Intermittent intraperitoneal infusion of peptide YY(3-36) reduces daily food intake and adiposity in obese rats

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Submitted 6 March 2007; accepted in final form 4 April 2007

Chelikani PK, Haver AC, Reidelberger RD. Intermittent intraperitoneal infusion of peptide YY(3-36) reduces daily food intake and adiposity in obese rats. Am J Physiol Regul Integr Comp Physiol 293: R39–R46, 2007. First published April 11, 2007; doi:10.1152/ajpregu.00164.2007.—Peptide YY(3-36) [PYY(3-36)] is a gut-brain peptide that decreases food intake when administered by intravenous infusion to lean and obese humans and rats. However, chronic administration of PYY(3-36) by osmotic minipump to lean and obese rodents produces only a transient reduction in daily food intake and weight gain. It has recently been shown that 1-h intravenous infusions of PYY(3-36) every other hour for 10 days produced a sustained reduction in daily food intake, body weight, and adiposity in lean rats. Here, we determined whether intermittent delivery of PYY(3-36) can produce a similar response in diet-induced obese rats. During a 21-day period, obese rats (body fat >25%) received twice daily intraperitoneal infusion of vehicle (n = 18) or PYY(3-36) (n = 24) during hours 1–3 and 7–9 of the dark period. Rats had free access to both a 45% fat solid diet and a 29% fat liquid diet; intakes were determined from continuous computer recording of changes in food container weights. To sustain a 15–25% reduction in daily caloric intake, the initial PYY(3-36) dose of 30 pmol·kg−1·min−1 was reduced to 10 pmol·kg−1·min−1 on day 10 and then increased to 17 pmol·kg−1·min−1 on day 13. This dosing strategy produced a sustained reduction in daily caloric intake of 11–32% and prevented body weight gain (8 ± 6 vs. 51 ± 11 g) and fat deposition (4.4 ± 7.6 vs. 41.0 ± 12.8 g). These results indicate that intermittent intraperitoneal infusion of PYY(3-36) can produce a sustained reduction in food intake and adiposity in diet-induced obese rodents consuming palatable high-fat foods.

Peptide YY (PYY), neuropeptide Y, and pancreatic polypeptide comprise a family of structurally related gut-brain peptides with diverse actions mediated by five known receptors (12). Endocrine cells of the distal gut provide a major source of PYY. Food intake releases at least two major forms of PYY into the circulation: PYY(1-36) and PYY(3-36); other predicted or detected isoforms include Ser13-phosphorylated PYY(1-36) and PYY(3-36), glycine-extended carboxyl termini of both the phosphorylated and nonphosphorylated forms, and [Pro34]PYY(3-36) (4, 17, 21, 24). Systemic administration of PYY(3-36) potently inhibits food intake in rodents, monkeys, and humans (11, 15, 19, 27, 28, 33, 40), whereas PYY(1-36) appears to be significantly less potent in rats (15) and humans (39). Targeted deletion of the PYY gene produces an obese phenotype in mice (13). Obese humans appear to have a blunted plasma PYY response to food intake (10, 28); however, PYY(3-36) appears to decrease food intake similarly in lean and obese humans (10, 39). These results suggest that PYY(3-36) may act physiologically to reduce food intake and body adiposity and that insufficient production of PYY(3-36) may promote obesity. Thus PYY(3-36) administration may prove to be an effective means for treating obesity.

Batterham et al. (11) initially reported that twice daily intraperitoneal (IP) infusions of PYY(3-36) for 7 days produced a sustained decrease in body weight gain in rats. This study soon became the subject of intense debate because numerous investigators could not reproduce this finding (41). Several studies have since shown that continuous systemic administration of PYY(3-36) by osmotic minipump can reduce food intake and body weight in rodents but only transiently (3, 36, 41, 42, 44). Other known anorexigenic substances (amylin, glucagon-like peptide-1 receptor agonists, cholecystokinin, melanocortin receptor agonists) have also been reported to produce only transient effects on daily food intake and body weight in rodents when administered continuously by osmotic minipump (3, 9, 18, 20, 30, 31, 35, 36, 38, 41, 42, 44). Reasons for these inconclusive results include development of a compensatory increase in food intake between bolus injections, tolerance to continuous or frequent administration of the substances, and redundancy and plasticity in the energy regulatory system.

We have developed a novel experimental model that permits precise intravenous (IV) or IP administration of anorexigenic substances to rats tethered via infusion swivels to computer-controlled pumps. Rats are free to move, eat, and drink within their individual cages, and their indwelling catheters remain functional for many months. Measurement of food bowl weight, recorded by computer every 20 s, permits daily assessment of the instantaneous effects of infused substances on food intake. Adjustments in dosing pattern can be made daily to define a dosing strategy that minimizes both compensatory hyperphagia between doses and tolerance. We used this experimental model to show that IV infusion of PYY(3-36) dose-dependently reduces short-term food intake in lean rats (15). We further demonstrated that intermittent IV infusion of PYY(3-36) can produce a sustained decrease in daily food intake and adiposity in lean rats but only when intervals between PYY(3-36) infusions are shortened sufficiently to minimize compensatory hyperphagia between infusions (14). These studies helped to resolve the intense debate regarding the inhibitory effects of exogenous PYY(3-36) on food intake and body weight (25, 34). It remains to be determined whether

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PYY(3-36) is similarly effective in reducing food intake and body weight in obese individuals. In our previous study of the effects of PYY(3-36) on daily food intake in lean rats (14), 1-h IV infusions of PYY(3-36) every other hour for 10 days at 30 pmol·kg⁻¹·min⁻¹ produced a sustained reduction in daily food intake of ~20% and decreased body weight and adiposity by 7 and 35%, respectively. The aim of the present study was to identify a dosing strategy for IP administration of PYY (3-36) that produces similar reductions in daily caloric intake, body weight, and adiposity in diet-induced obese rats.

**MATERIALS AND METHODS**

**Synthesis and Purification of PYY(3-36)**

Rat PYY(3-36) was synthesized manually by utilizing Fmoc batch-wise solid-phase methodology (6). Purification was accomplished by reverse-phase HPLC. Proof of structure was provided by coelution with a known sample and by electrospray mass spectrometry. PYY(3-36) stock was prepared by dissolving the purified peptide in 0.15 M NaCl and 0.1% BSA. Single-use aliquots were stored at ~80°C.

**Animals**

Male Sprague-Dawley rats (Sasco, Charles River, Portage, MI; initially weighing 250–350 g) were housed in standard shoe-box cages in a room with controlled temperature (19–21°C) and a 12:12-h light-dark cycle (lights off at 1700). Rats were provided pelleted rat chow (Labdiet, 5001 Rodent diet; PMI Nutrition International, MO) and water ad libitum for ~1 wk before they were subjected to experimental procedures. The Animal Studies Subcommittee of the Omaha Veterans Affairs Medical Center approved the experimental protocol.

**Dietary Induction of Obesity**

Rats in standard shoe-box cages were provided a high-fat pelleted food (45, 35, and 20% calories from fat, carbohydrate, and protein, respectively; 4.73 kcal/g, D12451, Research Diets, New Brunswick, NJ) and vanilla Ensure liquid food (29, 36, and 15% calories from fat, carbohydrate, and protein respectively; 1.5 kcal/ml, Ross Nutrition, Abbott Laboratories, Columbus, OH) during a 6- to 8-mo period. The combined use of a high-fat solid food and palatable Ensure liquid food induces obesity in a high proportion of rats (7, 8, 29, 32). We measured total body fat monthly in unanesthetized rats using an EchoMRI-700 quantitative nuclear magnetic resonance (QMR) analyzer (Echo Medical Systems, Houston, TX). The criterion for obesity was total body fat >25%.

**Surgical Implantation of IP Catheter**

Obese rats were surgically implanted with an IP catheter under isoflurane anesthesia, for which we used procedures similar to those described previously (47). The IP catheter was constructed from an 18-cm-long Tygon tubing (ID = 0.51 mm, OD = 1.52 mm; Norton Plastics, Akron, OH), with a 1-cm² Dacron felt pad glued 2 cm from the distal end. The distal end of the catheter was inserted into the IP cavity through a puncture wound and anchored by suturing the pad to the abdominal musculature. The proximal portion of the catheter was pulled through a subcutaneous tunnel and a skin incision in the dorsal cervical region. The catheter was plugged with stainless steel wire and kept patent by flushing on alternate days with 1 ml of normal saline.

An IP catheter was chosen in lieu of the venous catheter used in our previous study in lean rats because IP catheters are easier to maintain and remain functional for a longer period of time. Rats were allowed 4 wk to regain lost body weight before being subjected to further experimental procedures.

**Experiments**

**Effects of intermittent IP infusion of PYY(3-36) on caloric intake, body weight, and body fat in diet-induced obese rats with access to high-fat solid food and Ensure liquid food.** Obese rats (n = 32) were housed individually in a metabolism cage modified to include a stainless steel side compartment with a 3-cm-diameter hole in the base. Below the hole was a food cup for powdered food, which was fixed to a digital balance. The opposite side of the cage contained a 2-cm-diameter opening, through which the rat drank liquid diet from the spout of a bottle fixed to a digital balance. The 64 balances in this 32-cage system were connected to two computers through code-activated switches (CAS-161, Western Telematic, Irvine, CA). Output from each balance was monitored at ~20-s intervals, and changes in food container weights were recorded. The data were processed to determine the amount of each food ingested each hour and total caloric intake cumulated hourly. Another 10 obese rats were housed in the same type of metabolism cages with the same type of food containers, which were not fixed to digital balances. For these animals, daily ingestion of the two foods was determined by manually weighing the food containers at the start and end of each day. Manual and automated weighing of the food containers gave the same results.

Thus daily food intakes were measured in all 42 rats, and cumulative hourly intakes were measured each day in 32 of the 42 rats. Each of the 42 rats had its IP catheter connected to a 40-cm length of tubing passed through a protective spring coil connected between a light-weight harness (IITC, Woodland Hills, CA) worn by the rat and a single-channel infusion swivel (Instech Laboratories, Plymouth Meeting, PA), which allowed free movement of the rat in its individual cage. Animals were then allowed 2 wk to regain body weight and to adapt to experimental conditions. Rats were provided powdered high-fat solid food (D12451), the Ensure liquid food, and water each day from 1100 to 0900 the next morning (dark period was from 1100 to 2300). Experimental setup and routine maintenance were performed each day between 0900 and 1100. During an initial 7-day baseline period, all rats received an IP infusion of vehicle (0.15 M NaCl, 0.1% BSA; 1 ml/h) during hours 1–3 and 7–9 of the dark period (1100–1400 and 1700–2000, respectively). Rats were weighed at the beginning and end of the baseline period, and their total body fat was determined by QMR at the end of the baseline period. They were then divided into two groups, one that would receive vehicle (n = 18) and the other PYY(3-36) (n = 24) for 21 days. The groups were matched for average daily caloric intake during the last 3 days of the baseline period, weight gain during the baseline period, and body weight and percent body fat at the end of the baseline period.

On the first day of treatment, PYY(3-36) was infused at 30 pmol·kg⁻¹·min⁻¹ during hours 1–3 and 7–9 of the dark period. We previously determined that IV infusion of this dose of PYY(3-36) during the first 3 h of the dark period produces a significant inhibition of food intake in lean rats (15). This initial twice-daily dosing regimen permitted us to evaluate the extent to which 1) caloric intake is reduced during the first 3-h treatment period, 2) desensitization to PYY(3-36)-induced anorexia occurs during the second 3-h treatment period, 3) rebound hyperphagia occurs between treatment periods, and 4) daily caloric intake is reduced in response to the two treatment periods. On subsequent days, dosing level and/or pattern of administration in the PYY(3-36)-treated group was adjusted, as necessary, in an attempt to induce a sustained 15–25% reduction in average daily caloric intake, compared with average daily caloric intake in the rats administered vehicle at the same infusion rate during the same intervals. At the end of the 21-day treatment period, rats were weighed and their body fat was measured by QMR.

**Effects of intermittent IP infusion of PYY(3-36) on caloric intake in diet-induced obese rats with access only to high-fat solid food.** This experiment was conducted to determine whether PYY(3-36) would be similarly effective in reducing daily caloric intake in the obese rats if only the high-fat solid food (D12451) was provided. Rats from the
experiment described above were used. After 4 wk of adaptation to the high-fat solid food and when daily caloric intakes had become stable, the rats were assigned to two groups, matched as before, to receive IP infusion of either vehicle (n = 18) or PYY(3-36) at 17 pmol·kg⁻¹·min⁻¹ (n = 19) during hours 1–3 and 7–9 of the dark period for 4 consecutive days. The experimental setup, peptide administration, and data acquisition and analysis were as described for the previous experiment.

Comparative effects of IP and IV infusion of PYY(3-36) on food intake in lean rats. Results of the experiments described above, compared with those of our previous study (14) of the effects of intermittent IV infusion of PYY(3-36) in lean rats, suggested either that PYY(3-36) is more potent in reducing daily food intake in obese vs. lean rats or that PYY(3-36) is more effective in suppressing food intake when given by IP vs. IV infusion. Thus our aim here was to compare the effects of IV and IP infusion of PYY(3-36) on short-term food intake in lean rats. Experimental procedures were similar to those described above. Lean rats (398 ± 17 g) were surgically implanted with a jugular vein catheter, as well as an IP catheter, using procedures similar to those described previously (45). The IV catheter, which also exited the skin in the dorsal cervical region, was plugged with stainless steel wire and kept patent by flushing on alternate days with 0.2 ml of 50% dextrose. Rats, tethered to double-channel infusion swivels, had free access to ground chow, which was provided fresh each day at 1100 (dark period: 1400–0200). Animals were adapted to experimental conditions for at least 1 wk before the start of experiments. Nondeprived rats (n = 15) received two, 3-h IP infusions of vehicle (0.15 M NaCl and 0.1% BSA; 1 ml/h) or PYY(3-36) (30 pmol·kg⁻¹·min⁻¹) or two, 3-h IV infusions of PYY(3-36) (30 pmol·kg⁻¹·min⁻¹) during hours 1–3 and 7–9 of the dark period. Food intake was measured by continuous computer recordings of changes in food bowl weight. Each rat received each of the three treatments in random order at ~48-h intervals. The effect of IV infusion of vehicle was not tested in this experiment because we previously determined that food intake was not different in rats receiving vehicle by either IP or IV infusion (data not shown). At the end of the experiment, patency of jugular vein catheters was determined by IV injection of 0.2 ml of the short-acting anesthetic propofol (Abbott Laboratories, North Chicago, IL). A catheter was considered patent if the rat lost consciousness immediately on injection of the anesthetic; only data from such propofol-positive rats were included in statistical analyses.

Statistical analyses. Values are presented as group means ± SE. Data from the first two experiments comparing the effects of intermittent IP infusion of PYY(3-36) on caloric intake, body weight, and body fat in obese rats were analyzed separately by repeated-measures ANOVA. Data from the last experiment comparing the effects of two 3-h IP and IV infusions of PYY(3-36) on food intake in lean rats were analyzed by one-way repeated-measures ANOVA. Planned comparisons of treatment means were evaluated by paired t-tests. Differences were considered significant if P < 0.05.

RESULTS

Effects of Intermittent IP Infusion of PYY(3-36) on Caloric Intake, Body Weight, and Body Fat in Diet-Induced Obese Rats With Access to High-Fat Solid Food and Ensure Liquid Food

By the end of the 7-day baseline period, the two groups of rats that were to receive IP infusions of either vehicle (n = 18) or PYY(3-36) (n = 24) had distributions of body weight (687 ± 12 vs. 672 ± 13 g), percent body fat (29 ± 1 vs. 29 ± 1%), weight gain during the baseline period (23 ± 5 vs. 16 ± 3 g), and average daily caloric intake (111 ± 5 vs. 109 ± 4 kcal) that were not statistically different (P > 0.05; Figs. 1 and 2 and Table 1). During the baseline period, the rats consumed four to five times more calories from the Ensure liquid food than from the high-fat solid food (Fig. 1). During the first 9 days of treatment, PYY(3-36) infusion at 30 pmol·kg⁻¹·min⁻¹ during hours 1–3 and 7–9 of the dark period significantly reduced daily caloric intake on days 2 through 9 by 11, 19, 27, 22, 30, 27, 25, and 32%, respectively (Fig. 1). On day 10, the PYY(3-36) dose was reduced in all rats from 30 to 10 pmol·kg⁻¹·min⁻¹ without a change in the pattern of administration in an attempt to define a dose that would produce a sustained reduction in average daily caloric intake in the range of 15–25%. Intermittent infusion of PYY(3-36) at this dose significantly reduced daily caloric intake on days 10–12 by 16, 22, and 13%, respectively (Fig. 1). The PYY(3-36) dose was then increased on day 13 in all rats from 10 to 17

Fig. 1. Effects of twice daily intraperitoneal (IP) infusions of peptide YY (3-36) [PYY(3-36)] for 21 days on daily total caloric intake (A), caloric intake of liquid Ensure (B), and caloric intake of a high-fat solid food (C) in diet-induced obese rats. During a 7-day baseline period (days –9 to –3), rats (n = 42) received IP infusions of vehicle (0.15 M NaCl, 0.1% BSA) during the intervals of 0–3 and 6–9 h of the dark period. During the 21-day treatment period, separate groups of rats received IP infusions during the same periods of either vehicle (n = 18) or PYY(3-36) (n = 24) at 30 pmol·kg⁻¹·min⁻¹ on days 1–9, at 10 pmol·kg⁻¹·min⁻¹ on days 10–12, and at 17 pmol·kg⁻¹·min⁻¹ on days 13–21 (a, b, and c designate start of each dose; d designates end of infusions). Values are means ± SE. *P < 0.05, †P < 0.01, ‡P < 0.001 compared with vehicle-treated group.
pmol·kg\(^{-1}\)·min\(^{-1}\) without the pattern of administration being changed. Intermittent infusion of PYY(3-36) at this dose produced a sustained reduction in daily caloric intake on days 13–21 by 21, 13, 24, 18, 21, 22, 19, 11, and 18%, respectively (Fig. 1).

PYY(3-36) primarily reduced caloric intake during infusion intervals, and there was no development of compensatory hyperphagia during noninfusion intervals (Fig. 3). PYY(3-36) reduced caloric intake by selectively decreasing ingestion of the Ensure liquid food (Fig. 1). Body weights and fat contents of vehicle- and PYY(3-36)-treated rats before and after treatment are shown in Table 1. Compared with the vehicle-treated rats, intermittent infusion of PYY(3-36) prevented body weight gain across the 21-day period (8 ± 6 vs. 51 ± 11 g; \(P < 0.01\)) by preventing fat deposition (4.4 ± 7.6 vs. 41.0 ± 12.8 g; \(P < 0.01\)). During the 4 days immediately after cessation of vehicle and PYY(3-36) infusions, daily caloric intake in the PYY(3-36)-treated rats rapidly increased to levels observed in vehicle-treated rats (Fig. 1).

**Effects of Intermittent IP Infusion of PYY(3-36) on Daily Caloric Intake in Diet-Induced Obese Rats With Access Only to High-Fat Solid Food**

During the 3-day baseline period, the two groups of rats that were to receive infusions of either vehicle (\(n = 18\)) or PYY(3-36) (\(n = 19\)) had distributions of body weight (676 ± 16 vs. 657 ± 15 g) and average daily caloric intake (73 ± 2 vs. 75 ± 1 kcal) that were not different (\(P > 0.05\)). During the next 4 days, PYY(3-36) infusion at 17 pmol·kg\(^{-1}\)·min\(^{-1}\) during
PYY(3-36) on Food Intake in Lean Rats

Comparative Effects of Intermittent IP and IV Infusion of the PYY(3-36)-treated rats rapidly increased to levels observed in vehicle and PYY(3-36) infusions, daily caloric intake in the (Fig. 4). During the 3 days immediately after cessation of daily caloric intake by 19, 18, 23, and 31%, respectively sustained reduction in daily caloric intake of PYY(3-36) at 30 pmol recently showed that, in lean rats, intermittent IV infusion of rodents but only transiently (3, 36, 41, 42, 44). Our group (14) motric minipump can reduce food intake and body weight in that continuous systemic administration of PYY(3-36) by osmotically administered peptide YY(3-36) [PYY(3-36)] infusions.† Values are means ± SE. Experiment is described in Fig. 1. *Baseline values before animals received peptide YY(3-36) infusions.‡

hours 1–3 and 7–9 of the dark period significantly reduced daily caloric intake by 19, 18, 23, and 31%, respectively (Fig. 4). During the 3 days immediately after cessation of vehicle and PYY(3-36) infusions, daily caloric intake in the PYY(3-36)-treated rats rapidly increased to levels observed in the vehicle-treated rats.

**Comparative Effects of Intermittent IP and IV Infusion of PYY(3-36) on Food Intake in Lean Rats**

Two 3-h infusions of PYY(3-36) at 30 pmol·kg⁻¹·min⁻¹ during hours 1–3 and 7–9 of the dark period reduced food intake similarly whether administered by IP or IV infusion (Fig. 5A). PYY(3-36) primarily reduced food intake during infusion intervals, and there was no development of compensatory hyperphagia during noninfusion intervals (Fig. 5B).

**DISCUSSION**

Batterham et al. (11) initially reported that twice-daily IP injections of PYY(3-36) for 7 days produced a sustained decrease in body weight gain in rats. This study became the subject of intense debate because numerous investigators could not confirm this finding (41). Several studies have since shown that continuous systemic administration of PYY(3-36) by osmotic minipump can reduce food intake and body weight in rodents but only transiently (3, 36, 41, 42, 44). Our group (14) recently showed that, in lean rats, intermittent IV infusion of PYY(3-36) at 30 pmol·kg⁻¹·min⁻¹ for 10 days produced a sustained reduction in daily caloric intake of ~20% and decreased body weight and adiposity by 7 and 35%, respectively. In the present study, we show that intermittent IP infusion of PYY(3-36) produced similar reductions in daily caloric intake, body weight, and adiposity in diet-induced obese rats consuming palatable foods. Together, these results indicate that dosage pattern is critical for producing a sustained effect of PYY(3-36) on food intake and adiposity in lean and obese rodents.

In obese rats in the present study, IP infusion of PYY(3-36) produced a sustained reduction in daily caloric intake when administered at a dose of either 17 or 30 pmol·kg⁻¹·min⁻¹ during hours 1–3 and 7–9 of the dark period each day. PYY(3-36) primarily reduced food intake during infusion intervals, and there was no development of compensatory hyperphagia during noninfusion intervals. In lean rats in our previous study (14), IV infusion of PYY(3-36) at 30 pmol·kg⁻¹·min⁻¹ during the same intervals also reduced food intake during infusion intervals but did not produce a sustained reduction in daily food intake across the 10-day test period because compensatory hyperphagia developed during noninfusion intervals (14). In contrast, a sustained reduction in daily food intake was produced in the lean rats when intervals between PYY(3-36) infusions were reduced to 1 h. The different
PYY(3-36) reduces adiposity

Fig. 4. Effects of twice-daily IP infusions of PYY(3-36) for 4 days on caloric intake in diet-induced obese rats when only the high-fat solid food was provided. Rats were assigned to 2 groups, which received IP infusions of either vehicle (n = 18) or PYY(3-36) (n = 19) at 17 pmol·kg⁻¹·min⁻¹ during the intervals of 0–3 h and 6–9 h of the dark period on days 1–4 [a designates 1st day of PYY(3-36) infusions; b designates end of infusions]. Values are means ± SE. *P < 0.01, †P < 0.001 compared with vehicle-treated group.

Fig. 5. Comparative effects of intermittent IP and IV infusions of PYY(3-36) on cumulative hourly food intake (A) and food intake during infusion and noninfusion intervals (B) in lean rats. Nondeprived rats (n = 15) received two 3-h IP infusions of vehicle (0.15 M NaCl, 0.1% BSA) or PYY(3-36) (30 pmol·kg⁻¹·min⁻¹) or two 3-h IV infusions of PYY(3-36) (30 pmol·kg⁻¹·min⁻¹) during the intervals of 0–3 and 6–9 h of the dark period. Values are means ± SE. In A, *P < 0.05, †P < 0.01, ‡P < 0.001 compared with vehicle. In B, values within the same time intervals that are labeled with the same letter (a or b) are not statistically different (P > 0.05).

Obese rats are more sensitive than lean rats to the anorexic effects of PYY(3-36). Widdowson et al. (46) reported that diet-induced obese rats have increased ¹²⁵I-labeled PYY binding to Y2 and/or Y5 receptors in the arcuate and dorsomedial hypothalamic nuclei, as well as in a number of other brain regions. Because intracerebroventricular injection of PYY(3-36), a Y2-receptor agonist, reduces food intake in rats (10), the upregulation of Y2 receptors in this region in diet-induced obese rats may contribute to the apparent enhanced anorexic response to PYY(3-36) in these animals. Whether Y2 receptors are also upregulated in peripheral tissues linked to the control of food intake (e.g., vagal sensory nerves) remains to be determined.

It also remains to be determined whether obese humans are more sensitive than lean humans to the anorexic effects of PYY(3-36). A single dose of PYY(3-36) has been reported in two different studies to reduce short-term food intake similarly in lean and obese humans (10, 39).

Continuous osmotic minipump administration of many known anorexigenic substances [PYY(3-36), amylin, glucagon-like peptide-1 receptor agonists, cholecystokinin, melanocortin receptor agonists] has been reported to produce transient reductions in daily food intake in rodents (3, 9, 18, 20, 30, 31, 35, 36, 38, 41, 42, 44). One possible explanation for these transient responses is that early substance-induced reductions in daily food intake and adiposity elicit a delayed compensatory response to restore energy balance mediated by a reduction in leptin signaling to the brain (5, 22). Another possibility is that continuous or frequent administration of the substances cause desensitization and downregulation of their receptors. Each of these anorexigenic substances act at G-protein-coupled receptors. Numerous studies have demonstrated that prolonged exposure of G-protein-coupled receptors to agonists can induce receptor downregulation and tolerance (23, 37). This likely explains why continuous infusion of PYY(3-36) produces a transient decrease in food intake (3, 36, 41, 42, 44), whereas intermittent infusion of PYY(3-36) in our studies produces a sustained reduction in daily food intake. Whether intermittent infusion of other anorexigenic substances, either alone or in combination, can produce a sustained reduction in food intake and adiposity in obese individuals remains to be determined.

Our results show that intermittent PYY(3-36) infusion not only produces a sustained reduction in caloric intake in diet-induced obese rats given palatable foods but also prevents the significant weight gain and fat deposition that occurs when these foods are consumed. Previous studies have shown that continuous peripheral administration of PYY(3-36) by osmotic minipump can reduce body weight in obese rodents despite producing only a transient reduction in daily food intake (3, 36, 44). However, the loss in body weight reported in these studies was apparently caused by the initial period of anorexia, because 1) weight gain normalized when food intake returned to normal, 2) weight loss was similar in PYY(3-36)-treated and pair-fed animals (36), and 3) PYY(3-36) does not appear to increase energy expenditure (3, 43, 44). Together, these results suggest that intermittent administration of PYY(3-36) is more transient in nature, and our results indicate that intermittent administration of PYY(3-36) is more...
likely than continuous administration to produce steady weight loss in obese subjects. Several studies have assessed whether the anorexigenic response to administration of PYY(3-36) is due in part to production of nonspecific malaise. In humans, IV infusion of PYY(3-36) at 0.2–0.8 pmol·kg⁻¹·min⁻¹ was reported to inhibit food intake in normal-weight men and women without producing adverse effects (28). In contrast, Degen et al. (19) reported that a low IV dose of PYY(3-36) of 0.2 pmol·kg⁻¹·min⁻¹ reduced food intake in normal-weight men without producing adverse effects, whereas higher anorexigenic doses of 0.4 and 0.8 pmol·kg⁻¹·min⁻¹ produced nausea, vomiting, and/or abdominal discomfort in 25 and 65% of the subjects, respectively. Sloth et al. (39) also noted significant malaise and nausea in humans in response to IV infusion of PYY(3-36) at 0.8 pmol·kg⁻¹·min⁻¹. Differences in assessment of adverse effects may explain these contradictory results. In the studies of Le Roux et al. (28) and Sloth et al. (39), in which test meals were presented 2 h after a 90-min PYY(3-36) infusion, Sloth et al. reported the occurrence of significant malaise and nausea during and after PYY(3-36) infusion but not at meal initiation, whereas Le Roux et al. only noted the absence of adverse effects at meal initiation. In the study of Degen et al. (19), a 90-min infusion of PYY(3-36) began 60 min before the test meal, and adverse events were noted during both PYY(3-36) infusion and meal ingestion. A conditioned taste aversion paradigm is frequently used to assess whether an experimental treatment produces malaise in rodents. Our group (16) recently reported that a 2-h IV infusion of PYY(3-36) (8, 15, and 30 pmol·kg⁻¹·min⁻¹) inhibits food intake and produces a dose-dependent conditioned taste aversion in lean rats that consume flavored chow. Bolus IP injection of PYY(3-36) has also been reported to produce conditioned taste aversion in mice (26), although others have observed no conditioning of a taste aversion in rodents when using similar methods (40, 44). Together, these studies suggest that acute administration of anorexigenic doses of PYY(3-36) may produce malaise. Such evidence does not preclude the possible use of PYY(3-36) to treat obesity. Anorexigenic substances recently approved for treatment of diabetes, amylin analog pramlintide (Symlin) and GLP-1 receptor agonist exenatide (Byetta), frequently produce transient nausea at initiation of therapy, which is minimized by gradual escalation of doses (1, 2). It remains to be determined whether chronic administration of weight-reducing doses of PYY(3-36) produces transient, delayed, or sustained malaise in obese individuals.

In summary, in this study, we show that intermittent IP infusion of PYY(3-36) for 21 days produces a sustained reduction in daily caloric intake, body weight, and adiposity in diet-induced obese rats consuming palatable foods. It remains to be determined whether intermittent IP infusion of PYY(3-36) can produce a sustained decrease in daily food intake, body weight, and adiposity in obese humans without producing significant or prolonged adverse effects. Programmable pumps are presently being used in some diabetic patients to deliver insulin intermittently as needed. It remains to be determined whether a similar approach will prove useful in delivering PYY(3-36) at an optimum pattern to produce steady weight loss in obese humans.

ACKNOWLEDGMENTS

We thank Linda Kelsey and Dean Heimann for expert technical assistance. The Structural Proteomics Facility at Creighton University performed the mass spectrometry of PYY(3-36).

GRANTS

This work was supported by the Medical Research Service of the Department of Veterans Affairs, National Institutes of Health Grants DK-55830, DK-73152, and P20 RR-16469, Nebraska EPSCoR Grant EPS-034-6476, and the Canadian Institutes of Health Research.

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