In the intestine, butyrate constitutes the major energy fuel for colonocytes. However, little is known about the transport of butyrate and its regulation in the intestine. In this study we demonstrate that the monocarboxylate transporter (MCT-1) is apically polarized in model human intestinal epithelia and is involved in butyrate uptake by Caco2-BBE cell monolayers. The butyrate uptake by Caco2-BBE cell monolayers displayed conventional Michaelis-Menten kinetics and was found to be pH-dependent, Na\(^+\)-independent, 4,4\(^{-}\)-diisothiocyanatostilbene-2,2\(^{-}\}-disulfonic acid-inhibitive, and inhibited by the monocarboxylate transporter inhibitor α-cyano-4-hydroxycinnamate and by an excess of unlabeled butyrate. We show that MCT-1 associates with CD147 at the apical plasma membrane in Caco2-BBE cell monolayers. Using antisense CD147, we demonstrate that the association of CD147 with MCT-1 is critical for the butyrate transport activity. Interestingly, we show for the first time hormonal regulation of CD147/MCT-1 mediated butyrate uptake. Specifically, luminal leptin significantly up-regulates MCT-1 mediated butyrate uptake by increasing its maximal velocity (V\(_{\text{max}}\)) without any modification in the apparent Michaelis-Menten constant (K\(_{\text{m}}\)). Finally, we show that luminal leptin up-regulates butyrate uptake in Caco2-BBE monolayers by two distinct actions: (i) increase of the intracellular pool of MCT-1 protein without affecting CD147 expression and (ii) translocation of CD147/MCT-1 to the apical plasma membrane of Caco2-BBE cell monolayers.
colon is in the low nanomolar range. We suggest that this leptin is coming from the gastric gland because no leptin staining was detected from the epithelial cells along normal small and large intestine. Interestingly, under inflammatory states, we have detected a strong leptin staining from colonic epithelial cells and the luminal leptin concentration increased significantly (10 times greater compared with noninflamed tissues). During inflammation the luminal colonic leptin concentration is likely to be the addition of the leptin produced by the gastric gland and the leptin produced by the colonic epithelial cells. These results suggest that luminal leptin could have an important physiological and/or pathological role in the colon. Indeed, the different leptin receptor isoforms including the functional long isoform (Ob-Rb) have been detected in the rat intestine from duodenum to colon and in the model intestinal cell line Caco2 (36-40). The demonstration of leptin receptor in intestinal tract has initiated several investigations on the possible role of leptin in the digestive physiology as absorption and secretion. Evidence has been provided that leptin can regulate intestinal triglyceride transport by inhibiting apolipoprotein AIV expression via activation of a jejunal leptin receptor in mice (38). Similarly, in rat, intravenous leptin infusion attenuates the increase in synthesis and secretion of apoAIV induced by intraduodenal infusion of lipids (39). In addition, leptin administered to the basolateral side of Caco2 cells inhibits the triglyceride secretion, the biosynthesis of apoB-100 and apoB-48, as well as the output of chylomicron and low density lipoproteins (40). More recently, we have reported that luminal

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leptin improves the transport of oligopeptides across the intestinal epithelium through the H\(^+\)-dependent, di- and tripeptide transporter PepT-1 \textit{in vitro} and \textit{in vivo} (36). Together, the results clearly demonstrate that leptin is a key hormone of the intestinal tract. This study aims to investigate the regulation of butyrate uptake by luminal leptin using the model human intestinal epithelial cell line Caco2-BBE.

**MATERIALS AND METHODS**

**Cell Culture and Treatments**—Caco2-BBE (41) cells (between passages 30 and 50) were grown in high glucose Dulbecco’s Vogt modified Eagle's medium (DMEM, Invitrogen) supplemented with 14 mmol/liter NaHCO\(_3\) and 10% newborn calf serum. Cells were kept at 37 °C in 5% CO\(_2\) and 90% humidity, and medium was changed every day. Monolayers were subcultured every 7 days by trypsinization with 0.1% trypsin-EDTA during 1 h at 37 °C. Subconfluent Caco2-BBE monolayers on filters were transfected with CD147 construct (Antisense CD147), vector alone (Vector) using the Lipofectin technique or nontransfected Caco2-BBE monolayers (CTRL). Butyrate uptake was determined 2 days after transfection. Caco2-BBE monolayers were incubated at 37 °C for 5 min with varying concentrations of \([^{14}\text{C}]\) butyrate (specific activity, 16 mCi/mmol) added to the apical reservoir. The pH of the medium was 6.4 (apical reservoir) and 7.5 (basolateral reservoir). Thereafter, medium was aspirated, cells were rapidly washed twice with ice-cold HBSS-HEPES medium, and amount of \([^{14}\text{C}]\) butyrate accumulated by Caco2-BBE monolayers was determined by liquid scintillation counting. Values represent means ± S.E. of three experiments performed in triplicate. *, p < 0.05 versus control; ##, p < 0.01 versus vector.

**Cross-linking and Immunoprecipitation**—Cross-linking was carried out using the bifunctional stilbene disulfonate (DIDS; Sigma), as described previously (20). Cells seeded on six-well plates were washed twice with PBS and incubated with 100 μM DIDS during 1 h at 37 °C. The cells were then washed in ice-cold PBS and lysed with the lysis buffer (1% Triton X-100 in 20 mM Tris, pH 5.0, 50 mM NaCl, 5 mM EDTA, 0.2% bovine serum albumin (BSA), and protease inhibitors). The resulting supernatants were immunoprecipitated with the appropriate amount of specific antibody (0.05 μg/ml mouse anti-human CD147 (Cymbus Biotechnology Ltd, Chandlers Ford, UK); 0.05 μg/ml of the polyclonal rabbit anti-human MCT-1 (Alpha Diagnostic, San Antonio, TX) was added and gently rocked overnight at 4 °C. Subsequently, 50 μl of protein G suspension was added to the mixture and incubated overnight at 4 °C. The complexes were collected by centrifugation at 12,000 × g for 1 min by microcentrifuge. The beads were washed one time with buffer 1 (1% Triton X-100 in 20 mM Tris, pH 5.0, 50 mM NaCl, 5 mM EDTA, 0.2% BSA) and two times with buffer 2 (20 mM Tris-HCl, pH 8.0). The protein solution was then boiled 5 min at 100 °C in Laemmli buffer and subjected to SDS-PAGE and transferred at 4 °C to nitrocellulose membranes. The blots were blocked 1 h with 5% nonfat.
Butyrate uptake was determined by liquid scintillation counting. Values represent means ± S.E. of three experiments in triplicate. **, $p < 0.01$ versus control.

B, apical uptake of [14C]butyrate in Caco2-BBE cell monolayers treated with varying concentrations of luminal leptin for 24 h. Caco2-BBE cell monolayers were pre-incubated with various concentrations of luminal leptin (0.1–100 nM) or vehicle for 24 h. Afterward, they were incubated with 20 μM [14C]butyrate for 1 h in HBSS-MES (pH 6.4) in apical compartment. The pH was 7.5 in the basolateral compartment (HBSS-HEPES). Thereafter, medium was aspirated, cells were rapidly washed twice with ice-cold HBSS-HEPES medium, and the amount of butyrate accumulated by Caco2-BBE cell monolayer radioactivity was determined by liquid scintillation counting. Values represent means ± S.E. of three experiments in triplicate. **, $p < 0.01$ versus control.

C, inhibitory effect of various compounds on the butyrate uptake by Caco2-BBE cell monolayers. Caco2-BBE cell monolayers were pre-incubated with 100 nM luminal leptin or vehicle for 24 h before transport was measured. Caco2-BBE monolayers were incubated for 1 h at 37 °C with 20 μM [14C]butyrate (specific activity, 16 mCi/mmol) alone (CTRL), with 1 mM CHC, 50 mM cold butyrate (Butyrate 25 mM) added to the apical reservoir. The pH of the medium was 6.4 (apical reservoir) and 7.5 (basolateral reservoir). Amount of butyrate accumulated by monolayer was then measured. Thereafter, medium was aspirated, cells were rapidly washed twice with 3 ml of ice-cold incubation medium, and radioactivity was determined by liquid scintillation counting. Each bar represents mean ± S.E. of three experiments in triplicate. **, $p < 0.01$ versus control; ###, $p < 0.001$ versus leptin alone.
Luminal Leptin Enhances Butyrate Uptake in Caco2-BBE Cells—Previous studies from Kirk et al. (18) demonstrated that CD147 is associated to MCT-1 in the plasma membrane, and this association was shown to be critical for the MCT-1 activity in heart cell line and in transfected cells. We next investigated whether there was an interaction between CD147 and MCT-1 in Caco2-BBE cells by using DIDS to cross-link the two proteins. After DIDS treatment of cells for 1 h, Western blot of the MCT-1 immunoprecipitated with mouse anti-CD147 antibody revealed the presence of 100-kDa immunoreactive band corresponding to the expected size of MCT-1/CD147 complex (Fig. 2A, lanes 7 and 8). Similarly, Western blotting of CD147 immunoprecipitated with a rabbit anti-MCT-1 revealed an identical 100-kDa immune complex (Fig. 2A, lanes 3 and 4). When cell lysates were not immunoprecipitated (lanes 1, 2, 5, and 6), the presence of ~40–45 kDa (lanes 1 and 2) and ~50–55 kDa (lanes 5 and 6) corresponding to MCT-1 and CD147, respectively, were detected. These results demonstrate that CD147 and MCT-1 are associated to the Caco2-BBE cell membranes. To study the functional role of CD147 in the butyrate uptake, Caco2-BBE monolayers were transfected with vector alone, antisense CD147 cDNA (full-length) inserted into pTarget/CMC vector. The uptake of butyrate was determined 48 h after transfection. As shown in Fig. 2B, the antisense CD147 inhibited butyrate uptake by ~25% when compared with the vector alone or nontransfected cells. This inhibition is significant, given that the transfection efficiency in Caco2-BBE is not 100%. These results confirm the functional role of CD147 in the butyrate uptake by Caco2-BBE cell monolayers.

Luminal Leptin Increases Butyrate Uptake in Caco2-BBE Monolayers—To investigate the effect of luminal leptin on butyrate uptake, Caco2-BBE cells were pre-incubated with 10 nM leptin for 1–24 h. Although 10 nM leptin added to the apical compartment of the Caco2-BBE monolayers did not increase
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Fig. 5. A, effect of leptin on CD147 and MCT-1 protein expression. Caco2-BBE cell monolayers were pre-incubated with 10 nM luminal leptin or vehicle for various times (0, 4, 8, 12, and 24 h) and subjected to total protein extraction. Total cell protein (40 μg/lane) was subjected to 4–20% SDS-polyacrylamide gel electrophoresis, followed by transfer to nitrocellulose membrane. The blot was immunostained with a mouse anti-CD147 (Anti-CD147) or with a rabbit anti-MCT-1 (Anti-MCT-1). B. scanning densitometry of CD147 and MCT-1 proteins. The changes are expressed as mean ± S.E. of four analyses. The levels of CD147 and MCT-1 at each incubation time were calculated in relation to the vehicle-treated cells, and the value of each time control was arbitrarily set to 1. **, p < 0.01 versus vehicle. C. luminal leptin increases MCT-1 mRNA expression. Caco2-BBE cell monolayers were pre-incubated with 10 nM luminal leptin or vehicle (CTRL) for 4 h. Northern blot analysis was performed on total RNA (20 μg/lane) of Caco2-BBE cells. Using a MCT-1 probe, 3.3-kb hybridizing signal was present in Caco2-BBE cells. The same blot was stripped and reprobed with the glyceraldehyde-3-phosphate dehydrogenase (GAPDH) cDNA.

Butyrate uptake after 1–6 h, it did significantly increase butyrate uptake after 12 and 24 h (p < 0.01): 20 and 25% increase, respectively (without luminal leptin for 12 h: 439 ± 18 versus 525.5 ± 14 with 10 nM luminal leptin for 12 h; without luminal leptin for 24 h: 513 ± 33 versus 640 ± 25 pmol/cm²/h with 10 nM luminal leptin) (Fig. 3A). The effect of luminal leptin on butyrate uptake is specific to leptin, because an unrelated peptide, interleukin-8, did not induce any change in butyrate uptake in Caco2-BBE monolayers (data not shown). In addition, the effect of luminal leptin on butyrate uptake was concentration-dependent and reached a plateau at 10 nM (without luminal leptin: 231 ± 87; 10 nM luminal leptin: 367 ± 21; 100 nM luminal leptin: 370 ± 11 pmol/cm²/h) (Fig. 3B). Moreover, the MCT inhibitor, 1 μM CHC, reversed luminal leptin induced increase in butyrate uptake (507 ± 22 versus 203 ± 18 pmol/cm²/h) (Fig. 3C). Furthermore, the addition of an excess of butyrate (50 mM) to the apical compartment completely suppressed (98%) the leptin-induced increase in [14C]butyrate uptake (507 ± 22 versus 10 ± 1 pmol/cm²/h) (Fig. 3C). In addition, the presence of 100 μM DIDS or the absence of Na⁺ in the uptake solution did not affect the butyrate uptake induced by luminal leptin in Caco2-BBE monolayers.

To determine whether leptin may affect monocarboxylate uptake by modifying the intrinsic activity of the transporters, the effect of apical leptin on the kinetics of butyrate uptake was studied. Kinetic analysis of the data (Fig. 4) indicates that apical leptin treatment significantly increased the V_max (V_max(apical leptin) = 14.4 ± 1.28 μmol/cm²/h versus V_max(control) = 8.25 ± 1.75 μmol/cm²/h), but did not modify the K_m of the transporters (K_m(apical leptin) = 3.3 ± 0.21 versus K_m(control) = 2.65 ± 0.2 mM). These data demonstrate that leptin does not change the affinity of MCT-1 localized on the apical membrane of the Caco2-BBE cell monolayers.

Luminal Leptin Increases MCT-1 Expression but Does Not Affect the Expression of CD147—Western blot analysis was performed using mouse anti-MCT-1 or rabbit anti-CD147 antibody on total protein lysate from Caco2-BBE monolayers treated with leptin for various periods of time. The total amount of MCT-1 immunoreactive protein (~40–45 kDa), was not significant at 12 h, but was significant at 24 h after leptin treatment (Fig. 5A). In contrast, the total amount of CD147 immunoreactive protein (~50–55 kDa) was not increased after luminal leptin (Fig. 5A).

Luminal Leptin Increases MCT-1 mRNA Expression—mRNA levels of MCT-1 were analyzed by Northern blot in Caco2-BBE cells. Total RNA was obtained from untreated monolayers or monolayers treated with 10 nM luminal leptin for 4 h. Fig. 5B showed that MCT-1 mRNA (3.3 kb) levels were significantly increased (2-fold) in cells treated by leptin compared with controls. This increase was transient, as the mRNA levels returned to basal levels at 8 h (data not shown).

Luminal Leptin Induces the Translocation of MCT-1/CD147 to the Apical Plasma Membranes of Caco2-BBE Cell Monolayers—To visualize the outline of the monolayers, the actin was labeled with rhodamine phalloidin as described under “Materials and Methods.” The membrane localization of MCT-1 and CD147 was assessed in confluent Caco2-BBE cell monolayers. We examined the effect of luminal leptin treatment (10 nM for 24 h) on the membrane expression of MCT-1 and CD147 by using confocal immunofluorescence microscopy. The staining for the immunoreactive CD147 protein in control cells was localized mainly in the tight junction associated with a staining below the apical membrane (Fig. 6). After luminal leptin stimulation (10 nM for 24 h), the major localization of CD147 was steadily below the apical membrane, suggesting a translocation of CD147 to the apical plasma membrane of the cells (Fig. 6). The staining for MCT-1 protein was primarily localized in the apical membrane and in the cytoplasm just below the apical plasma membrane and no staining in the basolateral membranes (Fig. 6). The degree of expression of MCT-1 varied between cells, as judged by both the vertical xy image and the horizontal zx image (Fig. 6). After apical leptin treatment, the level of immunostaining for MCT-1 increased with a strong signal both in the apical membrane and in the cytoplasm compartment below the membrane (Fig. 6). Moreover, the number of positive cells for MCT-1 was increased, consistent with an
increase of the MCT-1 mRNA and MCT-1 protein after luminal leptin treatment.

To confirm that CD147 and MCT-1 are translocated to the plasma membrane after luminal leptin treatment, Caco2-BBE cell membranes were isolated from Caco2-BBE cells treated with 10 nM leptin for 24 h or without treatment. Western blot analysis was performed using these membrane cell lysates and probed with anti-MCT-1 (A) and CD147 (B) antibodies. As is apparent from Fig. 7, luminal leptin treatment for 24 h increased the amount of MCT-1 and CD147 proteins in the plasma membrane of Caco2-BBE cell monolayers. Together, these results demonstrate a translocation of both CD147 and MCT-1 to the apical plasma membranes of Caco2-BBE monolayers after luminal leptin treatment.

**DISCUSSION**

In this study, we demonstrate that MCT-1 is apically polarized in model human intestinal epithelia and is involved in the butyrate uptake by Caco2-BBE cell monolayers. The butyrate uptake by Caco2-BBE cell monolayers is pH-dependent, Na⁺-independent, DIDS-insensitive, and inhibited by the MCT inhibitor CHC and by an excess of unlabeled butyrate. Together, these results indicate that apical butyrate uptake by Caco2-BBE cell monolayers are mainly the result of a single carrier MCT-1 and are in agreement with previous studies (13). Caco2-
BBE at 15 days after plating exhibited partially small intestinal characteristics in HT29-C1.19A (data not shown), which exhibited colonocyte features. Thus, with respect to butyrate uptake studies, Caco2-BBE cells represent an appropriate cellular model.

In the present study, we bring important information to the field of MCT by providing the first evidence for its stimulation by a hormone. Indeed, luminal leptin significantly increased the maximal velocity ($V_{\text{max}}$) for butyrate uptake, whereas the apparent Michaelis-Menten constant ($K_m$) did not change. Moreover, the addition of an excess of butyrate or the use of the MCT inhibitor, CHC, suppressed the luminal leptin-induced increase in butyrate uptake. These results demonstrate that the increased of butyrate uptake induced by luminal leptin is mediated by the same transporter (MCT-1) involved in baseline conditions.

We show that MCT-1 and CD147 are localized to the apical plasma membrane in Caco2-BBE monolayers. Furthermore, we demonstrate that the CD147/MCT-1 association is critical for the butyrate transport activity. The inhibition of butyrate uptake with an antisense construct to CD147 transiently transfected into Caco2-BBE cell monolayers supports the requirement of CD147 in butyrate transport. CD147 protein is probably specifically interacting with MCT-1, because previous studies using MCT-1 antisense show similar inhibition (~35%) of butyrate uptake by Caco2 monolayers (13). These data are consistent with similar findings in murine heart plasma membrane and in cells co-transfected with CD147 and MCT-1 in which CD147 was reported to facilitate proper expression of MCT-1 at the cell surface, where they remained tightly associated (18–20). This interaction has potential significance for the regulation of MCT-1 activity. Proteins acting as a protein chaperone for other transporter have been described. For example, glycoporin associates with the anion exchanger AE1 (42, 43), CD98 that associates with amino acid transporters (44, 45), or CD36 that associates with the long chain fatty acid transporter (46). All these associations have been shown to be essential for the appropriate function of these transporters.

Interestingly, we show that luminal leptin increases the total amount of MCT-1 proteins, attributable to a relative increase in expression of MCT-1 mRNA, but did not change the total mRNA or protein level of CD147. Moreover, luminal leptin treatment induced an increase in the number of positive cell for MCT-1 at the cell surface, where they remained tightly associating. These data are consistent with similar findings in murine heart plasma membrane and in cells co-transfected with CD147 and MCT-1 in which CD147 was reported to facilitate proper expression of MCT-1 at the cell surface, where they remained tightly associated (18–20). This interaction has potential significance for the regulation of MCT-1 activity. Proteins acting as a protein chaperone for other transporters have been described. For example, glycoporin associates with the anion exchanger AE1 (42, 43), CD98 that associates with amino acid transporters (44, 45), or CD36 that associates with the long chain fatty acid transporter (46). All these associations have been shown to be essential for the appropriate function of these transporters.

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