

Daily, intermittent intravenous infusion of peptide YY(3-36) reduces daily food intake and adiposity in rats

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¹Department of Veterans Affairs, Nebraska Western Iowa Health Care System, Omaha; ²Biomedical Sciences Department, Creighton University, Omaha, Nebraska; ³Center for Ulcer Research and Education: Digestive Diseases Research Center, Department of Veterans Affairs, Greater Los Angeles Healthcare System, Los Angeles; and ⁴Digestive Diseases Division, David Geffen University of California at Los Angeles School of Medicine, Los Angeles, California

Submitted 15 September 2005; accepted in final form 3 October 2005

Chelikani, Prasanth K., Alvin C. Haver, Joseph R. Reeve, Jr., David A. Keire, and Roger D. Reidelberger. Daily, intermittent intravenous infusion of peptide YY(3-36) reduces daily food intake and adiposity in rats. *Am J Physiol Regul Integr Comp Physiol* 290: R298–R305, 2006. First published October 6, 2005; doi:10.1152/ajpregu.00674.2005.—The gut hormone peptide YY(3-36) [PYY(3-36)] decreases food intake when administered by intravenous infusion to lean and obese humans and rats. Whether chronic administration of PYY(3-36) produces a sustained reduction in food intake and adiposity is the subject of intense debate. Batterham et al. (R. L. Batterham, M. A. Cowley, C. J. Small, H. Herzog, M. A. Cohen, C. L. Dakin, A. M. Wren, A. E. Brynes, M. J. Low, M. A. Ghatei, R. D. Cone, and S. R. Bloom. *Nature* 418: 650–654, 2002) first reported that PYY(3-36) reduces food intake and weight gain in rats when injected into the peritoneal cavity twice daily for 7 days. Numerous laboratories have failed to confirm that daily injections of PYY(3-36) decrease body weight. Continuous subcutaneous administration of PYY(3-36) by osmotic minipump has been reported to reduce daily food intake in rodents but only during the first 3–4 days of administration. Here we show the effects of different daily patterns of intravenous infusion of PYY(3-36) on food intake, body weight, and adiposity in rats tethered via infusion swivels to computer-controlled pumps. Measurement of food bowl weight recorded by computer every 20 s permitted daily assessment of the instantaneous effects of PYY(3-36) administration on food intake and meal patterns. One-hour intravenous infusions of PYY(3-36) at 30 pmol·kg⁻¹·min⁻¹ every other hour for 10 days produced a sustained reduction in daily food intake of ~20% and decreased body weight and adiposity by 7 and 35%, respectively. Thus dosage pattern is critical for producing a sustained effect of PYY(3-36) on food intake and adiposity.

gastrointestinal; body weight; body composition

THE GASTROINTESTINAL SYSTEM plays an important sensing and signaling role in control of food intake and regulation of energy reserves (5). A growing number of peptide signals of gastric, intestinal, and pancreatic origin have been shown to inhibit short-term food intake when administered acutely to experimental animals and humans. These include cholecystokinin, amylin, glucagon-like peptide-1 (GLP-1), oxyntomodulin, peptide YY(3-36) [PYY(3-36)], pancreatic polypeptide, gastrin-releasing peptides (GRPs) GRP-27 and GRP-10, enterostatin, and apolipoprotein A-IV (38). The therapeutic potential of

these peptides and their analogs for treatment of obesity remains to be determined.

An important early step in the development of obesity drugs is determining whether chronic administration of anorexigenic substances can produce a sustained decrease in daily food intake and adiposity in experimental animals. Methods of administration typically include either daily injections (subcutaneous, intraperitoneal, intramuscular) or insertion of an osmotic minipump beneath the skin or into the peritoneal cavity to deliver peptides continuously for a week or more. Results from such studies are often inconclusive. Reasons include development of a compensatory increase in food intake between injections and tolerance to continuous or frequent administration of the anorexigenic substances (19, 34).

We have developed an experimental model that permits precise control of intravenous (IV) administration of anorexigenic peptides to rats tethered via infusion swivels to computer-controlled pumps. Rats are free to move within their individual cages and have free access to food and water. Indwelling jugular vein catheters are generally functional for several 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 and meal patterns. Adjustments in dosing pattern can be performed daily to minimize compensatory hyperphagia between doses and tolerance.

Using this technology, we recently demonstrated that IV infusion of PYY(3-36) dose dependently inhibits food intake in rats (10). This finding helped resolve the debate on whether exogenous PYY(3-36) inhibits food intake (7, 22, 39). Here we report the effects of different daily patterns of IV infusion of PYY(3-36) on food intake, body weight, and adiposity in rats with free access to food.

MATERIALS AND METHODS

Animals

Male Sprague-Dawley rats (310–530 g, Charles River, Kingston, NY) were surgically implanted with a jugular vein catheter and adapted to experimental procedures as described previously (40). The Animal Studies Subcommittee of the Omaha Veterans Affairs Medical Center approved the experimental protocol.

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Experiments

Effects of two 3-h IV infusions of PYY(3-36) per day on food intake and weight gain in rats. For each of the animals used in this experiment, the jugular vein catheter was 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 an infusion swivel (Instech Laboratories, Plymouth Meeting, PA). Rats had free access to ground chow that was provided each day at 1400 h, 3 h before onset of the dark period. During an initial 3-day baseline period, all animals ($n = 30$) received two 3-h IV infusions of vehicle (0.15 M NaCl, 0.1% BSA) during hours 0–3 and 6–9 of the dark period. Food intake and meal pattern (meal sizes and number of meals) were determined from continuous computer recording of changes in food bowl weight (40). At the end of the baseline period, animals were randomly divided into two groups of 15 rats each, matched for daily food intake and body weight, to

receive, during the next 8 days, IV infusions of either vehicle or PYY(3-36) during the two 3-h periods. PYY(3-36) was administered at $10 \text{ pmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ on day 1, and at $30 \text{ pmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ on days 2–8. Rat PYY(3-36) was synthesized by solid-phase methodology using the 9-fluorenylmethoxycarbonyl protection strategy and purified by reverse phase HPLC as described elsewhere (9). The $10 \text{ pmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ dose of PYY(3-36) was initially chosen because it is slightly lower than the mean effective dose of PYY(3-36) for suppression of feeding in rats when administered IV during the first 3 h of the dark period (10). Infusions were administered by pumps (model PHD2000; Harvard Apparatus, South Natick, MA) turned on and off at scheduled intervals by a computer program. Body weights were measured every 2–3 days. At the end of the experiment, the patency of jugular vein catheters was determined by IV injection of 0.2 ml of the short-acting anesthesia Propofol (Abbott Laboratories, North Chicago, IL), and the weight of each rat was

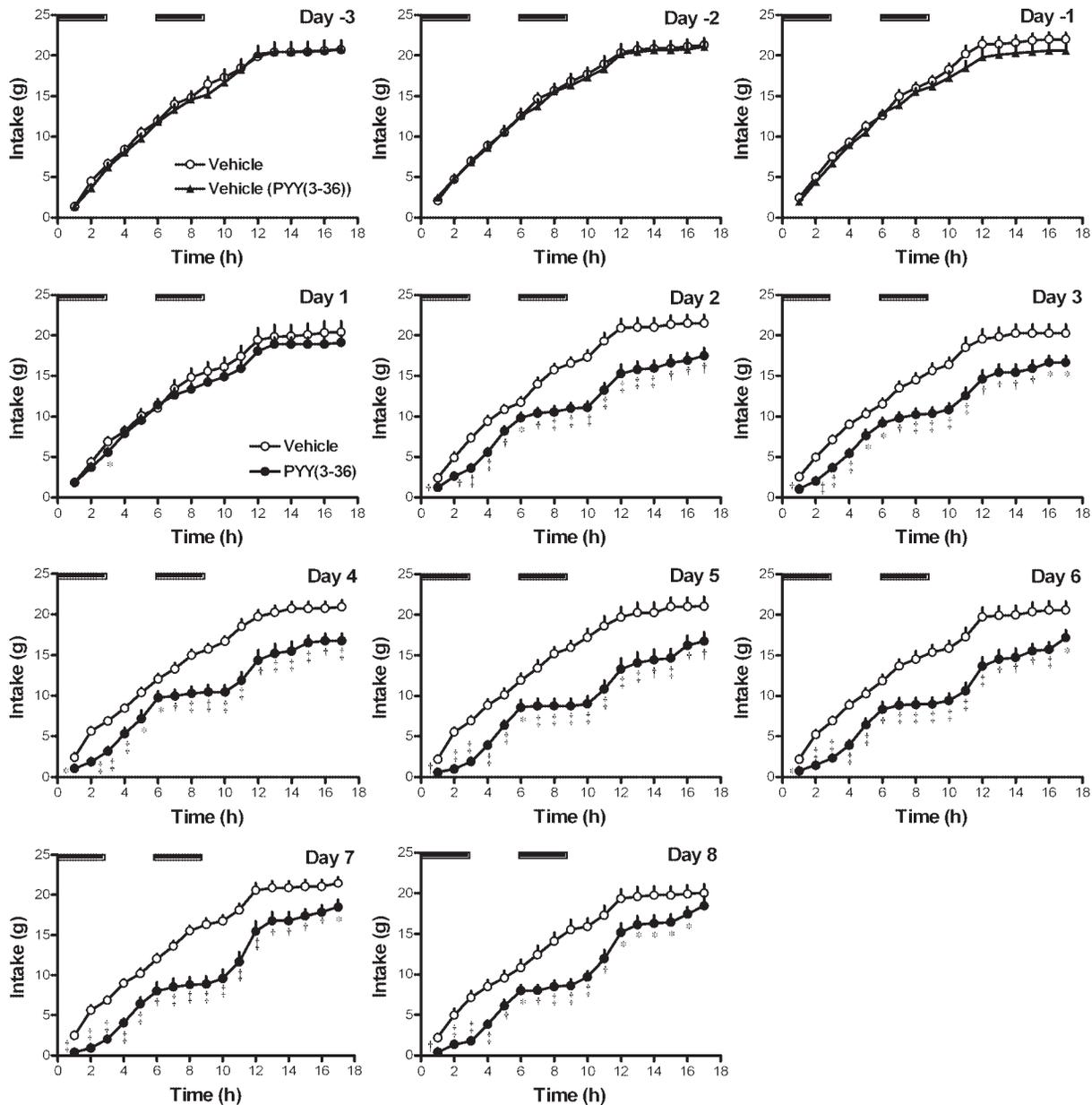


Fig. 1. Effects of twice-daily 3-h intravenous (IV) infusions of peptide YY(3-36) [PYY(3-36)] for 8 days on daily cumulative food intake. Rats ($n = 29$) received vehicle infusions during a 3-day baseline period (days –3 to –1) and then either infusions of vehicle ($n = 15$) or PYY(3-36) ($n = 14$) at $10 \text{ pmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ on day 1 and $30 \text{ pmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ on days 2–8. Bars indicate periods of infusion. Time 0 is the start of the dark period. Values are means \pm SE. $^{\dagger}P < 0.05$, $^{\ddagger}P < 0.01$, $^{\ast}P < 0.001$ compared with vehicle-treated group.

recorded. 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. At the end of this experiment, PYY(3-36) was administered for two additional days to the same rats to determine the effects of PYY(3-36) infusion every other hour at $30 \text{ pmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (day 9) and $10 \text{ pmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (day 10) on food intake.

Effects of 1-h IV infusions of PYY(3-36) every other hour on food intake, body weight, and body composition in rats. A new set of animals was surgically prepared and adapted as described for the first study. During a 7-day baseline period, all animals ($n = 30$) received 1-h IV infusions of vehicle every other hour beginning at 1200 h and

ending at 0900 h the following day (dark period: 2100–0900 h). Animals did not have access to food from 0900–1100 h during which routine maintenance and experimental setup were performed. At the end of the baseline period, animals were randomly divided into two groups of 15 rats each, matched for daily food intake and body weight gain during the baseline period, to receive during the next 10 days, 1-h IV infusions every other hour of either vehicle or PYY(3-36) at $30 \text{ pmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Peptide administration and data acquisition and analysis were as described for the first study.

Determination of PYY(3-36) stability in infusates. Samples of PYY(3-36) infusates collected from infusion lines at the end of a 24-h period were analyzed by reverse-phase HPLC to determine whether

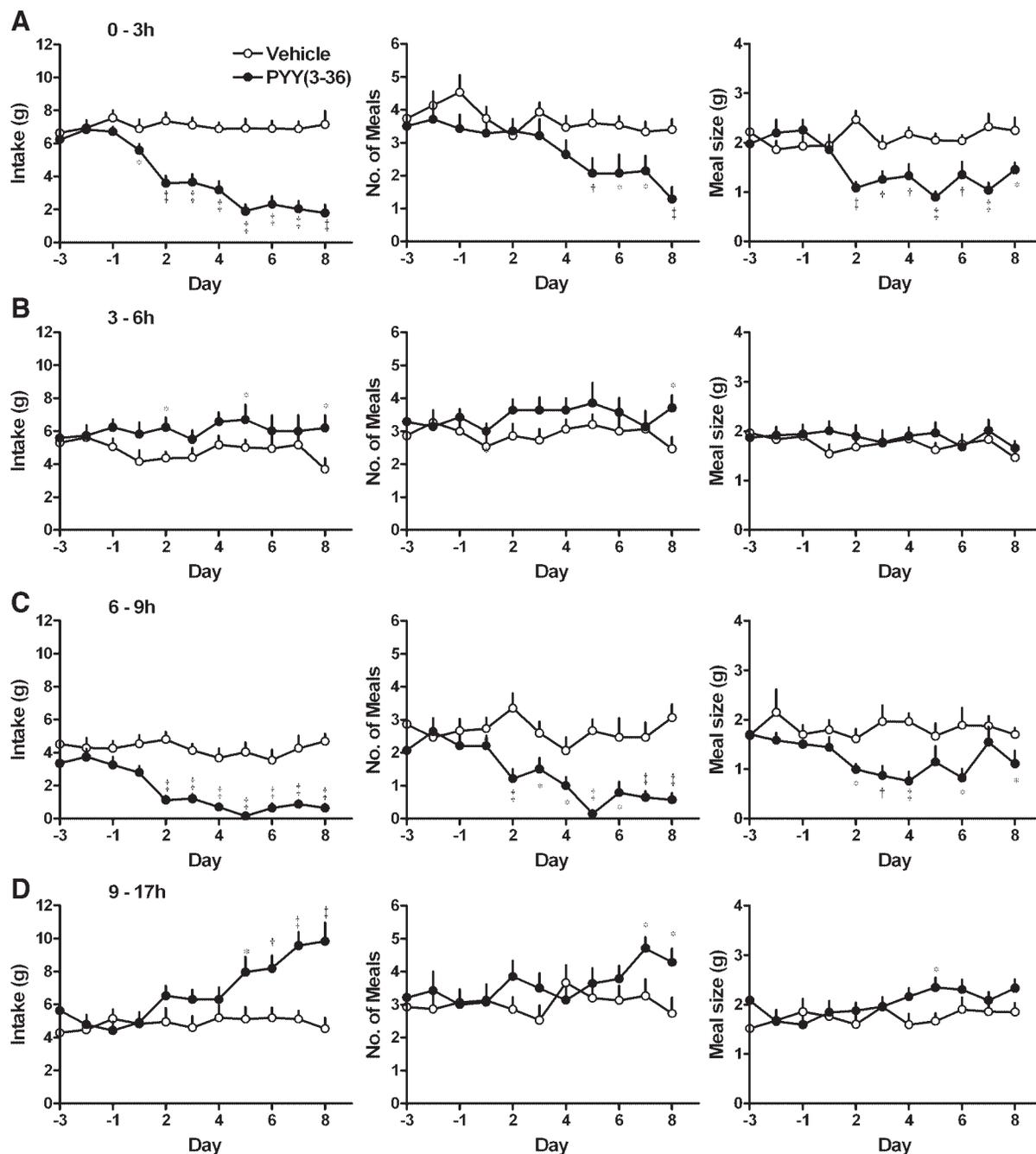


Fig. 2. Effects of twice daily 3-h IV infusions of PYY(3-36) for 8 days on food intake, number of meals, and mean meal size each day during infusion periods (A and C) and noninfusion periods (B and D). Data are from the experiment described in Fig. 1. Values are means \pm SE. * $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$ compared with vehicle-treated group.

peptide degradation and loss occurred. Stock solution of PYY(3-36) was made by dissolving peptide in 0.1% acetic acid at a concentration of ~ 150 nmol/ml, and its precise concentration was determined by measuring its absorbance at 280 nm. The stock solution was diluted with 0.1% acetic acid containing 0.2% BSA to make a working stock solution of 50 nmol/ml; aliquots of 50 μ l were stored at -80°C . On the day of chromatography, aliquots were diluted with 0.1% acetic acid containing 0.2% BSA so 1-ml samples contained 1, 2, 3, and 5 nmol of PYY(3-36) standards. For construction of the standard curve of PYY(3-36) absorbance, standard samples (1 ml) were injected onto an analytical reverse-phase HPLC column (Vydac 218TP54, 5 μm , 4.6×250 mm) and then eluted with a linear gradient of acetonitrile containing 0.1% trifluoroacetate. The gradient was 0–30% acetonitrile over 5 min followed by the elution step of 30–42.5% acetonitrile over 60 min. Four samples each of 1, 2, 3, and 5 nmol of PYY(3-36) were run, and the integrated area at 280 nm was determined by Gilson Unipoint integration software. The integrated area of the standards was used to construct a standard curve. PYY(3-36) infusate samples were chromatographed in the same manner as the PYY(3-36) standards except for loading volume (7.3 ml for the infusate samples). Infusate concentrations were determined by comparing the integrated area of the peak in the position of PYY(3-36) to the standard curve.

Body Composition Analysis

At the end of the second study, the patency of jugular vein catheters was tested by injecting 0.2 ml of Propofol into the catheters; only data from animals that lost consciousness immediately were included for analysis. The abdomen of each animal was quickly opened, the gastrointestinal tract was removed from distal esophagus to rectum, gastrointestinal contents were removed by flushing with water, the weight of the carcass including the empty gastrointestinal tract was recorded, and the carcass was stored in an air-tight bag at -20°C until further analysis. Carcass composition (total water, fats, proteins, and minerals) was determined according to AOAC methods of analysis for meat and meat products (3).

Statistical Analyses

Values are presented as group means \pm SE. Data from the two studies comparing the effects of intermittent infusions of PYY(3-36) and vehicle on food intake, mean meal size, number of meals and body composition (weights of carcass, gut contents, water, fats, proteins, and minerals) were analyzed separately using either repeated-measures ANOVA or Student's *t*-test. Following 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 Two 3-h IV Infusions of PYY(3-36) Per Day on Food Intake and Weight Gain in Rats

During the 3-day baseline period, IV infusions of vehicle produced no significant differences in food intake or meal patterns between the two groups (Figs. 1 and 2). On *day 1* of the treatment period, PYY(3-36) infusion at $10 \text{ pmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ during *hours 0–3* and *6–9* of the dark period reduced food intake only during the first 3-h interval of infusion. On *days 2–8* of the treatment period, PYY(3-36) infusion at $30 \text{ pmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ during the same intervals reduced food intake during the first 3-h period by 51, 49, 54, 73, 66, 70, and 75%, respectively, and the second 3-h period by 77, 71, 81, 96, 82, 80, and 86%, respectively (Fig. 2, A and C). Reductions in food intake during the first 3-h period occurred through a decrease in meal size during *days 2–4*

and a decrease in meal size and meal frequency during *days 5–8* (Fig. 2A). Reductions in food intake during the second 3-h period each day occurred through both a reduction in meal size and meal frequency (Fig. 2C). Our analysis of PYY(3-36) stability in infusates showed that no loss or degradation of PYY(3-36) occurred in samples taken from infusion lines at the end of a 24-h infusion period (4.3 ± 1.0 vs. 4.3 ± 0.8 nmol/ml in infusate samples immediately frozen after preparation). Thus the anorexic response to PYY(3-36) at $30 \text{ pmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ was sustained within and across infusion intervals with no apparent loss of sensitivity to the peptide. However, rats developed a compensatory increase in food intake between PYY(3-36) infusions (Fig. 2, B and D). Nevertheless, PYY(3-36) slightly reduced body weight gain across the 7-day period of PYY(3-36) infusion at $30 \text{ pmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (0.2 ± 1.6 vs. 5.0 ± 2.0 g in vehicle-treated rats, $P < 0.05$).

To assess whether increasing the frequency of PYY(3-36) infusion would reduce this hyperphagia between infusions, on *day 9* PYY(3-36) was administered every other hour at $30 \text{ pmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, whereas control rats received vehicle infusions during the same intervals. PYY(3-36) reduced total food intake that day by 28% (18.0 ± 1.0 vs. 25.1 ± 0.8 g in vehicle-treated rats, $P < 0.001$; Fig. 3A). On *day 10*, PYY(3-36) was administered every other hour at a lower $10 \text{ pmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$

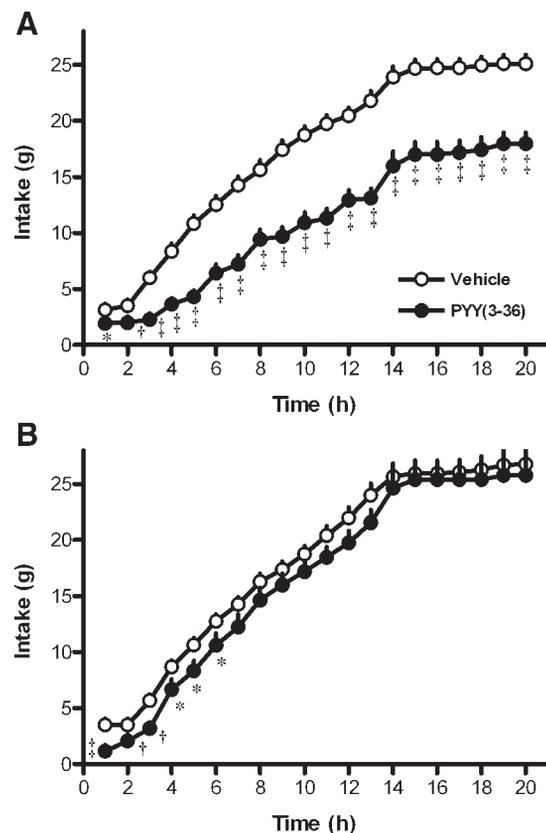


Fig. 3. Effects of 1-h IV infusions of PYY(3-36) every other hour on daily cumulative food intake on two consecutive days (A and B). One group of rats ($n = 15$) received vehicle infusions each day, and the other group of rats ($n = 14$) received PYY(3-36) infusions at $30 \text{ pmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ on the first day and $10 \text{ pmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ on the second day. Infusions began at *time 0*, which was the start of the dark period. Values are means \pm SE. * $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$ compared with vehicle-treated group.

$\text{kg}^{-1} \cdot \text{min}^{-1}$ dose, and only a transient reduction in food intake occurred (Fig. 3B).

Effects of 1-h IV Infusions of PYY(3-36) Every Other Hour on Food Intake, Body Weight, and Body Composition in Rats

During the 7-day baseline period, body weights in the two groups that were to eventually receive either infusions of vehicle or PYY(3-36) were 395 ± 6 and 397 ± 12 g at the start of the period and 405 ± 7 and 404 ± 13 g at the end of the period, respectively. During the 7-day baseline period, 1-h IV infusions of vehicle every other hour produced no significant differences in food intake or meal patterns between the two groups (Fig. 4). During the subsequent 10-day treatment period, 1-h IV infusions of PYY(3-36) at $30 \text{ pmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ significantly reduced food intake on successive days by 31, 20, 24, 21, 25, 17, 19, 16, 15 and 23%, respectively, compared with the vehicle-treated group (Figs. 4 and 5). A gradual reduction in cumulative food intake occurred throughout the light and dark periods each day, primarily through reductions in meal sizes (Fig. 4). Thus the anorexic response to PYY(3-36) was sustained within and across experimental days with no

apparent loss of sensitivity. Importantly, PYY(3-36) also reduced body weight gain across the 10-day period (-1.9 ± 3.1 vs. 12.9 ± 1.9 g in the vehicle-treated group, $P < 0.001$), and reduced carcass content of total fats, proteins, and water at the end of the 10-day period by 35, 6, and 6%, respectively (Table 1). The 15-g reduction in weight gain became a 27-g difference when body weights minus gut contents were compared, because gut contents were 55% larger in the PYY(3-36)-treated rats (Table 1).

DISCUSSION

Results of these experiments indicate that intermittent IV infusions of PYY(3-36) can produce a sustained decrease in daily food intake, body weight gain, and adiposity in rats, but only when intervals between PYY(3-36) infusions are shortened sufficiently to minimize compensatory hyperphagia between infusions. Anorexic responses to intermittent infusions of PYY(3-36) exhibit a rapid onset, little if any desensitization within and across infusions, and a rapid cessation when each infusion ends. PYY(3-36) has also been reported to exhibit a short functional life when administered by subcutaneous or intraperitoneal injection to mice (36). This likely explains why many laboratories have failed to

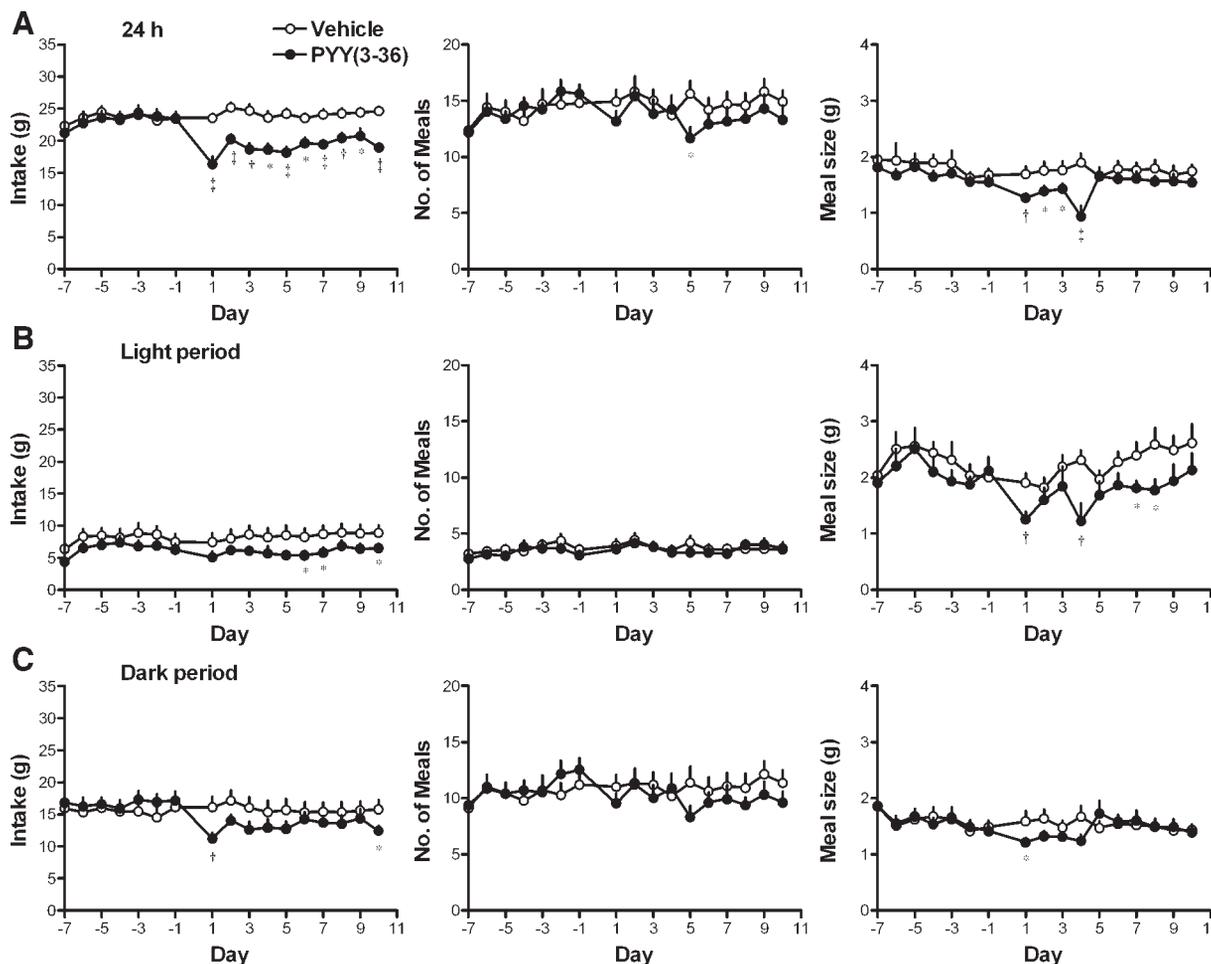


Fig. 4. Effects of 1-h IV infusions of PYY(3-36) every other hour for 10 days on food intake, number of meals, and mean meal size each day during the entire day (A), the light period (B), and the dark period (C). During a 7-day baseline period (days -7 to -1) rats ($n = 27$) received vehicle infusions. During the next 10 days, rats received either infusions of vehicle ($n = 14$) or PYY(3-36) at $30 \text{ pmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ($n = 13$). Values are means \pm SE. * $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$ compared with vehicle-treated group.

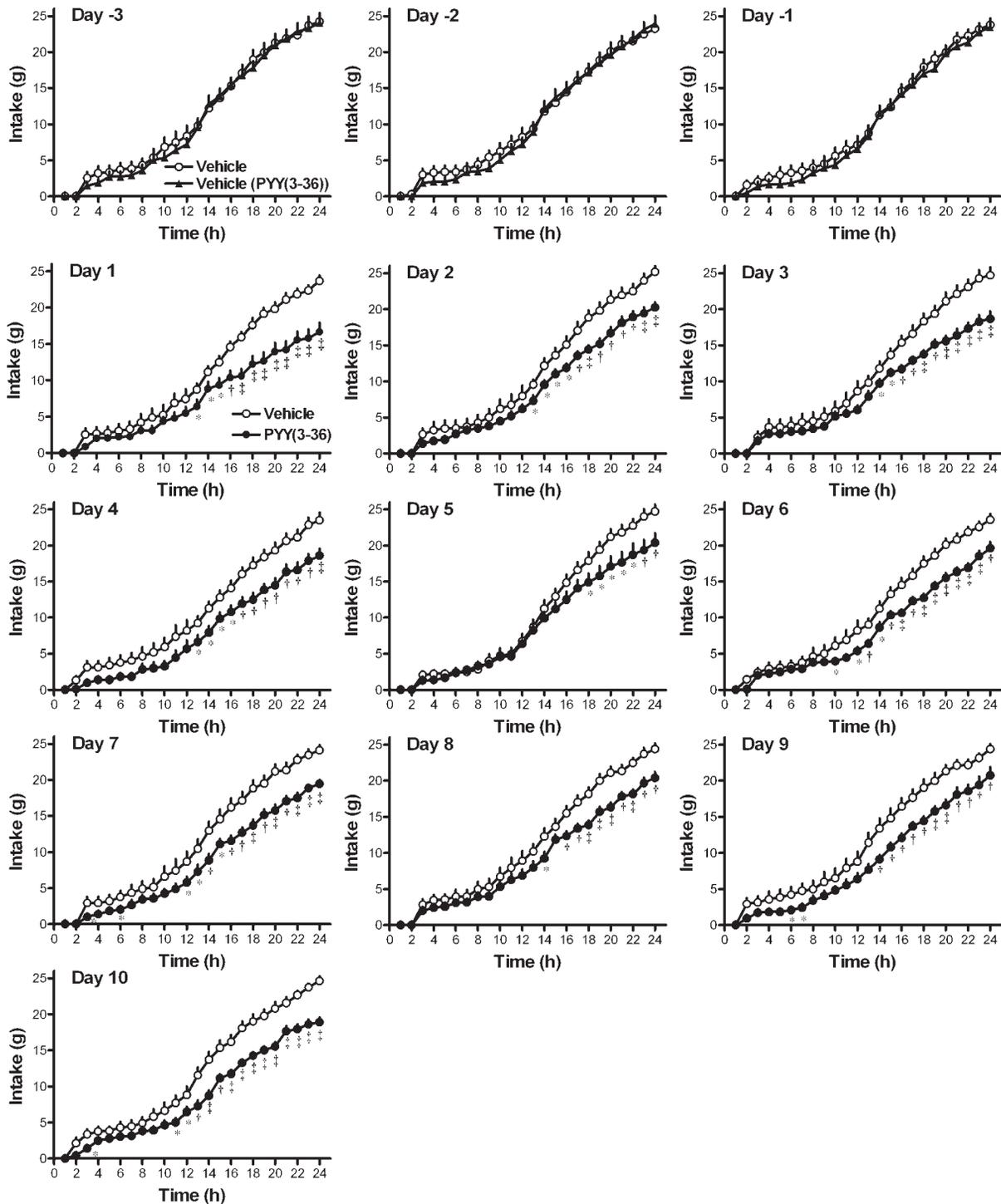


Fig. 5. Effects of 1-h IV infusions of PYY(3-36) every other hour for 10 days on daily cumulative food intake. Data are from the experiment described in Fig. 4. Values are means \pm SE. Time 0 is the start of the light period. * $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$ compared with vehicle-treated group.

demonstrate that one or two systemic injections of PYY(3-36) per day can reduce daily food intake and body weight gain in rodents (39) and monkeys (29).

We previously determined that a single 3-h infusion of PYY(3-36) at dark onset in our rat model dose dependently inhibited short-term food intake with a minimal effective dose and potency (mean effective dose) of 5 and 15 pmol·

$\text{kg}^{-1}\cdot\text{min}^{-1}$, respectively (10). Here we show that two 3-h infusions of PYY(3-36) at 10 pmol· $\text{kg}^{-1}\cdot\text{min}^{-1}$ during hours 0–3 and 6–9 of the dark period reduced food intake only during the first period of infusion. In contrast, two 3-h infusions of PYY(3-36) at 30 pmol· $\text{kg}^{-1}\cdot\text{min}^{-1}$ during the same periods produced significant reductions in food intake during both intervals of infusion each day of administration. The

Table 1. Effect of 1-h intravenous infusions of PYY(3-36) every other hour for 10 days on body weight and composition

	Body Weight, g			Body Composition, g				
	Day 1	Day 10	Gain	Gut Contents	Water	Proteins	Fats	Minerals
Vehicle	405±7	418±7	12.9±1.9	20.4±2.2	272±5	84.3±1.7	19.1±1.3	15.7±0.4
PYY(3-36)	404±13	402±11	-1.9±3.1†	31.7±2.0†	257±7*	79.2±2.5*	12.4±1.3†	15.6±0.6

Values are means ± SE. Peptide YY(3-36) [PYY(3-36)]. Rats ($n = 27$) received 1-h vehicle infusions every other hour for 7 days and then either vehicle ($n = 14$) or 30 pmol·kg⁻¹·min⁻¹ of PYY(3-36) ($n = 13$) at the same intervals for 10 days. * $P < 0.05$, † $P < 0.001$ compared with vehicle.

reasons for this difference in sensitivity to sequential administration of the two doses are not clear.

We previously determined that a single 3-h infusion of PYY(3-36) at dark onset in our rat model dose dependently reduced food intake primarily by decreasing meal size (10). Here we show that two 3-h infusions of PYY(3-36) for 8 days reduced meal frequency as well as meal size during infusion periods on most days. Infusion of PYY(3-36) every other hour produced a more gradual reduction in food intake each day, due primarily to decreases in meal size. Together, these results suggest that PYY(3-36) acts to both reduce meal size and increase the duration of postprandial satiation produced by meals, since PYY(3-36) reduced meal sizes without decreasing intermeal intervals (increasing meal frequency).

Our finding that chronic PYY(3-36) administration increased gut contents is consistent with prior studies (9, 24, 29, 35) demonstrating that acute systemic administration of PYY(3-36) and/or PYY slows gastric emptying and intestinal transit. Factors that promote gastric distention by inhibiting gastric emptying can reduce food intake by decreasing meal size (28, 32, 33). Thus PYY(3-36) may reduce meal size in part by slowing gastric emptying. Whether PYY(3-36) prolongs the intermeal interval by slowing intestinal transit remains to be determined.

Continuous subcutaneous administration of PYY(3-36) by osmotic minipump has been reported to produce a transient 3- to 4-day reduction in daily food intake in normal and obese mice and rats (31, 39). Continuous administration of other anorexigenic peptides (cholecystokinin, amylin, GLP-1) by osmotic minipump has also been reported to produce either no effect or a transient reduction in daily food intake in rodents (2, 4, 11, 12, 25). One possible explanation for these transient responses is that early peptide-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 (2, 17). Another possibility is that continuous administration of these anorexigenic peptides causes receptor downregulation and tolerance. PYY(3-36), cholecystokinin, amylin, and GLP-1 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 (6, 14, 19, 26, 37). This likely explains why intermittent IV infusions of PYY(3-36) in our experimental model produced a sustained reduction in daily food intake, whereas continuous subcutaneous infusion of PYY(3-36) produces only a transient suppression of feeding (31, 39).

Whether endogenous PYY(3-36) plays a role in satiation and regulation of adiposity remains to be determined. A likely mechanism is an endocrine one involving a meal-induced

secretion of PYY(3-36) from the distal intestine, which then acts as a hormonal signal to the brain to produce satiety and reduce adiposity. Batterham et al. (7) reported that intraperitoneal injection of an anorexic dose of PYY(3-36) increases plasma immunoreactive PYY in rats to a level similar to that produced by food intake in rats. However, PYY(3-36) administered intraperitoneally could act locally to affect feeding before being absorbed into the circulation, which would preclude the establishment of a meaningful correlation between the feeding response to PYY(3-36) and an increase in plasma PYY(3-36). In the same paper, Batterham et al. (7) provided evidence that IV infusion of PYY(3-36) inhibits food intake in humans when administered at a dose that increases plasma immunoreactive PYY to a level within the normal postprandial range previously reported for humans. However, PYY(3-36) accounts for only about 50% of total PYY immunoreactivity in postprandial human blood (20). The other major molecular form appears to be PYY(1-36) (20, 21), which is an order of magnitude less potent than PYY(3-36) in reducing food intake (10). Thus it remains to be determined whether PYY(3-36) acts as a blood-borne signal to decrease food intake in humans or rats. Target tissues also have not been defined. Recent studies (1, 23) suggest that PYY(3-36) may act, in part, through control of vagal signaling to the brain. On the other hand, high-affinity PYY(3-36) binding sites are located throughout the brain in regions with and without a blood-brain barrier (13, 18). It is not clear whether the source of endogenous ligand for these receptors is in the brain or periphery. Systemically administered PYY(3-36) readily penetrates the blood-brain barrier (30). On the other hand, PYY-like immunoreactivity has been detected in various brain regions linked to control of food intake including hypothalamus and brain stem (8, 15, 16, 27). Thus it remains to be determined whether PYY(3-36) acts in the periphery and/or brain to reduce food intake and body adiposity, whether the PYY(3-36) source for these actions is in gut and/or brain, and whether gut PYY(3-36) acts in part through endocrine and/or paracrine control of vagal signaling to the brain.

ACKNOWLEDGMENTS

We thank L. Kelsey, D. Heimann, R. Diedrickson, Peter Chew, and Brian Wiggins for their expert technical assistance. The Structural Proteomics Facility at Creighton University performed the mass spectrometry of PYY(3-36).

GRANTS

This study was supported by the Medical Research Service of the Department of Veterans Affairs and the National Institutes of Health Grants DK-55830, DK-56805, RR-16469, and DK-41301.

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