0013-7227/07/$15.00/0
Printed in U.S.A.

Endocrinology 148(2):501–506

doi: 10.1210/en.2006-1275

Normal Food Intake and Body Weight in Mice Lacking the G Protein-Coupled Receptor GPR39

Frédéric Tremblay, Mylène Perreault, Lori D. Klaman, James F. Tobin, Erica Smith, and Ruth E. Gimeno

Cardiovascular and Metabolic Diseases (F.T., M.P., L.D.K., J.F.T., R.E.G.) and Women's Health and Musculoskeletal Biology (E.S.), Wyeth Research, Cambridge, Massachusetts 02140

It has been recently proposed that obestatin, a peptide encoded by the ghrelin gene, reduces food intake by activating the orphan G protein-coupled receptor GPR39. To gain further insights into the role of GPR39 in body weight homeostasis, we characterized the phenotype of mice with targeted disruption of the GPR39 gene. Body weight, adiposity, and food intake were found to be similar between GPR39$^{+/+}$ and GPR39$^{-/-}$ mice. Furthermore, fasting glucose and insulin levels were similar between both genotypes. Injection of obestatin peptide (1 μmol/kg, ip) obtained from multiple sources did not consistently inhibit food intake in wild-type mice after an overnight fast, and no difference in food intake was observed between wild-type and GPR39 knockout mice after injection of the peptide. Finally, ectopic expression of GPR39 in HEK293T cells revealed a constitutive activation of the receptor that was unaffected by stimulation with obestatin. Our phenotypic characterization suggests that GPR39 is not a major modulator of food intake in mice, although a more subtle role cannot be excluded. The role of GPR39 in normal physiology requires further study and should be conducted independently of the function of obestatin. (*Endocrinology* 148: 501–506, 2007)

GUT-DERIVED PEPTIDES, such as glucagon-like peptide (GLP)-1, peptide YY (PYY) and ghrelin, are increasingly recognized as important regulators of both food intake and the metabolic response to nutrients (1–5). These peptides are secreted by enteroendocrine cells in the gastrointestinal tract and transmit signals by interacting with specific G protein-coupled receptors in the enteric nervous system as well as other tissues including the hypothalamus, adipose tissue, and pancreas (1–5). Whereas some of these peptides (*e.g.* PYY, GLP-1) act as satiety factors, others (*e.g.* ghrelin) stimulate food intake (1–5). Importantly, the systemic concentrations of the satiety peptides PYY and GLP-1 are up-regulated by nutrient ingestion, whereas serum concentrations of the orexigenic peptide ghrelin are up-regulated by fasting and decrease after meal initiation (1–5).

Obestatin is a recently identified 23-amino acid peptide that is encoded by the same gene as ghrelin and is present at low concentrations (~0.3 ng/ml) in rat serum (6). Intraperitoneal or intracerebroventricular injection of human obestatin was found to decrease food intake acutely in wild-type mice (6). Chronic administration of the same peptide to normal rats led to a small (~0.5 g) decrease in body weight gain over a 7-d period, suggesting that obestatin may function to modulate body weight (6). In contrast to ghrelin (7, 8), the serum levels of obestatin were found to be unchanged upon fasting or in response to nutrients in rats (6). Obestatin administration was also found to decrease gastric emptying and inhibit the motility of jejunum muscle strips, suggesting that obestatin may also affect gastrointestinal transit time (6). Whereas data from the original publication as well as one additional report (6, 9) suggest that obestatin is a new satiety peptide, several recent reports were unable to find an effect of obestatin injection on food intake or body weight in rodents (10–13), challenging the view of obestatin as a satiety peptide.

GPR39 is a G protein-coupled receptor highly expressed in the gastrointestinal tract in both mice and humans (6, 14). GPR39 belongs to the ghrelin receptor family, which includes several receptors activated by peptide hormones and neuropeptides, such as the ghrelin receptor, the neurotensin receptors 1 and 2, the motilin receptor, and the neuromedin U receptors 1 and 2 (15). Similar to other members of the ghrelin receptor family, GPR39 shows a high degree of constitutive activity particularly with respect to activation of a serum response element (SRE)-coupled reporter gene (15). Recently obestatin was proposed to be a ligand for GPR39 (6). Obestatin was found to bind to human GPR39 with high affinity (dissociation constant = 1 nM) and specificity (6) and activate cAMP production and SRE-dependent transcription in two different cell lines transfected with human GPR39 (6). An independent study, however, could not reproduce obestatin binding to GPR39 or GPR39-dependent obestatin signaling (10), raising doubts whether GPR39 is indeed the obestatin receptor.

Here we use GPR39 knockout mice to directly evaluate the role of GPR39 in the regulation of body weight and food intake. Furthermore, we examine the effects of obestatin on GPR39 signaling *in vitro* and on food intake *in vivo*.

Materials and Methods

Animals

Seven- to 8-wk-old C57BL/6J male mice were purchased from Jackson Laboratory (Bar Harbor, ME). GPR39 heterozygous mice were ob-

First Published Online November 9, 2006

Abbreviations: GLP, Glucagon-like peptide; PYY, peptide YY; SRE, serum response element.

***Endocrinology* is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.**

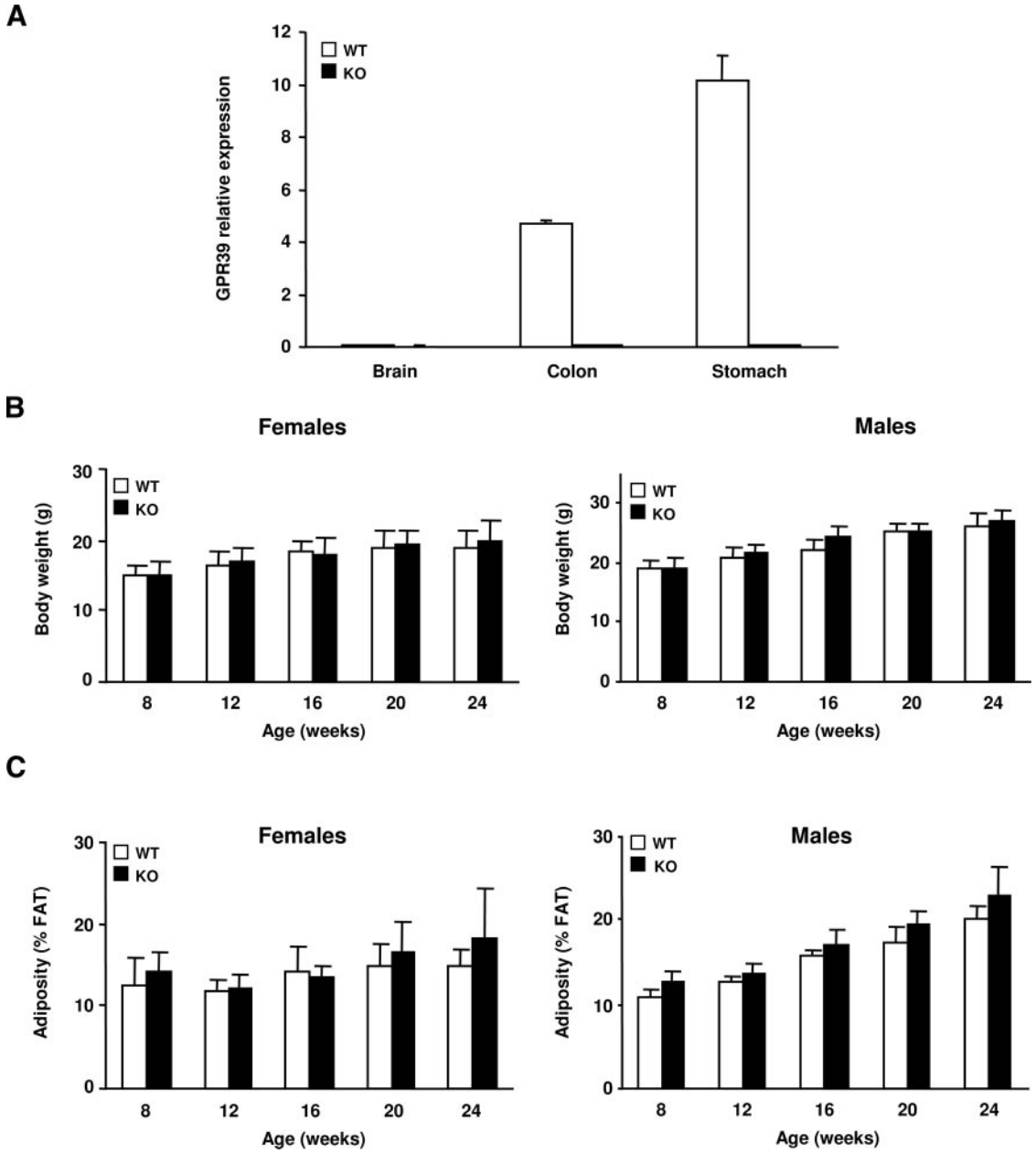

FIG. 1. Characterization of GPR39$^{-/-}$ mice. A, GPR39 transcripts levels in brain, colon, and stomach from wild-type and knockout mice were measured by Taqman real-time PCR as described in *Materials and Methods*. Body weight (B) and adiposity (C) (percent fat) in GPR39$^{+/+}$ (WT) and GPR39$^{-/-}$ (KO) females (*left*) and males (*right*) from 8 to 24 wk of age. The means ± SEM from eight animals/group are shown.

tained from Deltagen (San Carlos, CA). The GPR39 deletion allele was generated by replacing nucleotides 278–647 of the open reading frame with a cassette encoding the neomycin resistance marker using homologous recombination in a 129/OlaHsd ES cell line. The targeting event was confirmed by Southern blotting using probes directed against chromosomal DNA flanking the targeting vector at both the 5′ and 3′ ends. Mice carrying the targeted allele were backcrossed into the C57BL/6 background for six generations and maintained as heterozygotes. Knockout and wild-type littermates from heterozygous mating pairs were used for phenotyping. All mice were singly housed in a temperature-controlled (25 C) facility with a 12-h light, 12-h dark cycle and had free access to water and a normal chow diet (Rodent chow 5001; PharmaServ, Framingham, MA). All experimental work was conducted in accordance with the humane guidelines for ethical and sensitive care of the Institutional Animal Care and Use Committee of the U.S. National Institutes of Health.

Food intake and body composition measurements

Amidated human and mouse obestatin peptides were synthesized by Synpep (Dublin, CA). Amidated human obestatin peptides were also obtained from Peptides International (Louisville, KY) and Global Peptide (Fort Collins, CO). Peptide purity (>95% for all peptides) and identity (within 1 Da of theoretical molecular mass for all peptides) was confirmed by HPLC and mass spectrometry. Acclimated C57BL/6J mice were fasted overnight (16 h) and injected with vehicle (saline, ip), mouse obestatin (1 μmol/kg = 2.52 mg/kg, ip), human obestatin (1 μmol/kg = 2.55 mg/kg, ip), or dexfenfluramine (30 mg/kg, ip). Thirty minutes after injection, animals were given a preweighed amount of food, and food intake was recorded 30 min and 1, 2, 4, 7, and 24 h after refeeding. Similar experiments were performed in female and male GPR39$^{+/+}$ and GPR39$^{-/-}$ littermates. Peripheral dual-energy x-ray absorptiometry images were acquired from GPR39$^{-/-}$ and GPR39$^{+/+}$ mice using a PIXI-

mus mouse densitometer (Lunar Corp., Madison, WI) at 8, 12, 16, 20, and 24 wk of age. Body composition, including total tissue mass, lean body mass, and percent fat were determined from peripheral dual-energy x-ray absorptiometry images.

Serum analysis

Serum glucose was measured with an oxidase/peroxidase assay kit (Sigma-Aldrich, St. Louis, MO). Serum insulin levels were determined with an ultrasensitive rat ELISA kit (Crystal Chem, Downers Grove, IL).

RNA extraction and RT-PCR

Total RNA was extracted using Trizol (Invitrogen, Carlsbad, CA) and purified using the RNeasy minikit (QIAGEN, Valencia, CA). Taqman real-time quantitative PCR was performed on a 7900HT fast real-time PCR system (Applied Biosystems, Foster City, CA) according to the manufacturer's instructions using 18S as an endogenous control. Primers and probe for mouse GPR39 were obtained from Applied Biosystems. Data were analyzed using the comparative cycle threshold method according to the manufacturer's instructions.

Reporter assay

The human GPR39 coding sequence (untagged; sequence 100% identical with NM_001508) was inserted into pcDNA3.1. HEK293T were maintained in DMEM containing 10% fetal bovine serum. Cells were transfected with the SRE-luciferase construct (Stratagene, La Jolla, CA) together with pcDNA3.1 or pcDNA3.1-GPR39 using Fugene 6. A β-galactosidase reporter construct was included to monitor transfection efficiency. One day after transfection, cells were placed in DMEM/Ham's F12 supplemented with 1% BSA and stimulated with obestatin for 16 h. SRE-mediated transcriptional activity was assayed by measuring luciferase activity according to the manufacturer's instruction (Promega, Madison, WI). Data are expressed as luminescence/β-galactosidase activity.

Results

GPR39 KO mice have normal body weight and food intake

We obtained mice with targeted deletion of GPR39 (see *Materials and Methods*). By real-time RT-PCR, GPR39 transcripts were readily detectable in stomach and colon of wild-type mice, as expected, but were absent in these tissues in knockout animals (Fig. 1A). GPR39 knockout mice were born at the expected mendelian ratio and developed normally. We monitored body weight and adiposity of male and female wild-type and knockout mice for 24 wk on a chow diet (Fig. 1, B and C). No significant differences between wild-type and knockout mice were observed at any of the time points and for either sex. Accordingly, GPR39 deficiency in both males and females did not affect lean body mass throughout the period investigated (data not shown). As expected, body weight as well as relative adiposity increased with age for both female and male mice (Fig. 1, B and C).

We monitored food consumption over 7 d under *ad libitum* conditions. No difference in food intake was observed between knockout and wild-type mice of either sex (Fig. 2). We also examined serum glucose and insulin parameters after an overnight fast in 24-wk-old wild-type and knockout animals (Table 1). Similar to the lack of an effect on body weight, we observed no significant differences in glucose and insulin levels in 24-wk-old wild-type and knockout animals (Table 1).

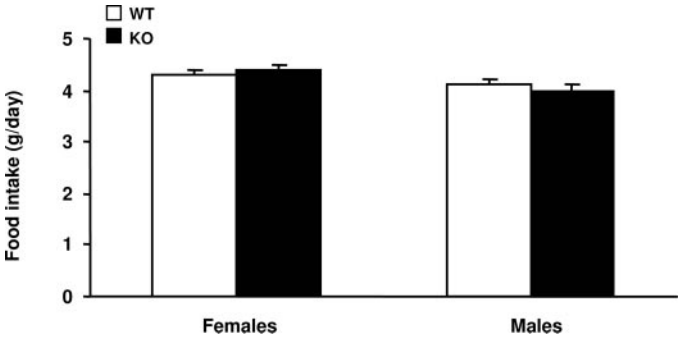

FIG. 2. Food intake in GPR39$^{+/+}$ and GPR39$^{-/-}$ mice. Daily food intake (grams per day) in GPR39$^{+/+}$ (WT) and GPR39$^{-/-}$ (KO) females (*left*) and males (*right*) was measured and averaged over a period of 7 d. The mean ± SEM from nine (WT, female), 10 (KO, female), seven (WT, male), and five (KO, male) animals are shown.

Effect of obestatin on food intake in wild-type and GPR39 KO mice

To examine the ability of GPR39 to mediate the effects of obestatin *in vivo*, we determined the effect of obestatin injections. We initially injected wild-type C57BL/6J mice fasted overnight with either mouse or human obestatin and followed food intake over a 24-h period; as a control, we also injected the appetite suppressant dexfenfluramine. Whereas dexfenfluramine injection resulted in a rapid and pronounced inhibition of food intake (85% reduction 30 min after refeeding, $P < 0.05$) that remained sustained for at least 7 h, we did not observe any inhibition of food intake by mouse obestatin (Fig. 3A). Human obestatin showed a small but significant inhibition of food intake in one experiment; however, we were unable to reproduce this result using either the same preparation or human obestatin peptide from two additional vendors (Fig. 3B).

We next compared food intake in wild-type and GPR39 knockout mice after injection of either saline (Fig. 3, C and D) or human obestatin (1 μmol/kg, ip) (Fig. 3, E and F). A crossover design was used in which mice were first injected with saline; 10 d later the experiment was repeated with obestatin. Food intake of knockout animals was indistinguishable from wild-type controls among both males and females and in both saline- and obestatin-injected animals (Fig. 3, C–F). Thus, the absence of GPR39 does not significantly affect fasting-induced food intake, even after administration of obestatin.

Effect of obestatin on GPR39 activity

We also examined the ability of human and mouse obestatin peptides to activate a SRE-coupled reporter gene in HEK293T cells transiently transfected with a cDNA encoding

TABLE 1. Metabolic parameters of fasted WT and GPR39$^{-/-}$ mice

	Females		Males	
	Wild-type	GPR39$^{-/-}$	Wild-type	GPR39$^{-/-}$
Glucose (mg/dl)	134 ± 21	106 ± 9	153 ± 19	143 ± 20
Insulin (ng/ml)	0.28 ± 0.08	0.40 ± 0.07	0.30 ± 0.05	0.19 ± 0.04

Each value represents the means ± SEM of eight mice.
$P < 0.05$ *vs.* wild-type mice.

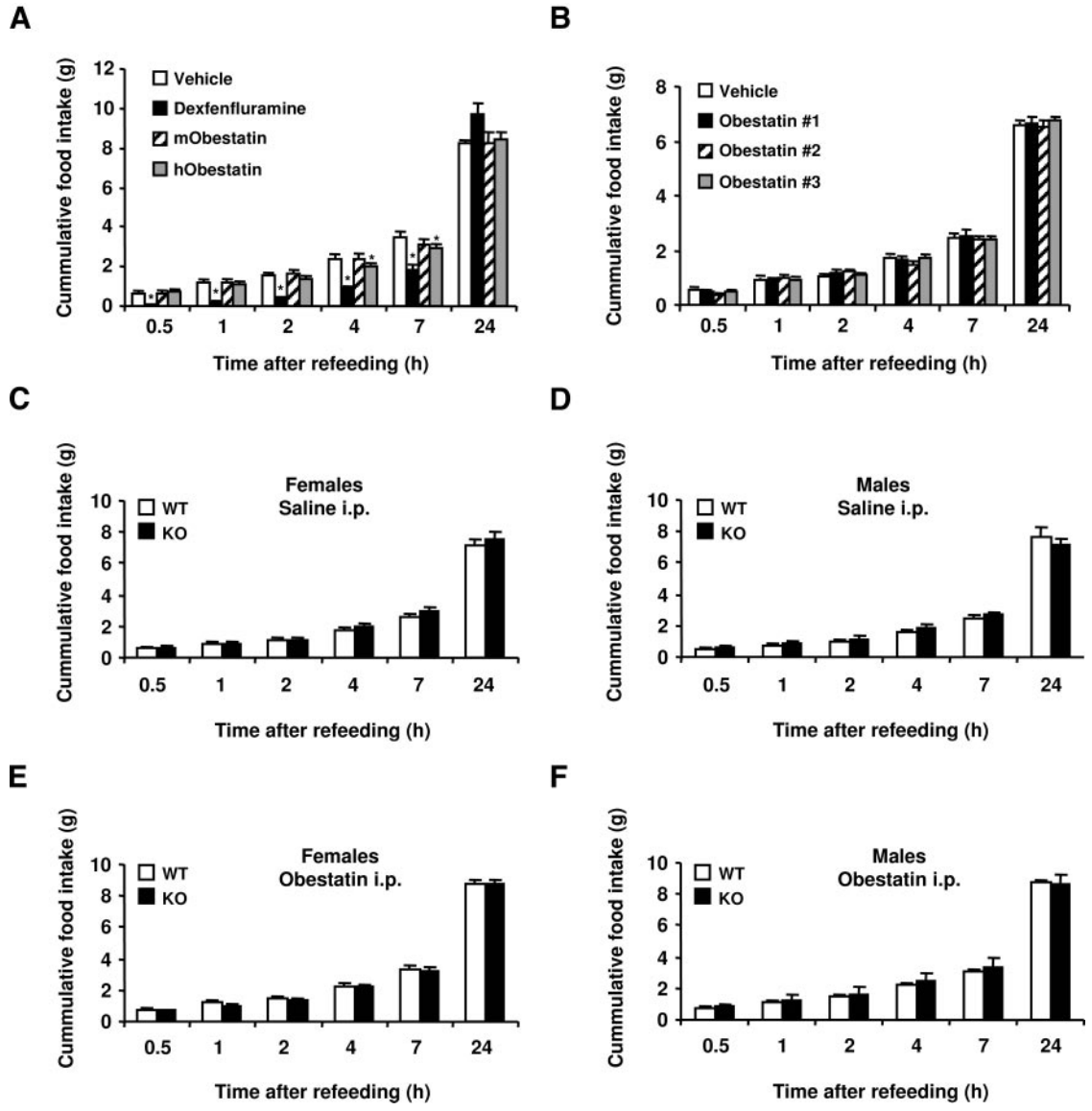

FIG. 3. Acute regulation of food intake in GPR39$^{+/+}$ and GPR39$^{-/-}$: effect of obestatin. A, Eight- to 9-wk-old C57BL/6J mice were fasted overnight and then injected with vehicle, dexfenfluramine (30 mg/kg), or mouse (m) or human (h) obestatin (1 μmol/kg, Synpep). B, Overnight-fasted C57BL/6J mice were injected with vehicle or human obestatin (1 μmol/kg) obtained from three different vendors: 1) Synpep; 2) Peptide International; 3) Global Peptide. Eighteen- to 24-wk-old females and males GPR39$^{+/+}$ (WT) and GPR39$^{-/-}$ (KO) mice were fasted overnight and then injected with saline (C and D) or human obestatin (1 μmol/kg; Synpep; E and F). Cumulative food intake (A–F) was measured over 24 h as described in *Materials and Methods*. The means ± SEM of eight (C57BL/6J, male), nine (WT, female), 10 (KO, female), seven (WT, male), and five (KO, male) animals are shown. *, $P < 0.05$ *vs.* vehicle-injected mice.

human GPR39. In the absence of obestatin peptides, GPR39-expressing cells showed a large (5- to 10-fold) increase in SRE-dependent transcriptional activity, compared with vector-transfected cells (Fig. 4A). Addition of human (Fig. 4A) or mouse (data not shown) obestatin failed to further increase SRE-dependent transcriptional activity. The lack of effect of obestatin on GPR39 activity was not due to a gene-dosage effect because lower expression of GPR39 reduced the overall SRE reporter activity and yet still failed to show any responsiveness to obestatin (Fig. 4B). We were also unable to detect an increase in cAMP levels in response to obestatin from several different vendors (data not shown). High constitutive activity of GPR39 with respect to SRE-dependent transcription has been described by others (15) but was not observed in the paper reporting GPR39 as an obestatin receptor (6).

Discussion

The recent identification of obestatin (6) raised the exciting possibility of yet another gut-derived peptide involved in the control of food intake (16). In addition, the identification of GPR39 as a receptor for obestatin in the same study (6) suggested that modulators of GPR39 might be useful for the treatment of obesity. Here we examined the potential of GPR39 as a target for obesity directly by evaluating the phenotype of GPR39 knockout mice. Contrary to expecta-

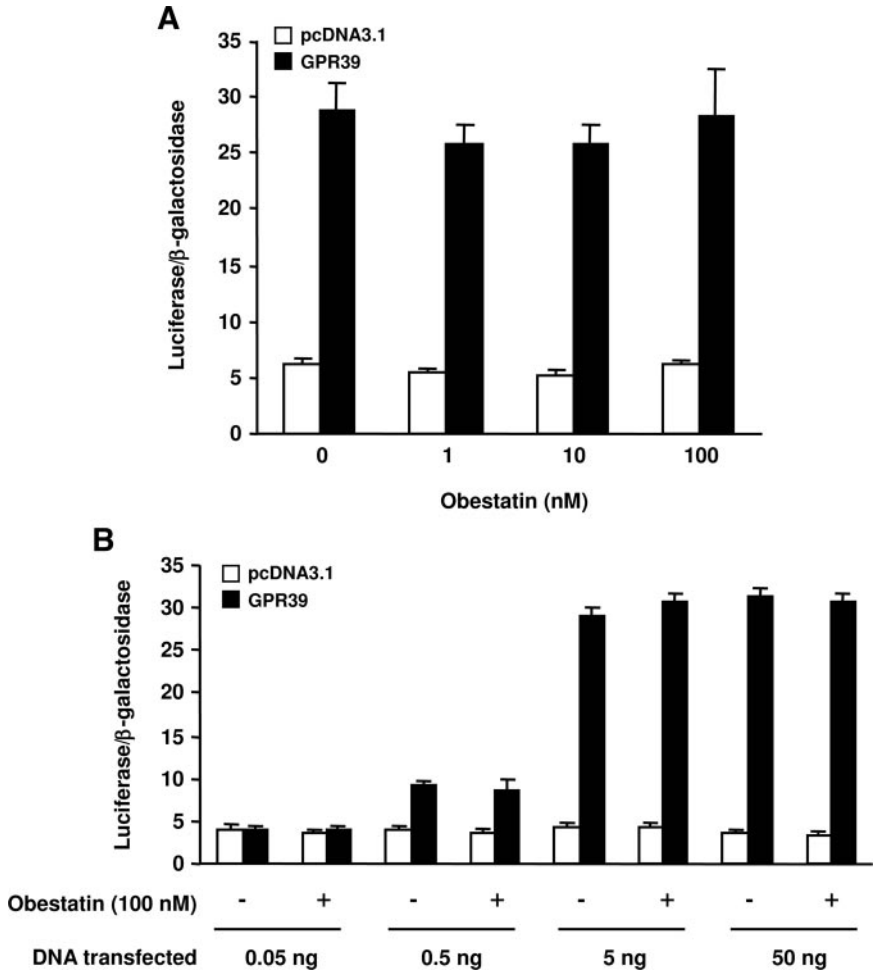

Fig. 4. Effect of obestatin on GPR39 activity. A, HEK293T cells were transfected with either an empty vector (pcDNA3.1) or a vector encoding human GPR39. One day after transfection, cells were left untreated or stimulated with human obestatin (1–100 nM) for 16 h. SRE-mediated transcriptional activity was measured as described in *Materials and Methods*. B, Increasing amounts of DNA (pcDNA3.1 or GPR39) were transfected in HEK293T cells. One day after transfection, cells were left untreated or stimulated with human obestatin (100 nM) for 16 h, and then SRE-mediated transcriptional activity was measured as described in *Materials and Methods*. The means ± SEM of three independent experiments performed in triplicate are shown.

tions, we found no evidence for abnormal body weight or feeding behavior in GPR39 knockout mice. Knockout mice showed similar body weight and adiposity, compared with age-matched littermate controls between 4 and 24 wk of age. Food intake over a 7-d period was not altered in GPR39 knockout mice. Similarly, no differences were found in short-term food intake after an overnight fast between wild-type and knockout mice. Consistent with the lack of a phenotype with respect to body weight, we also found little effect of GPR39 deletion on glucose and insulin levels. A recent study confirmed that deletion of GPR39 in mice does not affect *ad libitum* food intake and has no impact on body weight, body composition, and serum glucose up to 16 wk of age (17). However, this study found increased weight gain in aging GPR39 knockout mice (from 16 to 83 wk) as well as a paradoxical decrease in fasting-induced hyperphagia (17). It is important to note that our studies were performed in mice backcrossed to the C57BL/6J background, whereas the mice in the study of Moechars *et al.* (17) were on a mixed Sv129-C57BL/6 background. We have not yet examined GPR39 knockout mice older than 24 wk of age or mice fed a high-fat diet; it is possible that altering these parameters may be required to uncover a more subtle metabolic phenotype of GPR39 deletion.

The lack of an overt phenotype of GPR39 deletion may be due to compensatory up-regulation of other pathways. To address the role of GPR39 in the effects of obestatin more directly, we injected obestatin into wild-type and knockout mice. Whereas we were able to see a small inhibition of food intake upon injection of human obestatin into wild-type mice in one experiment, in the majority of studies, we saw no effect of either mouse or human obestatin on food intake. We currently do not know why our data differ from the original study describing obestatin as a modulator of food intake because we attempted to faithfully reproduce the experimental conditions described before (6). However, our data are similar to recent reports that also failed to observe inhibition of food intake upon obestatin injection into mice or rats (10–13). Our inability to detect effects of mouse obestatin injection may be explained by a recent study that showed that mouse obestatin has a very short half-life *in vivo*, with no intact obestatin remaining in serum samples 20 min after iv injection (18). No information is available on the half-life of human obestatin in mouse serum. Given that we observed little or no effects of human obestatin injections in wild-type mice, it is not surprising that we did not observe any difference with respect to food intake between wild-type and GPR39 knockout mice injected with obestatin.

We were also unable to confirm that obestatin peptides activate GPR39. Similar to the recent findings of Holst *et al.* (10), we failed to observe an activation of SRE-dependent transcription in cells transfected with human GPR39. Fur-

thermore, consistent with a previous report (15), we observed a strong constitutive, ligand-independent activation of SRE-dependent transcription in cells transfected with GPR39. Interestingly, the publication describing GPR39 as the receptor for obestatin (6) did not observe constitutive activity of GPR39 using the identical SRE-luciferase assay in the same cell line used by us as well as in a previous report (15). It is possible that polymorphisms in the cDNA, small differences in the particular HEK293T subline, or subtle differences in assay conditions are responsible for the differences in constitutive activity and obestatin signaling of GPR39 observed by us and others (15), compared with the obestatin report (6).

It is important to note that obestatin may have roles other than regulation of food intake. For instance, human obestatin has been reported to decrease gastric emptying (6). Interestingly, Moechars *et al.* (17) have shown accelerated gastric emptying in GPR39 knockout mice. However, the effect of obestatin was not tested in that study (17). Recent reports also showed that intracerebroventricular, but not peripheral, injection of rat obestatin promotes sleep in rats (19) and affects thirst (20).

Taken together, our findings suggest that GPR39 is not a major component of body weight regulatory pathways, at least in mice. The lack of effect of mouse obestatin injection on food intake raises doubts about the physiological role of obestatin as a satiety peptide in mice. Furthermore, the inability by us and others (15) to demonstrate activation of GPR39 by obestatin suggests that GPR39 may not be the obestatin receptor. The role of GPR39 in normal physiology requires further study and should be conducted independently of the function of obestatin.

Acknowledgments

We thank Paul Yaworsky for GPR39 cDNA, Loraine Warner for generating body composition data, Nelson Huang for HPLC and mass spectrometry on peptides, and Sarah Will for expert technical assistance.

Received September 19, 2006. Accepted October 30, 2006.

Address all correspondence and requests for reprints to: Dr. Ruth E. Gimeno, Cardiovascular and Metabolic Diseases, Wyeth Research, 200 Cambridge Park Drive (T4007E), Cambridge, Massachusetts 02140. E-mail: rgimeno@wyeth.com.

Author Disclosure: All authors are employed by Wyeth Research. M.P., J.F.T., E.S., and R.E.G. have equity interests in Wyeth.

References

1. **Otto B, Spranger J, Benoit SC, Clegg DJ, Tschop MH** 2005 The many faces of ghrelin: new perspectives for nutrition research? Br J Nutr 93:765–771
2. **Drucker DJ** 2006 The biology of incretin hormones. Cell Metab 3:153–165
3. **Perez-Tilve D, Nogueiras R, Mallo F, Benoit SC, Tschoep M** 2006 Gut hormones ghrelin, PYY, and GLP-1 in the regulation of energy balance and metabolism. Endocrine 29:61–71
4. **Strader AD, Woods SC** 2005 Gastrointestinal hormones and food intake. Gastroenterology 128:175–191
5. **Woods SC** 2005 Signals that influence food intake and body weight. Physiol Behav 86:709–716
6. **Zhang JV, Ren PG, Avsian-Kretchmer O, Luo CW, Rauch R, Klein C, Hsueh AJ** 2005 Obestatin, a peptide encoded by the ghrelin gene, opposes ghrelin's effects on food intake. Science 310:996–999
7. **Tschop M, Smiley DL, Heiman ML** 2000 Ghrelin induces adiposity in rodents. Nature 407:908–913
8. **Perreault M, Istrate N, Wang L, Nichols AJ, Tozzo E, Stricker-Krongrad A** 2004 Resistance to the orexigenic effect of ghrelin in dietary-induced obesity in mice: reversal upon weight loss. Int J Obes Relat Metab Disord 28:879–885
9. **Bresciani E, Rapetti D, Dona F, Bulgarelli I, Tamiazzo L, Locatelli V, Torsello A** 2006 Obestatin inhibits feeding but does not modulate GH and corticosterone secretion in the rat. J Endocrinol Invest 29:RC16–RC18
10. **Holst B, Egerod KL, Schild E, Vickers SP, Cheetham S, Gerlach LO, Storjohann L, Stidsen CE, Jones R, Beck-Sickinger AG, Schwartz TW,** GPR39 signaling is stimulated by zinc ions but not by obestatin. Endocrinology, in press
11. **Gourcerol G, Million M, Adelson DW, Wang Y, Wang L, Rivier J, St. Pierre DH, Tache Y** 2006 Lack of interaction between peripheral injection of CCK and obestatin in the regulation of gastric satiety signaling in rodents. Peptides 27:2811–2819
12. **Nogueiras R, Pfluger P, Tovar S, Myrtha A, Mitchell S, Morris A, Perez-Tilve D, Vazquez MJ, Wiedmer P, Castaneda TR, Dimarchi R, Tschop M, Schurmann A, Joost HG, Williams LM, Langhans W, Dieguez C,** Effects of obestatin on energy balance and growth hormone secretion in rodents. Endocrinology, in press
13. **Seoane LM, Al-Massadi O, Pazos Y, Pagotto U, Casanueva FF** 2006 Central obestatin administration does not modify either spontaneous or ghrelin-induced food intake in rats. J Endocrinol Invest 29:RC13–RC15
14. **McKee KK, Tan CP, Palyha OC, Liu J, Feighner SD, Hreniuk DL, Smith RG, Howard AD, Van der Ploeg LH** 1997 Cloning and characterization of two human G protein-coupled receptor genes (GPR38 and GPR39) related to the growth hormone secretagogue and neurotensin receptors. Genomics 46:426–434
15. **Holst B, Holliday ND, Bach A, Elling CE, Cox HM, Schwartz TW** 2004 Common structural basis for constitutive activity of the ghrelin receptor family. J Biol Chem 279:53806–53817
16. **Nogueiras R, Tschop M** 2005 Biomedicine. Separation of conjoined hormones yields appetite rivals. Science 310:985–986
17. **Moechars D, Depoortere I, Moreaux B, de Smet B, Goris I, Hoskens L, Daneels G, Kass S, Ver Donck L, Peeters T, Coulie B** 2006 Altered Gastrointestinal and metabolic function in the GPR39-obestatin receptor-knockout mouse. Gastroenterology 131:1131–1141
18. **Pan W, Tu H, Kastin AJ** 2006 Differential BBB interactions of three ingestive peptides: obestatin, ghrelin, and adiponectin. Peptides 27:911–916
19. **Szentirmai E, Krueger JM** 2006 Obestatin alters sleep in rats. Neurosci Lett 404:222–226
20. **Samson WK, White MM, Price C, Ferguson AV,** Obestatin acts in brain to inhibit thirst. Am J Physiol Regul Integr Comp Physiol, in press

Endocrinology **is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.**