Reduced Intestinal Absorption of Dipeptides via PepT1 in Mice with Diet-induced Obesity Is Associated with Leptin Receptor Down-regulation*

Received for publication, July 21, 2008, and in revised form, December 26, 2008 Published, JBC Papers in Press, January 14, 2009, DOI 10.1074/jbc.M805564200

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Leptin is a major determinant of energy homeostasis, acting both centrally and in the gastrointestinal tract. We previously reported that acute leptin treatment enhances the absorption of di- and tripeptides via the proton-dependent PepT1 transporter. In this study, we investigated the long term effect of leptin on PepT1 levels and activity in Caco2 cell monolayers in vitro. We then assessed the significance of the regulation of PepT1 in vivo in a model of diet-induced obesity. We demonstrated that 1) leptin regulated PepT1 at the transcriptional level, via the MAPK pathway, and at the translational level, via ribosomal protein S6 activation, in Caco2 cells and 2) this activation was systematically followed by a time- and concentration-dependent loss of leptin action reflecting desensitization. Deciphering this desensitization, we demonstrated that leptin induced a down-regulation of its own receptor protein and mRNA expression. More importantly, we showed, in mice with diet-induced obesity, that a 4-week hypercaloric diet resulted in a 46% decrease in PepT1-specific transport, because of a 30% decrease in PepT1 protein and a 50% decrease in PepT1 mRNA levels. As shown in Caco2 cells, these changes in PepT1 were supported by a parallel 2-fold decrease in leptin receptor expression in mice. Taken together, these results indicate that during induction of obesity, leptin resistance may also occur peripherally in the gastrointestinal tract, disrupting the absorption of oligopeptides and peptidomimetic drugs.

Leptin, the ob gene product, was first described as an adipocyte-derived hormone involved in fat and energy storage (1). Subsequent studies have shown that other tissues, such as the placenta, brain, bone marrow, and stomach produce leptin (2). This hormone produced by multiple sites is now thought to have pleiotropic functions, controlling not only food intake, but also immunity, the autonomic nervous system, or tissue remodeling and growth (reviewed in Ref. 3). In addition, several lines of evidence indicate that leptin is closely associated with intestinal functions, with potential indirect effects on energy balance. Indeed, leptin can be secreted by the gastric mucosa and is rapidly released into the intestine following the ingestion of a meal as an active protein, which may be free or bound to its receptor (4–7). Furthermore, leptin receptors are found on both the apical and basolateral sides of the enterocyte, facilitating the action of both adipocyte-derived leptin (on the basolateral side) and gastric leptin (on the apical side) (8–10). In this view, leptin has been shown to regulate the secretion of glucagon-like peptide 1 and cholecystokinin by enteroendocrine cells (6, 11) and to induce mucin secretion in the large intestine (12).

Leptin directly modulates nutrient absorption by decreasing carbohydrate absorption (via its action on the Na+/glucose cotransporter 1) and cholesterol absorption (13–15), enhancing butyrate uptake via its action on the CD147-monocarboxylate transporter 1 complex (16), and fatty acid uptake and transport by triggering the expression of intestinal fatty acid-binding protein (17).

In their studies of the role of leptin in the intestinal absorption of proteins and peptides, Kiely et al. (18) showed that the activity of the jejunal aminopeptidase and dipeptidylpeptidase IV, cleaving mono- and dipeptides, respectively, were lower in leptin-deficient mice than in wild-type mice. The relationship between leptin and PepT1 (H+−coupled peptide cotransporter 1), which transports most of the di- and tripeptides in the intestine, together with peptidomimetic drugs, has been the matter of studies. Gastric leptin has been shown to increase PepT1 activity within minutes by recruiting the preformed intracellular pool of the transporter to the brush border of the enterocytes, without modifying PepT1 mRNA levels (8). Interestingly, we and others have reported that leptin is capable of increasing the mRNA levels for this transporter, thereby reconstituting the pool of PepT1 after long term challenge in vitro and in vivo (19, 20). Building on these findings, this study was designed to investigate the regulation of PepT1 in a model of diet-induced obesity in mice characterized by progressive long term hyperleptinemia. It has been suggested that central desensitization to leptin is associated with obesity in this model. However, it was unknown whether such desensitiz-
zation also occurred in the small intestine. We found that Pept1 regulation was dependent on the duration of leptin treatment and diet and investigated the possible mechanisms underlying this phenomenon.

**EXPERIMENTAL PROCEDURES**

**Cell Culture**—Caco2 cells were cultured in Dulbecco’s modified Eagles medium (Invitrogen, Cergy Pontoise, France) supplemented with 20% fetal bovine serum (Invitrogen), 1% non-essential amino acids, and 1% penicillin/streptomycin in an environment containing 5% CO₂ with 95% humidity, at 37 °C. The cells were seeded on Costar Transwell® membrane inserts with 0.4-μm pores (Corning, NY) at a density of 5 × 10⁶ cells/cm². The experiments were conducted on the 17th day of culture, after treatment in both the apical and basal sides with leptin (R & D Systems, Minneapolis, MN) and/or with one of the mitogen-activated protein kinases (MAPK)² inhibitors U0126 (Cayman Chemicals, SPI-BIO, Montigny le Bretonneux, France) and PD98059 (Sigma-Aldrich, Saint Quentin Fallavier, France) or the mTOR (mammalian target of rapamycin) inhibitor rapamycin (Cayman Chemicals).

**Animals**—The experiments were conducted in male wild-type C57BL/6J mice (Janvier, Le Genest Saint Isle, France). The animals were housed in a room maintained at 21 °C, with 12-h light/12-h dark cycles and free access to water (accreditation number A92-01901). They were fed with standard laboratory chow (SC, control mice) (A04 biscuits; UAR, Villemoison, France) or a high fat diet (referred to as the hypercaloric (HC) diet; purchased from SAFE, Augy, France). The standard chow diet provides 2,820 kcal/kg of food and contains 3% fat (270 kcal/kg, accounting for 9.6% of the kilocalories), 48% complex carbohydrates (1,910 kcal/kg, 67.7% kcal, primarily starch), and 16% protein (640 kcal/kg, 22.7% kcal). The HC diet provides 5,320 kcal/kg and includes 36% fat (3,220 kcal/kg, 60.5% kcal, primarily lard), 18% protein (700 kcal/kg, 13.2% kcal). Actual food consumption was measured for both diets. All of the experiments were performed in accordance with European Committee Standards concerning the care and use of laboratory animals and were approved by the head of the staff responsible for laboratory animal care.

**Pept1 Activity in Caco2 Cells**—Pept1 activity was assessed by following the transport of cephalixin (Sigma-Aldrich), a specific Pept1 substrate, was monitored in the ex vivo jejunal loop model. Briefly, a 6-cm segment of jejunum was filled with 100 μl/cm Krebs modified buffer, pH 6, containing [³H]Gly-Sar (1 μmol/liter [³H]Gly-Sar Isobio, Fleurus, Belgium; specific activity, 0.5 Ci/mmol), 20 μmol/liter Gly-Sar (Sigma-Aldrich), and 500 mg/liter phenol red, to assess paracellular permeability. The segment was placed in a 37 °C thermostat-controlled bath of Krebs modified buffer at pH 7.4, through which a 95:5 mixture of O₂:CO₂ was continually bubbled. The samples were withdrawn from the bath at t = 5, 10, 15, 20, 25, and 30 min, and radioactivity was measured with a β counter. Apparent permeability to Gly-Sar was estimated as follows: P_app = (dQ/dt)(V/Q), where V is the volume of the bath, A is the area of the loop, Q₀ is the total amount of radiolabeled Gly-Sar introduced into the loop, and dQ/dt is the flux across the intestinal loop.

**Protein Extraction**—All of the procedures were carried out at 4 °C to inhibit proteolysis. For total protein extraction, Caco2 cells or samples scraped from the jejunum were homogenized in TEN'T® lysis buffer (containing 10 mM Tris-HCl, pH 7.4, 5 mM EDTA, 126 mM NaCl, 1% Triton X-100 (v/v), 0.1% SDS (v/v), and protease inhibitors) and incubated for 15 min. The homogenates were then centrifuged at 12,000 × g for 20 min. This supernatant corresponded to a total protein extract. For the study of protein phosphorylation, the cells were homogenized in lysis buffer (containing 90 mM NaCl, 50 mM Tris-HCl, pH 7.5, 5 mM EDTA, 1% Triton X-100 (v/v), protease inhibitors, 30 mM sodium pyrophosphate, 50 mM sodium fluoride, and 2 mM sodium orthovanadate as phosphatase inhibitors) and incubated for 30 min. The solution was then centrifuged at 12,000 × g for 15 min. The phosphorylated proteins were present in the supernatant.

**Western Blot Analysis**—The proteins (20–25 μg) were separated by SDS-PAGE in gels containing 8–12% acrylamide. The proteins were transferred to nitrocellulose membranes and subjected to immunoblotting. The dilutions of primary antibodies used were: 1:1000 for Pept1 (gift from Dr Merlin for in vitro studies or from Prof. Kapel for in vivo studies), 1:100 for Ob-R (H-300, Santa Cruz Biotechnology, Santa Cruz, CA), 1:5000 for phosphorylated signal transducer and activator of transcription (STAT) 3 (Tyr694®) and STAT5 (Tyr705®) (Cell Signaling Technology, Ozyme, Saint-Quentin-en-Yvelines, France), 1:1000 for total STAT3 and STAT5 (C-20 and C-17; Santa Cruz Biotechnology), 1:1000 for phosphorylated p44/42 MAPK (Th182/Y204®) (ERK1/2) (Cell Signaling Technology), and total ERK (K-23; Santa Cruz Biotechnology), 1:1000 for beta-actin (clone AC74; Sigma-Aldrich). Peroxidase-conjugated secondary antibodies (Dako, Glostrup, Denmark) were used at a dilution of 1:10,000, and the membranes were probed with ECL (PerkinElmer Life Sciences). The intensity of the bands was quantified with Scion Image (National Institutes of Health, Scion Corporation).

² The abbreviations used are: MAPK, mitogen-activated protein kinases; Gly-Sar, glycy1-sarcosine; HC, hypercaloric chow; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; STAT, signal transducers and activators of transcription; ERK, extracellular signal-regulated kinases; SOCS, suppressor of cytokine signaling.
Bethesda, MD). For the study of the expression of phosphorylated protein, the membranes were blotted with antibodies specific for phospho-STATs or phospho-ERK and then scraped and rebotted with antibodies recognizing total STATs or total ERK protein.

**Real Time PCR Analysis**—Total RNA was isolated by the guanidine thiocyanate method, with RNAble (Eurobio, Les Ulis, France), used according to the manufacturer’s instructions. The first strand cDNA was synthesized by reverse transcription from 5 μg of total RNA, with SuperScript II reverse transcriptase (Invitrogen).

We quantified cDNA with the Light Cycler system (Roche Applied Science), used according to the manufacturers instructions. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) or S14 was used as a housekeeping gene. The primers were designed with Primer3 software (Table 1).

**Statistical Analysis**—All of the values are expressed as the means ± S.E. Mann-Whitney tests (or Student’s t tests, as appropriate) were used to compare pairs of means, and Kruskal–Wallis tests were used to compare groups of more than two means. Statistical analysis was performed with GraphPad Prism (GraphPad software, San Diego, CA). The values of p < 0.05 were considered statistically significant for all analyses.

**RESULTS**

**Leptin Induces a Time- and Concentration-dependent Regulation of PepT1 Levels and Activity**—Challenging Caco2 cells with 0.2 nM leptin (corresponding to a normoleptinemia) for 7 days induced a significant 2.3-fold increase in cephalexin translocation across the Caco2 monolayer, consistent with an increase in PepT1 activity (Fig. 1A). The increase in PepT1 activity was associated with a parallel 3.2-fold increase in protein levels (Fig. 1B). Surprisingly, in Caco2 cells treated for 7 days with 1 nM (corresponding to hyperleptinemia), the increase in PepT1 protein levels and activity was no longer observed, indicating resistance to the administered leptin.

We investigated this phenomenon further by carrying out a time course study of the effect of leptin. As expected, the lower concentration (0.2 nM) of leptin, which increased PepT1 activity and total protein levels after a 7-day challenge, increased PepT1 protein levels in a time-dependent manner (Fig. 2). Indeed, 0.2 nM leptin induced a gradual increase in PepT1 levels, which peaked after 7 days of treatment. Interestingly, the higher concentration (1 nM) of leptin rapidly induced the expression of total PepT1 protein (2-fold increase) at 24 h, but this effect was transient and completely disappeared after 72-h treatment, reflecting desensitization.

We then investigated whether the change in PepT1 protein levels could be explained by changes in mRNA levels. For both

**TABLE 1**

| Gene   | Access number | Primer sequences (5' → 3') | Size |
|--------|---------------|-----------------------------|------|
| hPepT1 | NM_005073     | F-GTTGCGGACCTATGGTCTCT      | 149  |
| hGPDHD | NM_002046     | R-CCGCCTGTTGCTGTTAGT        | 112  |
| hObRa  | NM_002303     | F-TCACGACAAAGATGAAAAAC      | 119  |
| hObRb  | NM_001003679  | R-TCCTTGATAAAGATCTCCCAAC    | 137  |
| hSOCS3 | NM_003955     | F-CAAGCGACGAGACTCTTATT      | 137  |
| hPTP1B | NM_002827     | R-AACTCTGCTGTTGACTTATT      | 126  |
| mPepT1 | NM_053079     | F-CTGTATGCTGGGACTTTATT      | 66   |
| mObRb  | NM_146146     | R-GGCTTGATTCCTCCTGTAAGC     | 118  |
| mS14   | NM_020600     | F-CAGCGACGAGAGACTCTTATT     | 69   |

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**FIGURE 1. Effects of chronic leptin treatment on PepT1 activity and expression in vitro.** Caco2 cells were treated daily for 7 days with 0.2 nM or 1 nM leptin. A, PepT1 activity in leptin-treated Caco2 cells. The apparent permeability coefficient of cephalexin across Transwell® membranes was measured over a period of 30 min (n = 8–15; Kruskal-Wallis test; *, p < 0.05 versus control (CTL)). All of the data are the means ± S.E. B, densitometric analysis of PepT1 protein levels normalized on the basis of β-actin levels in leptin-treated Caco2 cells (n = 6–8; Kruskal-Wallis test; **, p < 0.05 versus control). All of the data are the means ± S.E.

**FIGURE 2. The time-dependent effect of leptin treatment on PepT1 total protein levels.** Densitometric analysis of PepT1 protein levels normalized as a function of β-actin levels in leptin-treated Caco2 cells. Caco2 cells were treated for 24, 48, or 72 h with 0.2 or 1 nM leptin (n = 4; Kruskal-Wallis test; *, p < 0.05 versus control (CTL); #, p < 0.05 versus 24 h, 1 nM leptin-treated cells). All of the data are the means ± S.E.
concentrations tested, leptin up-regulated PepT1 mRNA levels \((1.7 \text{ and } 1.4 \text{ for } 0.2 \text{ and } 1 \text{ nm leptin, respectively; Fig. 3A})\), but this effect was only transient, with PepT1 mRNA levels returning to basal levels after treatment. More importantly, we found that mRNA levels peaked after only 6 h for the 1 nm treatment, whereas the peak was reached later (48 h) with the 0.2 nm treatment. Thus, the time at which mRNA levels peaked also appeared to depend on leptin concentration. Indeed, with a 0.5 nm leptin challenge, peak mRNA levels were reached at 24 h of treatment, and there was an inverse correlation between the time taken to reach peak PepT1 levels and leptin concentration (Fig. 3B).

Leptin Increases PepT1 Protein Levels by Enhancing Its Translation—We then investigated the apparent discrepancy between the sustained levels of PepT1 protein at 7 days with the 0.2 nm treatment and the peak in mRNA levels observed after only 48 h of treatment. We hypothesized that an enhancement of translation might account for this pattern. We therefore analyzed phosphorylation of the ribosomal protein S6, which is involved in the activation of translation, in a time course experiment. Densitometric analysis of the ribosomal protein S6 showed that treatment with 0.2 nm leptin was associated with a significant increase in S6 phosphorylation at 24 h treatment, with higher levels of phosphorylation persisting for a further 7 days (Fig. 4A). By contrast, when cells were treated with 1 nm leptin, ribosomal protein S6 phosphorylation occurred earlier and was transient, peaking after 24 h of treatment and returning to basal level thereafter. Fig. 4B showed that the activation of S6 by leptin was, at least in part, mediated by the MAPK pathway as the inhibitor U0126 reversed the action of leptin on S6 phos-
Leptin Activates the Production of PepT1 mRNA through the ERK1/2 Pathway, but Not by STAT3 or STAT5 Activation—We then focused on intracellular events that might account for the effect of leptin on PepT1 mRNA levels. Interestingly, no phosphorylation of either STAT3 or STAT5 was observed under our conditions. However, a rapid and transient activation of extracellular signal-regulated kinases 1/2 (ERK1/2) occurred after 0.2 nM leptin treatment, corresponding to the phosphorylation of the two immunoreactive bands at 42 and 44 kDa (Fig. 5A). In addition, the effect of leptin was partially reversed by the MAPK/ERK1/2 kinase (MEK1/2) inhibitors U0126 and PD98059 (Fig. 5B and data not shown).

DISCUSSION

We provide here the first demonstration that the induction of obesity provokes a time-dependent loss of responsiveness in intestinal target genes. Indeed, diet-induced obesity is associated with a dramatic decrease in the PepT1-mediated transport of oligopeptides in the intestine, related to down-regulation of leptin receptor expression.

As shown in our previous study, leptin-deficient ob/ob mice display reduced levels of PepT1 activity and expression; furthermore, hyperleptinemia induced for 7 days in rats, associ-
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![Graph A](image)

**FIGURE 6. Effect of leptin challenge on Ob-R protein and mRNA levels.** A, densitometric analysis of Ob-Ra protein levels normalized with respect to β-actin levels (n = 5–10; Kruskal-Wallis test; *, p < 0.05 versus control (CTL); **, p < 0.01 versus control). All of the data are the means ± S.E. B and C, relative quantification of Ob-Ra or Ob-Rb mRNA levels normalized as a function of GAPDH mRNA levels (n = 3–11; Kruskal-Wallis test; *, p < 0.05 versus control; **, p < 0.01 versus control). All of the data are means ± S.E.

**TABLE 2**

|                      | Standard chow-fed control mice (n = 6) | Hypercaloric diet-fed mice (n = 6) |
|----------------------|----------------------------------------|-----------------------------------|
| Plasma glucose (mmol/liter) | 9.76 ± 0.14                            | 13.20 ± 0.82*                     |
| Plasma insulin (ng/ml)      | 0.31 ± 0.04                            | 0.71 ± 0.15*                      |
| Plasma leptin (ng/ml)       | 0.80 ± 0.17                            | 1.62 ± 0.19*                      |
| 4-week weight gain (g)      | 2.63 ± 0.20                            | 4.20 ± 0.21*                      |
| Daily food intake (g)       | 4.51 ± 0.50                            | 3.86 ± 0.41*                      |
| Daily caloric intake (kcal) | 12.69 ± 1.41                           | 20.53 ± 2.18*                     |
| Daily protein intake (g)    | 0.72 ± 0.08                            | 0.69 ± 0.08                       |

*p < 0.05 versus control mice.

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Alternatively, leptin may contribute to the intestinal regulation of the gene encoding its receptor. Ob-R down-regulation was evident in the animals fed the HC diet for 4 weeks, in which plasma leptin concentration increased steadily. A shorter duration of hyperleptinemia and/or the difference in the model may explain why such a regulation was not observed in the 7-day leptin-treated rats. A similar pattern of regulation was also observed following prolonged leptin treatment in Caco2 cells. The close association between the levels of Ob-R and PepT1 in both Caco2 cells and mouse jejunum suggests that the regulation of PepT1 levels depends on receptor abundance and the resulting level of signaling. Indeed, treatment in vitro with 0.2 or 1 nM leptin rapidly induced an increase in Ob-R expression and may induce PepT1 expression. However, prolonged leptin treatment in vitro or for four weeks of the HC diet in vivo may down-regulate expression of the receptor, leading to a net decrease in leptin signaling within enterocytes and the abolition of leptin effects on PepT1. Such a regulation has already been described in the central nervous system. Consistent with this, some authors showed, in neuroblastoma cells, that leptin down-regulates its own receptors (22) and that hypothalamic leptin receptors were down-regulated in hyperleptinemic rodents, leading to leptin resistance (23, 24).

We found that leptin treatment in vitro induced a transient increase in Ob-R and PepT1 mRNA levels, followed by a normalization of PepT1 levels or a larger decrease in leptin receptor expression. The pattern of change in expression was clearly time- and concentration-dependent. Indeed, the time required to reach peak PepT1 mRNA levels was inversely correlated with leptin concentration, with higher concentrations resulting in faster effects on PepT1 transcription.

A few studies have focused on the activation of PepT1 transcription. For example, the transcriptional factors Sp1 and peroxisome proliferator-activated receptor α have been shown to be involved in PepT1 induction (25, 26). Similarly, the authors of these studies demonstrated that PepT1 may also be induced by caudal-related homeobox 2 (27). Nduati et al. (20) identified a link between the induction of PepT1 by caudal-related homeobox 2 and leptin, because leptin was shown to increase cAMP levels, consequently activating caudal-related homeobox 2. We investigated the role of the MAPK pathway in PepT1 activation in our model. Leptin has been shown to activate ERK1/2 in the hypothalamus (28, 29) and many other tissues, including the colon and intestinal cells (12, 30, 31) and STC-1 enteroendocrine cells (6). Gong et al. (32)
We investigated the basis of the sustained effect of leptin on PepT1 protein levels, whereas the effect on mRNA is only transient by studying the action of leptin on the ribosomal protein S6, which has been implicated in mRNA translation.

It has been shown that S6 and its kinase (ribosomal S6 kinase) are phosphorylated via the MAPK pathway (32, 35, 36), which we demonstrated to be activated in our in vitro model. In Caco2 cells, we confirmed the leptin-stimulated phosphorylation of S6 via the ERK1/2 pathway using U0126. Moreover, we showed that the PepT1 sustained protein expression is induced by the activation of S6 by leptin.

Taken together, these data show, in vitro, that leptin regulates PepT1 levels and activity at the transcriptional level, via the MAPK pathway, and at the translational level, via ribosomal protein S6 activation. We have also shown, in vivo, that PepT1 levels and activity are downregulated in hyperleptinemic states of leptin resistance, such as obesity. Thus, obesity may be associated with decreases in oligopeptide absorption and the bioavailability of peptidomimetic drugs. These findings are of major interest because protein intake can induce satiety. Protein-induced satiety is supported by the aminostatic hypothesis developed by Melkoff et al. (37) in 1956 and has since been clearly demonstrated (38). Consistent with this hypothesis, Darcel et al. (39) showed that the activation of the vagal afferents known to induce satiety depends on PepT1. Further studies are now required to investigate the potential effects of PepT1 regulation on food intake in obesity.

Acknowledgment—We thank Lisa McErlean for careful reading of the manuscript.

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