recover from surgery. Rats were then adapted to being chronically tethered to infusion swivels for at least 1 week before start of experiments. The jugular vein catheter was connected to a 40-cm length of tubing passed through a protective spring coil connected between a light-weight saddle (IITC, Woodland Hills, CA) worn by the rat and an infusion swivel. Rats had ad libitum access to ground chow that was provided fresh each day 3 h before dark onset.

2.1.4 Effects of 3-h IV infusion of different forms of PYY(3–36) on food intake in non-food-deprived rats

In a series of 4 experiments, rats ($n=16$) received a single, 3-h jugular vein infusion per day beginning 15 min before dark onset, of PYY(3–36)-NH₂ (0, 15 pmol/kg/min), Ser¹³(PO₃)-PYY(3–36)-NH₂ (0, 15 pmol/kg/min), PYY(3–36)-NH₂ (0, 50 pmol/kg/min), and Ser¹³(PO₃)-PYY(3–36)-NH₂ (0, 50 pmol/kg/min). Peptides were administered in 0.15 M NaCl containing 0.1% BSA at 50 μ l/min via a syringe infusion pump (PHD2000, Harvard Apparatus, South Natick, MA); pumps were turned on and off by computer. Within each experiment, each rat received vehicle and peptide in counterbalanced order at approximately 48-h intervals. Food intake cumulated hourly for 20 h after dark onset was determined from continuous computer recording of changes in food bowl weight. At the end of an experiment, data from a rat were excluded if its jugular vein catheter was not patent. A catheter was deemed patent if the rat lost consciousness within 10 s of a bolus injection of the short-acting anesthetic Brevital into the catheter.

In 4 additional experiments of identical design, rats ($n=16$) received at dark onset, 3-h jugular vein infusions of PYY(3–36)-Gly-OH (0, 50 pmol/kg/min), Ser¹³(PO₃)-PYY(3–36)-Gly-OH (0, 50 pmol/kg/min), PYY(3–36)-Gly-OH (0, 150 pmol/kg/min), and Ser¹³(PO₃)-PYY(3–36)-Gly-OH (0, 150 pmol/kg/min).

2.1.5 Effects of 3-h IV infusion of different forms of PYY(1–36) on food intake in non-food-deprived rats

We previously determined that 3-h IV infusion of PYY(3–36)-NH₂ at dark onset is an order of magnitude more potent than PYY(1–36)-NH₂ in reducing food intake in rats. Here we compared the feeding effects of PYY(3–36)-NH₂, PYY(1–36)-NH₂, and Ser¹³(PO₃)-PYY(1–36)-NH₂ at 0 and 15 pmol/kg/min, the approximate mean effective dose for inhibition of food intake by PYY(3–36)-NH₂. The experimental design was the same as that described above for PYY(3–36) forms. In 2 additional experiments of identical design, we compared the feeding effects of PYY(1–36)-NH₂ and Ser¹³(PO₃)-PYY(1–36)-NH₂ at 2 higher doses, 50 and 150 pmol/kg/min.

The last 2 experiments determined the feeding effects of 3-h jugular vein infusion of PYY(1–36)-Gly-OH (0, 150 pmol/kg/min) and Ser¹³(PO₃)-PYY(3–36)-Gly-OH (0, 150 pmol/kg/min).

2.1.6 Statistical analyses

Values are presented as group means $\pm$ SE. Data were analyzed by repeated measures analysis of variance (ANOVA); planned comparisons of treatment means were evaluated by paired t-tests. Differences were considered significant if $P < 0.05$.

3.1 RESULTS

3.1.1 Effects of 3-h IV infusion of different forms of PYY(3–36) on food intake in non-food-deprived rats

PYY(3–36)-NH₂ was more potent than Ser¹³(PO₃)-PYY(3–36)-NH₂ in reducing food intake (Figs. 2A–D and 3). At 15 pmol/kg/min, PYY(3–36)-NH₂ significantly reduced 3-h food intake by 29%, while Ser¹³(PO₃)-PYY(3–36)-NH₂ had no statistically significant effect (Fig. 3A). PYY(3–36)-NH₂ also appeared to be more inhibitory than Ser¹³(PO₃)-PYY(3–36)-NH₂ at the 3-fold higher dose of 50 pmol/kg/min (42 vs. 31% inhibition, Fig. 3B). In contrast, PYY(3–36)-Gly-OH and Ser¹³(PO₃)-PYY(3–36)-Gly-OH did not reduce food intake at 50 or 150 pmol/kg/min (Fig. 2E–H).

3.1.2 Effects of 3-h IV infusion of different forms of PYY(1–36) on food intake in non-food-deprived rats

At 15 pmol/kg/min, PYY(3–36)-NH₂ significantly reduced food intake, while PYY(1–36)-NH₂ had a significantly smaller effect and Ser¹³(PO₃)-PYY(1–36)-NH₂ had no effect (Figs. 4A and 5A). At higher doses of 50 and 150 pmol/kg/min, PYY(1–36)-NH₂ and Ser¹³(PO₃)-PYY(1–36)-NH₂ similarly reduced food in a dose-dependent manner (Figs. 4B–C and 5B–C). In contrast, PYY(1–36)-Gly-OH and Ser¹³(PO₃)-PYY(1–36)-Gly-OH did not reduce food intake at 150 pmol/kg/min (Fig. 4D–E).

4.1 DISCUSSION

The proposed processing of proPYY to PYY(3–36)-NH₂ includes formation of the carboxyl terminus of PYY(1–36)-Gly-OH and PYY(1–36)-NH₂ by prohormone convertase [14], carboxypeptidase E [12], and PAM [5], and conversion of PYY(1–36)-Gly-OH to PYY(3–36)-Gly-OH and PYY(1–36)-NH₂ to PYY(3–36)-NH₂ by DPP-4 [10]. We previously determined that 3-h IV infusion of PYY(3–36)-NH₂ during the early dark period in freely-feeding rats is an order of magnitude more potent than PYY(1–36)-NH₂ in reducing food intake [2]. Sloth et al. [13] reported similar results for PYY(3–36)-NH₂ in humans. Our results here further support these findings for PYY(3–36)-NH₂ and PYY(1–36)-NH₂. No

previous study has characterized the anorexigenic effects of the other possible molecular forms of PYY.

We recently developed the RAPID method for extracting and purifying peptides from tissue [7,15]. Using this method and high-resolution mass spectrometry to quantify PYY forms, we determined that PYY(1–36)-NH₂, PYY(3–36)-NH₂, and PYY(1–36)-Gly-OH comprise about 79, 5, and 16%, respectively, of total PYY in canine ileum [7], and 64, 6, and 1%, respectively, of total PYY in rat ileum [8]. Here we demonstrate that PYY(1–36)-Gly-OH and PYY(3–36)-Gly-OH are significantly less anorexigenic than PYY(1–36)-NH₂ and PYY(3–36)-NH₂, respectively.

Chen et al. [3] used HPLC and mass spectrometry to detect Ser¹³(PO₃)-PYY(1–36)-NH₂ in extracts of porcine intestine. They noted that while the amount of phosphorylated PYY could not be determined from mass spectrometry, phospho-PYY appears to be a minor form compared to non-phosphorylated PYY. We did not detect significant amounts of either Ser¹³(PO₃)-PYY(1–36)-NH₂ or Ser¹³(PO₃)-PYY(3–36)-NH₂ in dog or rat distal small intestine [7,8]. Chen et al. showed that Ser¹³(PO₃)-PYY(1–36)-NH₂ binds with high affinity to Y1, Y2 and Y5 receptors, and inhibits forskolin-stimulated cAMP accumulation in SK-N-MC cells. Our work here extends these findings by showing that Ser¹³(PO₃)-PYY(1–36)-NH₂ and PYY(1–36)-NH₂ similarly reduce food intake, while Ser¹³(PO₃)-PYY(3–36)-NH₂ is less potent than PYY(3–36)-NH₂.

Previous studies of PYY forms in blood have reported that PYY(3–36)-NH₂ levels are equal to or greater than those of PYY(1–36)-NH₂ [6,9]. However, these studies did not use methods to monitor possible alteration of PYY forms during processing of blood samples, nor did they use mass spectrometry to identify and quantify the various molecular forms of PYY. Thus, it remains to be determined whether blood levels of PYY forms reflect those occurring in intestinal tissue [high PYY(1–36)-NH₂ and low PYY(1–36)-Gly-OH and PYY(3–36)-NH₂] or whether significant *in vivo* conversion of PYY(1–36)-NH₂ to PYY(3–36)-NH₂ by DPP-4 occurs following secretion of PYY(1–36)-NH₂ from intestinal cells [10].

In summary, our results indicate that i) PYY(3–36)-NH₂ is significantly more potent than PYY(1–36)-NH₂ in reducing food intake in rats, ii) Gly-extended forms of PYY(3–36)-NH₂ and PYY(1–36)-NH₂ are significantly less potent than their non-extended forms, and iii) phosphorylation of Ser¹³ slightly reduces the anorexigenic potency of PYY(3–36)-NH₂, but not PYY(1–36)-NH₂. Thus, PYY(3–36)-NH₂ is more potent than other processing intermediates of PYY for reducing food intake.

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Figure 1.

HPLC traces of PYY(3–36)-Gly-OH thawed from -70°C (A) and incubated at room temperature for 6 h after dilution (1:1) with infusate (0.15 M NaCl, 0.1% BSA) (B). Analysis was performed on a C18 Vydac (0.46×15 cm) analytical column using a Waters 600 HPLC system. Elution gradient was from 94% Buffer A/6% Buffer B to 40% Buffer A/60% Buffer B over 30 min. Buffer A was 0.1% trifluoroacetic acid (TFA)/ H_2O and Buffer B was 0.095% TFA/acetonitrile. Flow rate was 1 ml/min and detection was with UV at 214 nm.

Figure 2.

Effects of 3-h IV infusion of different molecular forms of peptide YY(3–36) [PYY(3–36)] on cumulative food intake for 20 h in 11–16 rats. Rats that were normally fed received 3-h jugular vein infusions beginning 15 min before dark onset (time 0) of the following: PYY(3–36)-NH₂ at 0 and 15 pmol/kg/min (A), Ser¹³(PO₃)-PYY(3–36)-NH₂ [PO₃-PYY(3–36)-NH₂] at 0 and 15 pmol/kg/min (B), PYY(3–36)-NH₂ at 0 and 50 pmol/kg/min (C), PO₃-PYY(3–36)-NH₂ at 0 and 50 pmol/kg/min (D), PYY(3–36)-Gly-OH at 0 and 50 pmol/kg/min (E), PO₃-PYY(3–36)-Gly-OH at 0 and 50 pmol/kg/min (F), PYY(3–36)-Gly-OH at 0 and 150 pmol/kg/min (G), and PO₃-PYY(3–36)-Gly-OH at 0 and 150 pmol/kg/min (H). Food intake was determined from continuous computer recording of changes in food bowl

weight. Values are means $\pm$ SE. * $P < 0.05$, † $P < 0.01$, § $P < 0.001$, compared with the vehicle-treated group.

Figure 3.

Effects of 3-h IV infusion of peptide YY(3–36)-NH₂ [PYY(3–36)-NH₂] and Ser¹³(PO₃)-PYY(3–36)-NH₂ [PO₃-PYY(3–36)-NH₂] on 3-h food intake in 11–16 rats. Data are a subset of those presented in Figs. 2A–D. Rats received PYY(3–36)-NH₂ and PO₃-PYY(3–36)-NH₂ at 0 and 15 pmol/kg/min (A) and at 0 and 50 pmol/kg/min (B). Values are means ± SE. §P < 0.001 compared with the vehicle-treated group.

Figure 4.

Effects of 3-h IV infusion of different molecular forms of peptide YY (PYY) on cumulative food intake for 20 h in 11–15 rats. Rats that were normally fed received 3-h jugular vein infusions beginning 15 min before dark onset (time 0) of the following: PYY(3–36)-NH₂, PYY(1–36)-NH₂, and Ser¹³(PO₃)-PYY(1–36)-NH₂ [PO₃-PYY(1–36)-NH₂] at 0 and 15 pmol/kg/min (A), PYY(1–36)-NH₂ and PO₃-PYY(1–36)-NH₂ at 0 and 50 pmol/kg/min (B), PYY(1–36)-NH₂ and PO₃-PYY(1–36)-NH₂ at 0 and 150 pmol/kg/min (C), PYY(1–36)-Gly-OH at 0 and 150 pmol/kg/min (D), and PO₃-PYY(1–36)-Gly-OH at 0 and 150 pmol/kg/min (E). Food intake was determined from continuous computer recording of changes in food bowl weight. Values are means $\pm$ SE. *P < 0.05, †P < 0.01, §P < 0.001, compared with the vehicle-treated group.

Figure 5.

Effects of 3-h IV infusion of peptide YY(3–36)-NH₂ [PYY(3–36)-NH₂], PYY(1–36)-NH₂, and Ser¹³(PO₃)-PYY(1–36)-NH₂ [PO₃-PYY(3–36)-NH₂] on 3-h food intake in 11–15 rats. Data are a subset of those presented in Figs. 4A–C. Rats received PYY(3–36)-NH₂, PYY(1–36)-NH₂ and PO₃-PYY(1–36)-NH₂ at 0 and 15 pmol/kg/min (A), PYY(1–36)-NH₂ and PO₃-PYY(1–36)-NH₂ at 0 and 50 pmol/kg/min (B), and PYY(1–36)-NH₂ and PO₃-PYY(1–36)-NH₂ at 0 and 150 pmol/kg/min (C). Values are means ± SE. Values with different letters are different (P<0.05).