Brief Report—Endocrine Research

Effects of a Single Dose of Exenatide on Appetite, Gut Hormones, and Glucose Homeostasis in Adults with Prader-Willi Syndrome

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Context: Prader-Willi syndrome (PWS) is associated with hyperphagia and obesity, without effective pharmacological treatment. Exenatide, recently developed for treatment of type 2 diabetes, induces appetite suppression and weight loss with common side effects.

Objective: The objective of the study was to investigate the initial safety and effectiveness of exenatide in adult PWS subjects compared with obese controls (OBESE).

Design, Setting, Patients, and Intervention: Eight PWS and 11 OBESE patients underwent standardized meal studies after a single sc injection of 10 μg exenatide or placebo in a single-blinded, crossover design.

Main Outcome Measures: Glucose, insulin, C-peptide, glucagon, peptide YY (PYY; total)/PYY (3-36), glucagon-like peptide-1, and ghrelin (total) were measured fasting and postprandially. Appetite and satiety were assessed by visual analog scales. Energy expenditure (EE) was measured by indirect calorimetry. Side effects were screened during and for 24 h after the meal.

Results: PWS and OBESE patients were matched for gender, age, body mass index, and central/total body fat. In both groups, exenatide increased satiety and lowered glucose and insulin levels but increased insulin secretion rate. Side effects were absent in PWS but common in OBESE patients. During the meal, PYY (total) and ghrelin were elevated in PWS patients. Exenatide decreased PYY (total) and glucagon-like peptide-1, whereas ghrelin remained unchanged. Energy expenditure was unchanged by exenatide.

Conclusions: Our pilot study demonstrates that exenatide is well tolerated in PWS patients. It increases satiety independently of measured appetite hormones, exerting glucose lowering, and insulinotropic effects similarly in PWS and OBESE patients. Larger prospective studies should investigate whether chronic exenatide administration will reduce hyperphagia and overweight in PWS patients without side effects. **(*J Clin Endocrinol Metab* 96: E1314–E1319, 2011)**

Prader-Willi Syndrome (PWS) is one of the most common known genetic cause of obesity with a prevalence of 1:10,000–1:25,000 (1). Genetic alterations on chromosome 15q11-q13 result in the characteristic hyperphagia accompanied by intellectual disability, behavioral abnormalities, and endocrine disorders.

The mechanisms of uncontrolled food intake leading to morbid obesity are still poorly understood, but an insufficient and delayed satiety response (2, 3) seems to play an essential role. Accordingly, much attention has been paid to appetite regulating hormones in PWS. Currently the only measure for weight control in PWS is constant supervision, which is demanding and distressing for both care givers and patients. Because various pharmacological trials have been unsuccessful, there is an urgent need for further treatment options.

Recently glucagon-like peptide-1 (GLP-1) receptor agonists have been introduced for therapy in type 2 diabetes

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Abbreviations: AUC, Area under the curve; BMI, body mass index; EE, energy expenditure; GLP-1, glucagon-like peptide-1; PWS, Prader-Willi syndrome; PYY, peptide YY; T2DM, type 2 diabetes mellitus; VAS, visual analog scale.

mellitus (T2DM) (4), and their use for weight loss, even in nondiabetic subjects, is promising (5). We considered exenatide as a novel treatment modality for hyperphagia and obesity in PWS, considering its potential effects on ghrelin suppression (6), central appetite suppression (7), raising energy expenditure (EE) (8–10), and stimulation of insulin secretion, which could counterbalance the hypoinsulinemia reported in PWS (11).

The aim of this study was to collect initial safety and effectiveness data for single-dose exenatide in adult PWS subjects compared with obese controls (OBESE). We specifically assessed hunger and satiety, appetite hormones, side effects, and changes in glucose metabolism.

Subjects and Methods

Subjects

Eight PWS subjects were recruited from the PWS Clinic, Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia, and 11 age-, gender-, and body mass index (BMI)-matched OBESE subjects were recruited by advertisement. This study was approved by the local Human Research Ethics Committee. Written informed consent was obtained from participants, parents, or guardians. Cytogenetic testing in PWS revealed four deletions and four uniparental disomies. Four PWS subjects had T2DM (taking metformin, metformin and gliclazide, or low dose Mixtard 30/70, respectively). One OBESE subject had T2DM (taking metformin, sitagliptin, and rosiglitazone). Four PWS and two OBESE subjects took psychotropic medications. No drugs were taken on the visit day. No PWS subject ever received GH. All subjects were nonsmokers with stable body weight 3 months before and during the study.

Study design

Subjects attended our Clinical Research Facility twice, at least 2 wk apart, after a 10-h fast. In a single-blinded, randomized, crossover design, subjects received either 10 μg exenatide (Byetta; Eli Lilly, West Ryde, New South Wales, Australia) or normal saline (Pfizer, West Ryde, New South Wales, Australia) injected sc 15 min before a standardized breakfast (600 kcal, 50% carbohydrates, 35% fat, 15% proteins), which resembled a usual breakfast for PWS subjects and was finished in less than 20 min. Blood samples were taken at −60, 0 (immediately before eating), 15, 30, 45, 60, 90, 120, 180, and 240 min.

Body composition and EE

Body composition was analyzed by dual-energy x-ray absorptiometry (GE Lunar DPX, Lunar Corp, Madison, WI). Central abdominal fat was assessed as previously described (12). Resting EE was determined by indirect calorimetry (ParvoMedics Inc., Sandy, UT) fasting (−45 to −15 min) and postprandially (210–240 min).

Assessment of hunger and satiety

Visual analog scales (VAS) were specifically adapted for the capabilities of PWS subjects by adding pictures/cartoons. The questions "how much could you eat now?" and "how full do you feel?" were taken from questionnaires by Hill and Blundell (13). Both VAS were rated at −60, 0, 30, 60, 120, 180, and 240 min.

Biochemical measures

Insulin, peptide YY (PYY; total), PYY (3-36), and ghrelin (total) were measured by RIA and GLP-1 (active) by ELISA (Linco Research, Inc., St. Charles, MO). Five hundred kilointernational units per milliliter aprotinin (Sigma, Sydney, Australia) and 10 μl/ml dipeptidyl peptidase-IV inhibitor (Linco Research) were added to EDTA blood collection tubes. Inter/intraassay coefficients of variations were 3.5–8%.

Statistical analysis

Meal responses were calculated as average postprandial values obtained from areas under the curves (AUC; t = 0–240 min) using the trapezoidal rule, divided by time. Rates of insulin secretion were calculated from C-peptide time-course data (14) after smoothing by a constrained cubic spline procedure designed to accommodate abrupt meal-related changes (see http://www.korf.co.uk/spine.pdf). Analyses of continuous variables were performed using analysis of covariance (insulin secretion response) or multivariate analysis of variance. The effects of exenatide treatment on fasting responses were assessed by compound multivariate analysis of variance (time, treatment, and time treatment effects), and meal responses were assessed by factorial repeated-measures ANOVA [treatment (placebo, exenatide), factorial group (OBESE, PWS), and group treatment effects]. Group effects on categorical variables were assessed using the Fisher's exact test. The statistical software JMP 8.0 (SAS Institute Inc., Cary, NC) was used. Results are expressed as mean ± SEM. $P < 0.05$ was considered significant.

Results

Clinical parameters

Anthropometric characteristics of PWS and OBESE subjects are summarized in Table 1. Subjects were matched for gender, age, BMI, and total body and abdominal fat mass.

All of the following postprandial measures are reported as average meal responses (AUC/time). The full time-course data are available in Supplemental Figs. 1 and 2, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org.

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TABLE 1. Anthropometric and metabolic characteristics

Variables	PWS	OBESE
Number (male/female)	8 (5/3)	11 (6/5)
Age (yr)	30.0 ± 2.8	31.3 ± 2.7
Height (cm)	154.5 ± 4.4[a]	167.4 ± 2.2
Weight (kg)	89.0 ± 9.0	95.6 ± 2.4
BMI (kg/m^2)	37.4 ± 3.4	34.4 ± 1.3
Waist (cm)	112.4 ± 7.4	105.4 ± 2.5
WHR	0.93 ± 0.03	0.90 ± 0.03
Systolic BP (mm Hg)	124.6 ± 2.6	125.2 ± 2.7
Diastolic BP (mm Hg)	77.3 ± 2.5[b]	65.9 ± 2.0
Whole body lean mass (kg)	43.4 ± 3.5	51.8 ± 2.7
Whole body fat mass (%)	47.3 ± 3.2	42.3 ± 3.2
Abdominal fat mass (%)	45.4 ± 2.9	46.6 ± 2.3
Total cholesterol (mmol/liter)	3.5 ± 0.2[b]	4.7 ± 0.2
HDL-cholesterol (mmol/liter)	0.9 ± 0.1	1.0 ± 0.0
LDL-cholesterol (mmol/liter)	2.1 ± 0.2[a]	3.1 ± 0.2
Triglycerides (mmol/liter)	1.0 ± 0.2	1.3 ± 0.2

Data are expressed as mean ± SEM. WHR, Waist to hip ratio; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

[a] $P < 0.05$.

[b] $P < 0.005$.

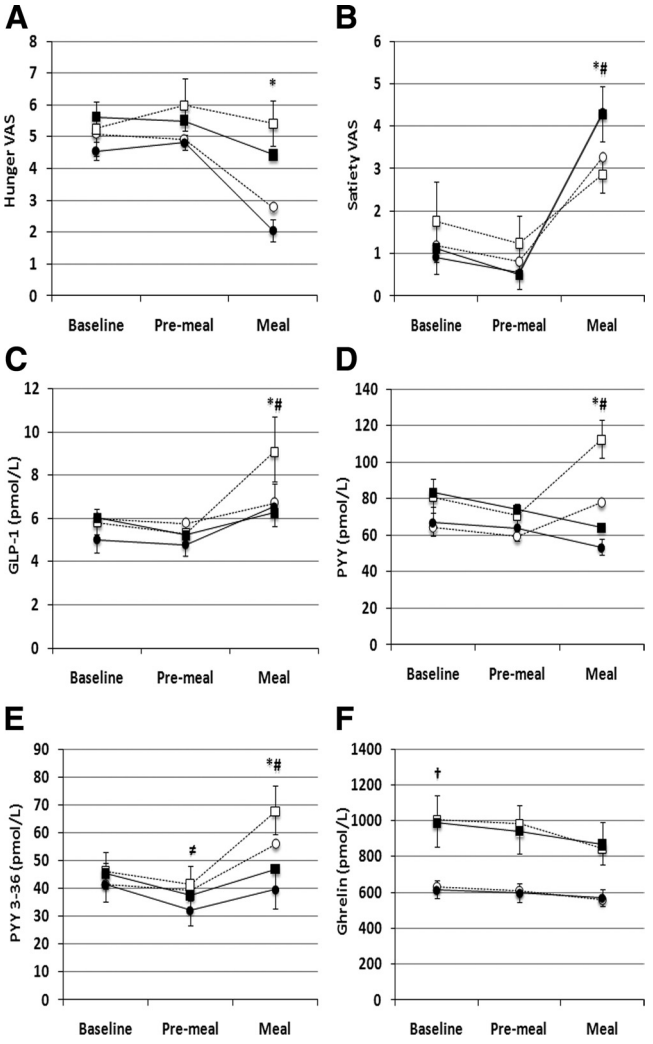

FIG. 1. VAS measures of hunger (A) and satiety (B), and circulating concentrations of the appetite regulating hormones GLP-1 (C), PYY (D), PYY3-36 (E), and ghrelin (F) at baseline (t = −60), premeal (t = 0) and during the meal (average t = 0–240 min) in OBESE (*circles*) and PWS (*squares*) subjects with either placebo (*open symbols*) or exenatide (*closed symbols*) administered at t = −15. Results are presented as mean ± SEM.†, Baseline difference between groups; ≠, exenatide effect premeal; *, meal effect; #, exenatide effect during the meal (main effect and/or meal exenatide interaction).

Hunger and satiety

Baseline (−60 min) satiety and hunger scores were similar between PWS and OBESE subjects. PWS subjects were resistant to the hunger-suppressing effects of the meal compared with OBESE controls ($P = 0.01$ Fig. 1A). Before eating, exenatide had no significant effects on hunger or satiety. During the meal, exenatide significantly increased satiety ($P = 0.003$, Fig. 1B), without significant effect on hunger.

Side effects, appetite, and food intake

No side effects were observed in PWS subjects, with placebo or exenatide, whereas nine of 11 OBESE subjects ($P < 0.001$) reported side effects with exenatide, most commonly bloating (n = 6), nausea (n = 5), and vomiting (n = 2). In the 24-h follow-up questionnaires, three of eight PWS subjects reported headaches (one on exenatide, two on placebo), whereas seven of the 11 OBESE subjects reported prolonged side effects after exenatide and five of 11 after placebo. The subjective estimates of appetite and food intake within 24 h were unaffected by exenatide in both groups.

Appetite-regulating hormones

At baseline (−60 min), only fasting ghrelin levels were significantly different between groups ($P = 0.01$, Fig. 1F), being approximately 2-fold higher in PWS than OBESE subjects; the apparent difference in PYY (total) between groups (Fig. 1D) was not significant ($P = 0.09$). Before eating, exenatide significantly decreased PYY (3-36) compared with placebo ($P < 0.01$, Fig. 1E) without affecting GLP-1, PYY (total), or ghrelin levels. Exenatide abolished the meal response (AUC/time) of PYY (total) ($P < 0.0001$, Fig. 1D) and substantially reduced the meal responses of PYY (3-36) ($P = 0.002$, Fig. 1E) and GLP-1 ($P = 0.01$, Fig. 1C) without significant effect on ghrelin ($P = 0.11$, Fig. 1F). There were no significant group treatment or group meal interactions for any appetite hormones.

Glucose and its regulating hormones

Fasting glucose, insulin, C-peptide, and glucagon levels were similar between PWS and OBESE subjects. Before eating, exenatide significantly reduced glucose ($P = 0.004$, Fig. 2A) and increased insulin ($P = 0.004$, Fig. 2C) and C-peptide ($P = 0.003$, Fig. 2D) concentrations. Consistently, the insulin secretion rate was significantly elevated by exenatide at

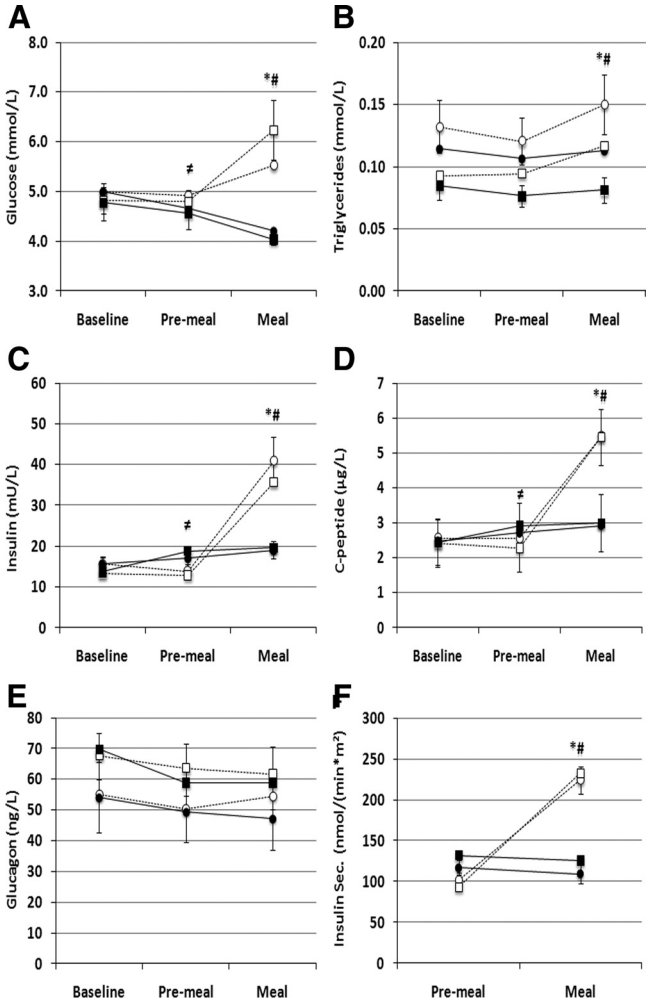

FIG. 2. Circulating glucose (A), triglycerides (B), insulin (C), C-peptide (D), glucagon (E), and calculated insulin secretion rate (F) at baseline (t = −60 min), premeal (t = 0), and during the meal (average t = 0–240) in OBESE (*circles*) and PWS (*squares*) subjects with either placebo (*open symbols*) or exenatide (*closed symbols*) administered at t = −15. Results are presented as mean ± SEM. ≠, Exenatide effect before a meal; *, meal effect; #, exenatide effect during the meal (main effect and/or meal exenatide interaction).

t = 0 ($P = 0.002$, Fig. 2F). During the meal, exenatide markedly reduced the glucose ($P = 0.002$, Fig. 2A), insulin ($P < 0.0001$, Fig. 2C), C-peptide ($P < 0.0001$, Fig. 2D), and insulin secretion ($P < 0.0001$, Fig. 2F) responses. Postprandial insulin secretion during the placebo treatment was consistent with a reduced glucose sensitivity of insulin secretion in PWS compared with OBESE subjects ($P = 0.001$, analysis of covariance). No treatment effects on glucagon were detected (Fig. 2E). There were no significant group treatment effects in any glucoregulatory variables. All analyses were substantially unchanged by exclusion of T2DM subjects (n = 5).

EE, substrate oxidation, and triglycerides

Resting EE corrected for lean body mass was not different between PWS and OBESE subjects and showed the expected meal induced increase ($P = 0.002$, data not shown) independent of group and unaffected by exenatide. The respiratory quotient was also similar between groups, but the postprandial increase ($P = 0.002$) was significantly suppressed by exenatide ($P = 0.02$, data not shown), accounted for by reduced postprandial suppression of fat oxidation ($P = 0.02$, data not shown). Exenatide also suppressed the postprandial rise of circulating triglycerides ($P = 0.008$, Fig. 2B).

Discussion

Administration of exenatide reduces body weight in obese subjects with (4) and without T2DM (5), but there are no data about whether it is effective and safe in PWS.

Exenatide is thought to reduce appetite and energy intake via delayed gastric emptying and direct central effects, both probably responsible for side effects such as bloating, nausea, and vomiting. More than 80% of our control subjects experienced these side effects during the study and the following 24 h. However, PWS subjects reported no side effects, possibly because of the known high threshold for pain and nausea. Whether the lack of nausea under acute high levels of GLP-1 agonists reflects disturbed appetite regulation, possibly due to abnormal GLP-1 signaling in the brain, requires further study. Long-term trials with GLP-1 agonists should determine whether the demonstrated increased satiety, without nausea and suppression of hunger, will reduce long-term food intake with subsequent weight loss in PWS.

One caveat regarding exenatide use in PWS subjects is the potential for delaying gastric emptying, which is already slower than in OBESE subjects (15). A theoretical increased risk of gastric rupture exists, especially if subjects gain unlimited access to food. Therefore, trials of exenatide in PWS subjects should be stringently supervised. However, recent reports suggest that newer long-acting GLP-1 agonists are associated with tachyphylaxis to the slowing of gastric emptying (16), possibly providing a safer option for PWS subjects.

The PWS and OBESE groups showed similar insulin and glucose responses after exenatide as previously described in healthy subjects (17). In T2DM, in which insulin secretion is impaired, exenatide has a clear insulinotropic effect, leading to lowered glucose levels (18, 19). On the other hand, in nondiabetic humans receiving exendin-4 (20) or GLP-1 (21, 22), insulin levels seem to fall secondary to declining glucose levels. This effect is only partly explained by lower blood glucose due to slowed gastric emptying, because the insulinotropic effect of GLP-1 is also present in healthy subjects. This was demonstrated by Meier *et al.* (17), who antagonized the effect of exenatide

on gastric emptying with erythromycin, showing only partial recovery of the glycemic response to a liquid meal. Exenatide is thought to suppress endogenous glucose output through activation of GLP-1 receptors remote from the gut (18, 23) and to increase the hepatic glucose uptake as well as insulin-mediated, whole-body glucose disposal (24).

PWS subjects had higher ghrelin levels than OBESE subjects, consistent with previous reports. Exenatide did not affect ghrelin levels in either group, supporting Brennan *et al.* (25), who found no effect of iv GLP-1 on ghrelin in healthy men. However, our data contradict those of Hagemann *et al.* (26), who reported a reduced rise in late postprandial ghrelin levels, and those of Perez-Tilve *et al.* (6), who suggested a mechanism specific to exendin-4 inhibiting ghrelin in fasting rats.

Exenatide markedly suppressed circulating GLP-1 and PYY (total) postprandially, confirming the findings of Näslund *et al.* (22), who reported suppression of postprandial PYY (total) during infusion of GLP-1 in healthy men and suggested a negative feedback on L cell secretion. Consequently, it becomes obvious that exenatide induced satiety is not mediated by the endogenous appetite hormones measured here, all of which were either unaffected (ghrelin) or affected in ways predicted to increase feeding drive (PYY, GLP-1).

We acknowledge that the mixed population (subjects with and without T2DM) poses a limitation of this study, especially regarding glucose homeostasis variables. We decided to include all subjects, irrespective of the presence of T2DM, because the primary outcomes were appetite regulation and side effects of exenatide. Our findings remain the same when excluding all diabetic subjects from the analysis.

Conclusion

This pilot study provides the first efficacy and safety data regarding a single dose of exenatide in PWS, demonstrating that it is well tolerated. It is equally effective in increasing satiety and in glucose-lowering and insulinotropic effects as in obese controls. These benefits could not be explained by its effects on endogenous appetite hormones. Rather, delayed gastric emptying and direct central effects likely play a major role. Larger, prospective studies must test whether chronic exenatide administration will decrease food intake and body weight in PWS patients.

Acknowledgments

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