$PYY_{3–36}$ and Oxyntomodulin Can Be Additive in Their Effect on Food Intake in Overweight and Obese Humans

Benjamin C.T. Field,[1] Alison M. Wren,[1,2] Veronique Peters,[1] Kevin C.R. Baynes,[1,3] Niamh M. Martin,[1] Michael Patterson,[1] Sara Alsaraf,[1] Vian Amber,[1] Katie Wynne,[1] Mohammad A. Ghatei,[1] and Stephen R. Bloom[1]

OBJECTIVE—Peptide $YY_{3–36}$ ($PYY_{3–36}$), a Y2 receptor agonist, and oxyntomodulin, a glucagon-like peptide 1 (GLP-1) receptor agonist, are cosecreted by intestinal L-cells after each meal. Separately each hormone acts as an endogenous satiety signal and reduces appetite in humans when infused intravenously. The aim of the current study was to investigate whether the anorectic effects of $PYY_{3–36}$ and oxyntomodulin can be additive.

RESEARCH DESIGN AND METHODS—Twelve overweight or obese human volunteers underwent a randomized, double-blinded, placebo-controlled study. An ad libitum test meal was used to measure energy intake during intravenous infusions of either $PYY_{3–36}$ or oxyntomodulin or combined $PYY_{3–36}$/oxyntomodulin.

RESULTS—Energy intake during coadministration of $PYY_{3–36}$ and oxyntomodulin was reduced by 42.7% in comparison with the saline control and was significantly lower than that during infusions of either hormone alone.

CONCLUSIONS—The anorectic effects of $PYY_{3–36}$ and oxyntomodulin can be additive in overweight and obese humans. Coadministration of Y2 receptor agonists and GLP-1 receptor agonists may be a useful treatment strategy for obesity.
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Obesity is a major risk factor for the development of type 2 diabetes and its prevalence is increasing rapidly throughout the world (1,2). Weight loss reduces that risk substantially (3) but is difficult to achieve and sustain. Bariatric surgery is the only obesity treatment proven to reduce mortality (4,5). Furthermore, the rapid improvement in glucose homeostasis after Roux-en-Y gastric bypass surgery (6,7) has led some to question whether type 2 diabetes, as well as obesity, should be considered a surgically curable disease (8,9). However, operative mortality and delayed complications are not uncommon (10,11). There is therefore a pressing need to develop safe, effective, nonsurgical treatments for obesity.

The main proposed mechanism by which Roux-en-Y gastric bypass causes weight loss is through altering the secretion of gut hormones (12). Two important such hormones, peptide $YY_{3–36}$ ($PYY_{3–36}$) and oxyntomodulin, are physiologically cosecreted after meals (13,14). Postprandial concentrations of both $PYY_{3–36}$ and oxyntomodulin are increased by Roux-en-Y gastric bypass (12,15–17). Intravenous infusion of each hormone individually has been shown to reduce appetite in humans (18–20). Furthermore, oxyntomodulin causes weight loss in obese human volunteers when administered by repeated subcutaneous injection (21). However, one proposed physiologic function of these hormones at higher concentrations is nausea (22). Thus, if significant appetite reduction is attempted by giving a large dose of a single hormone, nausea or even vomiting may result (20–23). We hypothesized that coadministered $PYY_{3–36}$ and oxyntomodulin would mimic the natural postprandial situation and have additive effects on appetite, but that neither hormone would reach concentrations associated with nausea.

RESEARCH DESIGN AND METHODS

Healthy male and female volunteers aged ≥18 years with a stable BMI of 25–40 kg/m^2 were recruited by advertisement. Potential participants were screened and determined to be healthy by medical history, physical examination, routine blood tests, and 12-lead electrocardiogram. The SCOFF questionnaire (24), the Dutch Eating Behavior Questionnaire (25), and a 3-day diet diary were used to exclude those with disordered eating or a high level of restrained eating. Palatability of the study meal was assessed using a 9-point hedonic scale. It was calculated that, for 90% power to detect a difference in energy intake of 10% between treatments, 12 participants would be required, assuming a within-subject SD of 6% and a significance level of 0.05. Thus, 12 volunteers were selected for the study (Table 1). Women of child-bearing age were advised to avoid pregnancy during the study and underwent urine tests to exclude pregnancy before each infusion.

The study was approved by the Hammersmith and Queen Charlotte's and Chelsea Research Ethics Committee (reference number 06/Q0406/50). All participants gave written informed consent, and the study was planned and performed in accordance with the Declaration of Helsinki.

The study followed a randomized, double-blind, placebo-controlled crossover protocol comparing the effect on energy intake of six different pairs of infusions, as shown in Table 2. Each subject received two 110-min intravenous infusions, A and B, simultaneously, at each visit. Infusion A consisted of either $PYY_{3–36}$ or saline control. Infusion B consisted of either oxyntomodulin or saline control. Infusion doses were based on previously established doses, with a twofold difference between high and low doses for each peptide. The infusion rate for high-dose $PYY_{3–36}$ was based on previous work by Batterham et al. (26). The infusion rate for high-dose oxyntomodulin was similar to that used by Cohen et al. (19). The duration of infusion was chosen to allow steady state to be reached and sustained during test meals. Peptides were synthesized by Bachem U.K. and were sterile on culture and negative for pyrogen, as previously described (26). The amino acid content of representative peptide vials was measured independently (Alta Bioscience, Edgbaston, Birmingham, U.K.). Control vials were prepared with sterile saline and were indistinguishable visually from those containing peptide. To reduce adsorption of peptide onto the walls of syringes and infusion lines, the contents of randomized vials were dissolved in Gelofusine (B. Braun Medical, Sheffield, U.K.).

Study visits were scheduled a minimum of 3 days apart. Subjects were asked to standardize their diet, abstain from alcohol, and avoid strenuous

From the [1]Department of Investigative Medicine, Imperial College London, U.K.; the [2]Department of Diabetes and Endocrinology, Chelsea and Westminster Hospital, London, U.K.; and the [3]Department of Diabetes and Endocrinology, Ealing Hospital, London, U.K.
Corresponding author: Stephen R. Bloom, s.bloom@imperial.ac.uk.
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B.C.T.F. and A.M.W. contributed equally to this study.

TABLE 1
Baseline characteristics of participants

Age (years)	33.74 ± 2.32
Sex: female/male	7/5
Height (m)	1.67 ± 0.03
Weight (kg)	86.13 ± 3.48
BMI (kg/m^2)	30.94 ± 1.03
Fasting insulin (pmol/l)	57.4 ± 0.86
Fasting plasma glucose (mmol/l)	4.96 ± 0.05
Fasting $PYY_{3–36}$ (pmol/l)	21.6 ± 0.98
Fasting OLI (pmol/l)	85.1 ± 5.94

Data are means ± SE or *n*.

exercise for 24 h before each visit. Food diaries were used to monitor dietary compliance. Subjects fasted and drank only water from 9:00 P.M. on the night before each visit. After arrival at 9:00 A.M., peripheral venous cannulae were inserted in both of the patient's forearms, one for infusions and one for blood sampling. A three-way tap with low internal volume (Becton Dickinson, Franklin Lakes, NJ) was attached to the infusion cannula to allow connection of two separate infusion lines. Subjects then relaxed for 30 min before the start of the infusions. All time cues were removed from the study room, and subjects were encouraged to relax by reading or watching films on DVD.

Blood samples were collected at −30, 0, 30, 60, 75, 90, 120, and 135 min into lithium-heparin–coated tubes containing 2,000 kallikrein inhibitor units (0.2 ml) aprotinin (Bayer Schering Pharma, Berlin, Germany). Samples were stored on ice until centrifugation at 4°C, after which plasma was separated immediately and stored at −20°C until analysis. Immediately before each blood sample was taken, subjects completed visual analog scales (VAS) rating hunger, satiety, prospective food consumption, and nausea (27). Pulse and blood pressure were measured every 30 min and at the end of each study visit.

Ninety minutes after the start of the infusions, subjects were offered a meal that was provided in excess and were asked to eat until they were comfortably full. Water was freely available. Both food and water were weighed pre- and postprandially, and energy intake was calculated. The test meal procedure was identical to that used in previous studies with $PYY_{3–36}$ and oxyntomodulin (18,19,26). At the end of the meal, the infusions were discontinued, and the subjects were asked to rate the palatability of the food using VAS.

Hormone assays. Plasma $PYY_{3–36}$ and oxyntomodulin-like immunoreactivity (OLI) concentrations were measured using established in-house radioimmunoassays. The PYY assay (28,29) could detect changes of 4.4 pmol/l (95% confidence limit) with an intra-assay variation of 11.5%. The OLI assay (14) could detect changes of 10 pmol/l (95% confidence limit) with an intra-assay variation of 5.7%. Because the radioimmunoassay technique is comparative and not absolute, all samples were assayed in duplicate and within a single assay to eliminate interassay variation. Plasma insulin and glucose concentrations at 0, 60, and 90 min were measured on an Olympus analyzer in the Department of Clinical Biochemistry, Hammersmith Hospital.

Statistical analysis. Combined data are represented as means ± SEM. Comparisons of energy intake were by repeated-measures ANOVA with a Tukey multiple comparison posttest. Effects on changes in energy intake of subjects' BMI and sex were analyzed by linear regression and repeated-measures two-way ANOVA, respectively. VAS scores were adjusted for baseline, and differences were compared by a repeated-measures nonparametric Friedman test with a Dunn multiple comparison posttest. Comparisons at each time point of plasma insulin and glucose levels and of cardiovascular parameters were made by one-way ANOVA with a Tukey multiple comparison posttest. Analyses were performed using Prism (version 4.03; GraphPad Software, San Diego, CA).

TABLE 2
Summary of infusions

Infusion pair designation	Infusion A	Infusion B
Saline	Saline	Saline
Low-dose $PYY_{3–36}$	0.25 pmol/kg/min $PYY_{3–36}$	Saline
Low-dose OXM	Saline	1.5 pmol/kg/min OXM
High-dose $PYY_{3–36}$	0.5 pmol/kg/min $PYY_{3–36}$	Saline
High-dose OXM	Saline	3.0 pmol/kg/min OXM
$PYY_{3–36}$ + OXM	0.25 pmol/kg/min $PYY_{3–36}$	1.5 pmol/kg/min OXM

OXM, oxyntomodulin.

RESULTS

Adverse effects. On one visit each, the first three participants experienced severe nausea and sweating. As a result, the randomization code on this single occasion was examined by an independent medical colleague appointed for the purpose before the study and not directly connected with the investigation. It was identified that each case of nausea had occurred during high-dose $PYY_{3–36}$ infusion, with symptoms commencing ~50 min after the start of the infusion. In each case, symptoms settled within 30 min of stopping the infusions, and the participants were able to leave the investigation ward as normal after the last blood sample. Mean peak plasma $PYY_{3–36}$ concentration achieved during these infusions was 156.5 ± 56.9 pmol/l ($n = 3$). It was not felt possible thereafter to continue the high-dose $PYY_{3–36}$ infusion arm, and the study then proceeded as a five-way crossover, maintaining the randomized, double-blind, placebo-controlled design. During the remainder of the study, four participants reported nausea, requiring early termination of their infusions, at one visit each. However, because the nausea was not associated with vomiting, the randomization code was not examined again until the end of the study.

Effect of $PYY_{3–36}$ and oxyntomodulin infusions on energy intake and appetite. In comparison with saline control infusion, energy intake during combined $PYY_{3–36}$ + oxyntomodulin infusion was reduced by 42.7% at the study meal ($P < 0.001$) and was also significantly lower than during infusions of either hormone alone (mean energy intake at buffet meal: 557 ± 88.9 kcal [saline], 511 ± 85.2 kcal [low-dose $PYY_{3–36}$], 480 ± 80.0 kcal [low-dose oxyntomodulin], 486 ± 86.2 kcal [high-dose oxyntomodulin], and 319 ± 61.9 kcal [combined $PYY_{3–36}$ + oxyntomodulin]; $P < 0.001$ vs. saline, $P < 0.01$ vs. low-dose $PYY_{3–36}$, and $P < 0.05$ vs. low-dose oxyntomodulin and high-dose oxyntomodulin; $n = 12$) (Fig. 1). There was no evidence that change in energy intake varied with either BMI or sex of the subjects.

Neither the palatability of the buffet meal nor other satiety-related VAS responses were altered significantly by any infusion except high-dose $PYY_{3–36}$. In particular, there were no significant differences in nausea scores between the five completed arms of the study at any time point (Fig. 2). However, four participants did report mild nausea, one during a high-dose oxyntomodulin infusion and the other three during combined $PYY_{3–36}$ + oxyntomodulin infusion. Even though the nausea settled rapidly in each case after the infusion was (prematurely) stopped, it may have reduced energy intake at the subsequent buffet meal. The energy intake data were therefore analyzed further, excluding all data from the four affected participants. In this analysis ($n = 8$), the combined $PYY_{3–36}$ + oxyntomodulin infusion significantly reduced energy intake by 33% in comparison with saline control ($P < 0.05$). However, the control low-dose $PYY_{3–36}$, low-dose oxyntomodulin, and high-dose oxyntomodulin infusions for these subjects did not reduce food intake significantly (mean energy intake: 593 ± 132.7 kcal [saline], 524 ± 129.9 kcal [low-dose $PYY_{3–36}$], 503 ± 121.3 kcal [low-dose oxyntomodulin], 532 ± 113.6 kcal [high-dose oxyntomodulin], and 398 ± 77.3 kcal [combined $PYY_{3–36}$ + oxyntomodulin]; $P < 0.05$ vs. saline; $n = 8$).

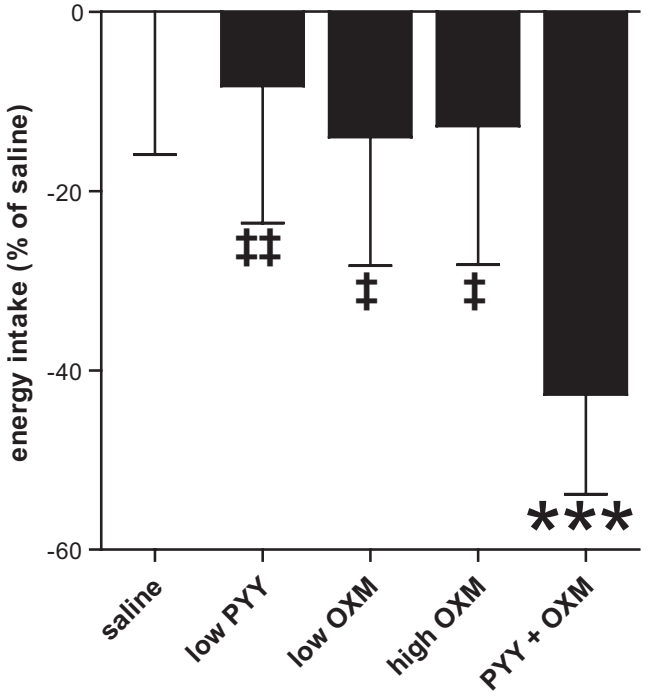

FIG. 1. Percent reduction in energy intake at the buffet meal, with reference to the mean intake during saline infusion (all subjects included, n = 12). ***P < 0.001 vs. saline. ‡P < 0.05 vs. $PYY_{3–36}$ + oxyntomodulin. ‡‡P < 0.01 vs. $PYY_{3–36}$ + oxyntomodulin.

Plasma concentrations of $PYY_{3–36}$, OLI, insulin, and glucose. Basal plasma concentration of $PYY_{3–36}$ was 22.2 ± 0.7 pmol/l. Infusion of low-dose PYY caused a threefold elevation in plasma $PYY_{3–36}$ concentration to a peak of 62.9 ± 7.2 pmol/l and had no effect on plasma OLI concentration. Basal plasma concentration of OLI was

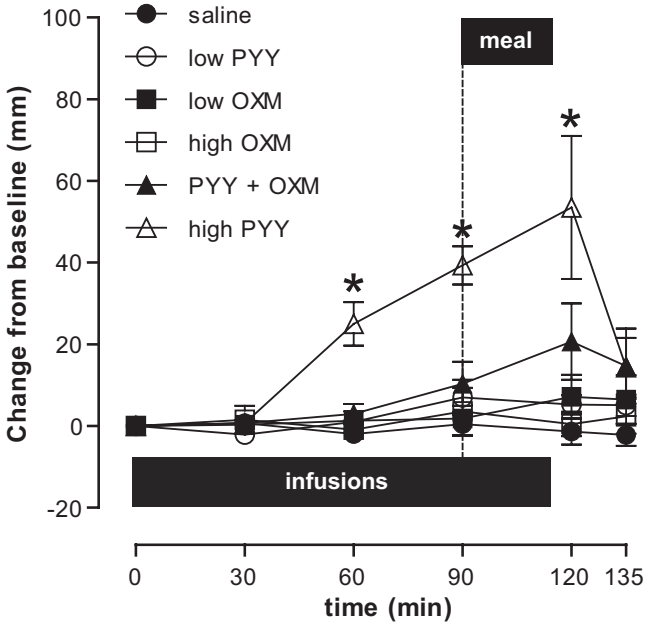

FIG. 2. Subjective rating of nausea, as measured by VAS response. Scores are depicted as change from baseline value (millimeters) (n = 12 for each treatment except high-dose $PYY_{3–36}$ where n = 3). ●, saline; ○, low-dose $PYY_{3–36}$; ■, low-dose oxyntomodulin (OXM); □, high-dose oxyntomodulin; ▲, $PYY_{3–36}$ + oxyntomodulin; △, high-dose $PYY_{3–36}$. *P < 0.05 versus saline. Horizontal black bar, infusion duration; dotted vertical line, meal time.

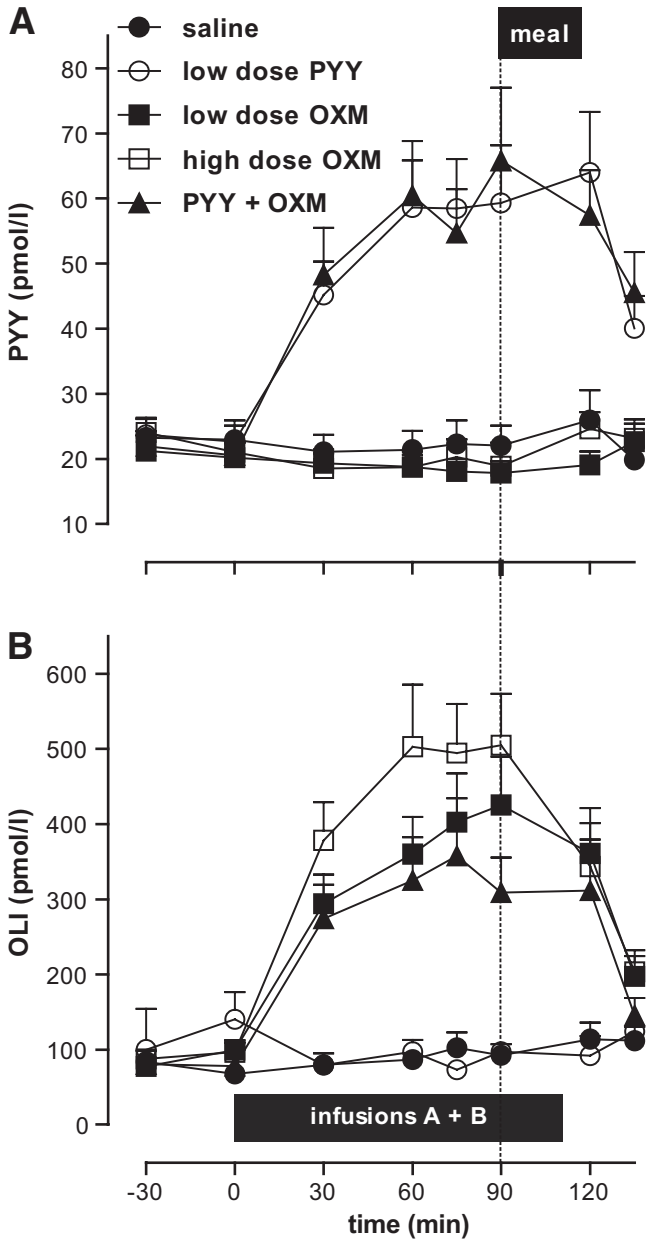

FIG. 3. Plasma concentrations of $PYY_{3–36}$ (A) and OLI (B) during study infusions. ●, saline; ○, low-dose $PYY_{3–36}$; ■, low-dose oxyntomodulin; □, high-dose oxyntomodulin; ▲, $PYY_{3–36}$ + oxyntomodulin. Horizontal black bar, infusion duration; dotted vertical line, meal time.

83.6 ± 4.1 pmol/l. Infusion of low-dose oxyntomodulin caused a fivefold elevation in plasma OLI concentration to a peak of 381.2 ± 49.0 pmol/l, whereas infusion of high-dose oxyntomodulin caused a sixfold elevation to a peak of 505.3 ± 68.3 pmol/l (Fig. 3). Plasma $PYY_{3–36}$ concentration remained at basal levels during low- and high-dose oxyntomodulin infusions. There were no statistically significant differences between treatments in insulin or glucose concentrations before the meal. Plasma insulin and glucose were not measured postprandially because energy intake was not fixed.

Effect of $PYY_{3–36}$ and oxyntomodulin infusions on cardiovascular parameters. No statistically significant differences in pulse or blood pressure were detected between treatments at any time point.

DISCUSSION

Combined administration of $PYY_{3–36}$ and oxyntomodulin at low dose resulted in a statistically significant reduction in energy intake of 42.7% in comparison with that on the saline control day. In contrast, mean energy intake during low-dose infusion of either $PYY_{3–36}$ or oxyntomodulin was 8.3 and 14% lower, respectively, than during saline infusion, but in neither case was this difference statistically significant from the food intake during saline infusion. In a separate analysis that excluded all data from subjects who had experienced nausea at any point during the study, the reductions in energy intake achieved by low-dose infusion of either hormone alone (12 and 15% for $PYY_{3–36}$ and oxyntomodulin, respectively) were again nonsignificant, but combined low-dose infusions of $PYY_{3–36}$ and oxyntomodulin reduced mean energy intake significantly by 33% compared with saline. This indicates that the combination of $PYY_{3–36}$ and oxyntomodulin reduces food intake to a greater extent than either hormone infused separately at this same dose.

Although not directly comparable, because the procedures were different, the anorectic effect of low-dose $PYY_{3–36}$ infusion in the current study was less than that observed by Batterham et al. (26) using a somewhat higher dose. The anorectic effects of both low- and high-dose oxyntomodulin infusions were also less than those previously observed by Cohen et al. (19). Furthermore, there was no difference in effect between these low- and high-dose oxyntomodulin infusions, despite the twofold difference in dose. However, the peak plasma OLI concentrations in the current study were substantially lower than those achieved previously, which may reflect differences in infusion preparation (19).

During high-dose $PYY_{3–36}$ infusion, the mean peak plasma $PYY_{3–36}$ concentration was sufficient to cause sweating and severe nausea in all subjects, in keeping with previous reports (20,22,23). In contrast, nausea did not occur with low-dose $PYY_{3–36}$ infusion, during which the peak plasma $PYY_{3–36}$ concentration was similar to that achieved in obese subjects by Batterham et al. (26). High-dose oxyntomodulin infusion resulted in a mean plasma OLI concentration ~60% of that achieved previously by intravenous infusion (19) and considerably lower than that previously reported to cause nausea (21). Nevertheless, 1 of the 12 subjects experienced nausea during high-dose oxyntomodulin infusion, suggesting that the threshold for oxyntomodulin-induced nausea may vary between individuals. There were no adverse effects with low-dose oxyntomodulin. However, combined low-dose infusions of $PYY_{3–36}$ and oxyntomodulin caused nausea in 3 of 12 subjects. Thus, although coadministration of $PYY_{3–36}$ and oxyntomodulin can produce a robust reduction in energy intake, this combination may increase the incidence of side effects.

When satiety-inducing hormones that act via different receptors are administered in combination, it can be hypothesized that the effects on appetite should be additive. However, studies performed on lean human volunteers do not always support this. Neary et al. (30) reported that pancreatic polypeptide, a Y4 receptor agonist, and $PYY_{3–36}$, a selective Y2 receptor agonist, did not reduce food intake when infused together. Others have found that, although cholecystokinin and glucagon-like peptide 1 (GLP-1) synergistically reduced hunger sensations, the combination did not reduce energy intake to a greater extent than infusion of either hormone separately (31). It is possible that the absence of additive effects results either from duplication of the principal mode of action or from unsuspected, mutually antagonistic actions within each pair of hormones. In contrast, and in agreement with the current study, Neary et al. (32) demonstrated that intravenous infusion of $PYY_{3–36}$ with GLP-1 reduced food intake to a greater extent than either hormone administered separately. Furthermore, exendin-4, which, like GLP-1 and oxyntomodulin, is a GLP-1 receptor agonist, acts synergistically with $PYY_{3–36}$ to reduce food intake in mice (33). The current study thus supports the concept that Y2 receptor agonists and GLP-1 receptor agonists have distinct and additive effects on appetite.

The plasma concentrations of $PYY_{3–36}$ and OLI during these infusions are within the range of those occurring after Roux-en-Y gastric bypass surgery. Measurement of oxyntomodulin concentration in plasma presents particular difficulties because of cross-reactivity of total glucagon (enteroglucagon) antibodies with several circulating products of preproglucagon cleavage (14). This may account for the 10-fold difference in postprandial levels reported after Roux-en-Y gastric bypass (16,17). Notwithstanding this discrepancy and differences in antibody specificity, the mean plasma OLI concentration achieved during the current study was similar to postprandial enteroglucagon levels reported after Roux-en-Y gastric bypass (15). With regard to plasma $PYY_{3–36}$ concentration, the mean peak level achieved during low-dose infusion in the current study was ~50% higher than the peak concentration reported after a 420-kcal mixed meal (34), but slightly lower than that measured after a 398-kcal liquid meal (35), both studies being performed on patients who had undergone Roux-en-Y gastric bypass. Thus, the results of the current study may throw light on the mechanism of food intake reduction after Roux-en-Y gastric bypass.

In summary, we have shown that combined infusion of $PYY_{3–36}$ and oxyntomodulin appear to have an additive anorectic effect in overweight and obese humans. These results and data from other recent studies suggest that Y2 receptor agonists and GLP-1 receptor agonists may be particularly suited to coadministration for the treatment of obesity. However, further studies are required to establish whether chronic coadministration of gut hormones can increase the potential anorectic effect without inducing a parallel increase in nausea.

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