Mechanisms underlying modulation of monocarboxylate transporter 1 (MCT1) by somatostatin in human intestinal epithelial cells

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Saksena S, Theegala S, Bansal N, Gill RK, Tyagi S, Alrefai WA, Ramaswamy K, Dudeja PK. Mechanisms underlying modulation of monocarboxylate transporter 1 (MCT1) by somatostatin in human intestinal epithelial cells. Am J Physiol Gastrointest Liver Physiol 297: G878–G885, 2009. First published August 27, 2009; doi:10.1152/ajpgi.00283.2009.—Somatostatin (SST), an important neuropeptide of the gastrointestinal tract has been shown to stimulate sodium chloride absorption and inhibit chloride secretion in the intestine. However, the effects of SST on luminal butyrate absorption in the human intestine have not been investigated. Earlier studies from our laboratory have shown that monocarboxylate transporter (MCT1) plays an important role in the transport of butyrate in the human intestine. The present studies were undertaken to examine the effects of SST on butyrate uptake utilizing postconfluent human intestinal epithelial Caco2 cells. Apical SST treatment of Caco-2 cells for 30–60 min significantly increased butyrate uptake in a dose-dependent manner with maximal increase at 50 nM (~60%, P < 0.05). SST receptor 2 agonist, seglitide, mimicked the effects of SST on butyrate uptake. SST-mediated stimulation of butyrate uptake involved the p38 MAP kinase-dependent pathway. Kinetic studies demonstrated that SST increased the maximal velocity (Vmax) of the transporter by approximately twofold without any change in apparent Michaelis-Menten constant (Km). The higher butyrate uptake in response to SST was associated with an increase in the apical membrane levels of MCT1 protein parallel to a decrease in the intracellular MCT1 pool. MCT1 has been shown to interact specifically with CD147 glycoprotein/chaperone to facilitate proper expression and function of MCT1 at the cell surface. SST significantly enhanced the membrane levels of CD147 as well as its association with MCT1. This association was completely abolished by the specific p38 MAP kinase inhibitor, SB203580. Our findings demonstrate that increased MCT1 association with CD147 at the apical membrane in response to SST is p38 MAP kinase dependent and underlies the stimulatory effects of SST on butyrate uptake.

butyrate absorption; human intestine; CD147; p38 MAPK

SHORT-CHAIN FATTY ACIDS (SCFAs), butyrate, propionate, and acetate are present at high concentrations in the colonic lumen and are produced by anaerobic bacterial fermentation of dietary fiber in the large bowel (43). Among these, butyrate plays a key role in colonic epithelial homeostasis and represents an important fuel for colonocytes (37). Butyrate is also known to stimulate colonic electroneutral NaCl absorption and to inhibit Cl− secretion in the colon (2, 35). In addition, butyrate has been shown to prevent colonic mucosal inflammation (22), and butyrate enemas have been reported to be effective in the treatment of ulcerative colitis (39). Hence, decreased availability of butyrate in the colonocytes as a consequence of reduced butyrate uptake has been implicated in various inflammatory conditions and in several cases of acute diarrhea (41) and in colon carcinogenesis (25). Because butyrate absorption is a critical factor in determining colonocyte health, epithelial integrity, and electrolyte absorption, it is essential to understand the cellular and molecular mechanism(s) regulating absorption of butyrate in the human intestine.

Previous studies from our laboratory and others have demonstrated the involvement of monocarboxylate transporter (MCT1) in the luminal absorption of butyrate in human intestinal epithelial cells (6, 10, 21, 36). Furthermore, studies have shown that MCT1 is the major butyrate transporter in the large intestine (21, 36). Earlier studies have shown that MCT1 expression and function are regulated by its substrate butyrate (4, 9) and leptin (6) in intestinal epithelial cells. Also recently it has been shown that MCT1 expression and function are downregulated in patients with inflammatory bowel disease and in colonic epithelial HT29 cells in response to the proinflammatory cytokines TNF-α and IFN-γ (41). Furthermore, studies from our laboratory have shown the acute inhibition of MCT1 by enteropathogenic Escherichia coli (E. coli) infection, a food borne human pathogen associated with diarrhea (3). However, to date, almost no information is available with respect to the acute effects of the anti-inflammatory/proabsorptive peptide hormone, somatostatin (SST), on butyrate uptake and MCT1 expression in intestinal Caco2 cells.

SST is an important neuropeptide of the human gastrointestinal tract, which is known to act as a neurotransmitter and hormone (20, 26). SST has been shown to function as a proabsorptive/anti-inflammatory molecule, and its longer acting analog octreotide has long been utilized as an antidiarrheal agent (33). SST is known to stimulate NaCl absorption and inhibit chloride secretion, cell proliferation, and gut motility (8, 30) in the gastrointestinal tract. SST also inhibited secretion of proinflammatory mediators IL-8 and IL-1β upon TNF-α stimulation in HT29 and Caco2 cells (7). Previous studies have emphasized the role of SSTR1 and 2 receptor subtypes (G protein coupled) in mediating the inhibitory effects of somatostatin on colonic ion secretion in animal models (27, 45) and cultured human colon cancer cell lines (44). The present studies were undertaken to examine in detail the effects of SST on butyrate uptake and the potential involvement of MCT1.

One of the mechanisms by which MCT1 surface expression and activity might be regulated is through an interaction with a chaperone protein, CD147 (23, 34). CD147 protein is a cell surface glycoprotein and has been shown to colocalize with MCTs (MCT1, MCT3, and MCT4) in different cell types (17, 23, 32, 34, 48), and its mRNA has recently been shown to be expressed in the human small intestine and colon (42). Earlier
studies have shown that the expression of MCT1 was reduced in CD147 knockout mice (31), indicating that CD147 is required for the proper targeting of MCT1 to the cell surface. Therefore, the potential role of CD147 in regulating MCT1 in Caco2 cells in response to SST was also examined.

Our studies demonstrated that SST stimulated butyrate uptake in human intestinal epithelial Caco2 cells via a SST receptor subtype 2 and involvement of p38 MAPK-mediated pathway. Moreover, this stimulation of butyrate uptake in response to SST was due to an increase in the membrane levels of MCT1 and CD147 as well as enhanced association of MCT1 with CD147 in Caco2 cells. We speculate that the anti-diarrheal effects of somatostatin on electrolyte absorption in the human intestine may also involve increased surface MCT1 levels to enhance SCFA absorption.

MATERIALS AND METHODS

Materials. Caco2 cells were obtained from American Type Culture Collection (Manassas, VA). $^{14}$C[Butyric acid (sodium salt) was procured from American Radiolabeled Chemicals (St. Louis, MO). SST and seglitide were obtained from Sigma (St. Louis, MO). p38 MAPK inhibitor, SB 203580, was obtained from Biomol (Plymouth Meeting, PA). Bisindolylmaleimide (BIM) was obtained from Calbiochem (San Diego, CA). Sulfo-NHS-SS-Biotin and streptavidin agarose were from Pierce, Rockford, IL. Affinity-purified mouse monoclonal antibody against CD147 was procured from AbCam (Cambridge, MA). Goat anti-mouse or goat anti-rabbit antibody conjugated to horseradish peroxidase and protein L agarose were purchased from Santa Cruz Biotechnology (Santa Cruz, CA). All other chemicals were of at least reagent grade and were obtained from either Sigma Chemicals or Fisher Scientific (Pittsburgh, PA).

Cell culture. Caco-2 cells were grown in Modified Eagle’s medium supplemented with 4.5 g/l glucose, 2 mM glutamine, 50 U/ml penicillin, 50 μg/ml streptomycin, 10 mM HEPES, 1% essential and nonessential amino acids, and 20% fetal bovine serum, pH 7.4 butyrate (1 μCi/ml) for a 10-day period. The uptake values were analyzed for simple Michaelis-Menten kinetics using a nonlinear regression data analysis from a computerized model (GraphPad; PRISM, San Diego, CA).

Cloning of human CD147 for transfection in Caco2 cells. Full-length cDNA of human CD147 was amplified from small intestine by RT-PCR. Briefly, 5 μg of total RNA was used for reverse transcription with random primers using SuperScript II reverse transcriptase kit (Invitrogen, Carlsbad, CA). The full-length cDNA of hCD147 was then amplified by PCR utilizing gene-specific primers and the proof-reading Elongase enzyme mix (Invitrogen) according to the manufacturer’s instructions. The primer sequences (designed on the basis of gene bank accession number BC009040) are 5’ primer: AAGGCTCTCTGCA-CACCATGGCGGTCGCTCCTGTCGTC (Kozak sequence is underlined); 3’ primer: AGAATTCGCAAGCTTGGAGAGTTC-CTCTGGCGGAGCCTCTTGTT.

PCR products were excised from 1% agarose gel and purified utilizing Sephaglas BandPrep Kit (Amersham Pharmacia Biotechnology, Piscataway, NJ). The amplified fragment was cloned into the pAcGFP1-N In Fusion expression mammalian vector (Clontech, Mountain View, CA) in frame with green fluorescent protein (GFP). The orientation and the sequence of the insert were confirmed by sequencing, and the expression of hCD147-GFP fusion protein was examined by Western blotting utilizing anti-GFP antibodies (AbCam).

Transient transfection. For transfection studies, Caco2 cells were transfected utilizing Amaxa Nucleofector System (Amaxa, Cologne, Germany) according to manufacturer’s instructions. Briefly, ~10 × 10^6 cells were harvested and then were electrotransfected in 100 μl of solution T (supplied by Amaxa) along with 30 μg of hCD147-GFP cDNA construct. The cells were transferred to full media and plated onto a 24-well plate. After 24 h, transfected cells were used for cell surface biotinylation.

Biotinylation of cell surface proteins. Cell surface biotinylation studies to measure surface protein expression of MCT1 and CD147 were done as described previously (38). It should be noted that CD147 is endogenously expressed in Caco2 cells; however, for determining CD147 expression in Caco2 cells, we used CD147-GFP-transfected cells because the commercially available anti-GFP antibody is more sensitive in detecting CD147 protein (GFP tagged to CD147) in biotinylated samples compared with the mouse antibody raised against the native human CD147 protein (Abcam). Briefly, untreated or SST-treated normal Caco2 or CD147/GFP cDNA-transfected cells were washed thrice with 1× PBS containing 0.1 mM CaCl2 and 1 mM MgCl2 at 4°C. The apical surface of Caco-2 cells was then exposed to Sulfo-NHS-SS-Biotin (Pierce) at a concentration of 1.5 mg/ml in borate buffer, pH 9.0, by incubating for an hour at 4°C in horizontal motion. Unbound NHS-SS-biotin was then quenched with PBS containing CaCl2, MgCl2 and 100 mM glycine for 20 min at 4°C. Cells were lysed in RIPA buffer (150 mM NaCl, 50 mM Tris-HCl, pH 7.4, 5 mM EDTA, 1% Triton X-100, 0.1% SDS, and protease inhibitor cocktail) and sonicated for 20 s. After centrifugation at 4°C for 30 min, the cell debris was removed and equal amounts of supernatant containing 2 mg/ml protein were incubated overnight with streptavidin agarose at 4°C and then washed thrice with lysis buffer. The streptavidin agarose beads were spun down and boiled in Laemmli sample buffer containing DTT. Proteins were separated on 10–12% SDS-PAGE gels and probed with human anti MCT1 (Alpha Diagnostics International, San Antonio, TX) as previously described (1) or anti-GFP (CD147 tagged to GFP) antibody. CD147 expression was detected by incubating protein-bound nitrocellulose membranes in blocking buffer containing 0.1% Tween 20, 0% nonfat milk for 1 h at room temperature. Membranes were then incubated with the mouse monoclonal anti-GFP antibody (1: 500 dilution) in 1× TBS and 1% milk overnight at 4°C followed by washes for 45 min with wash buffer containing 1× TBS and 0.1% Tween 20. Bands were visualized utilizing enhanced chemiluminescence reagent. The bands were quantified using densitometric analysis and expressed as arbitrary units indicating the relative surface expression of MCT1 or
CD147 over the total MCT1 or CD147 (sum of apical and intracellular) expression.

**Cell lysates, immunoprecipitation, and Western blotting.** Caco2 cells grown to confluence in six-well plates (10 × 10⁶ cells/ml; Corning Costar, Cambridge, MA) were serum starved overnight and treated with SST (25 and 50 nM) for 30 and 60 min or p38 MAPK inhibitor, SB203580 (30 μM). Cells were washed with ice-cold PBS three times and lysed in 20 mM Tris-HCl, pH 7.5, 150 mM NaCl, 1% Triton X-100, 1 mM EDTA, 1 mM EGTA, and 1% complete protease inhibitor cocktail. The cells were homogenized by passing 10 times through 26-gauge needle. The lysate was centrifuged at 5000 g for 5 min at 4°C, and protein concentration was determined by the method of Bradford (5). To detect association of MCT1 with CD147, CD147 expression was detected utilizing human anti MCT1 antibody (Alpha Diagnostics) (1). Statistical analysis. Results are expressed as means ± SE. Each independent set represents means ± SE of data from at least nine wells used on three separate occasions. Student’s t-test was used for statistical analysis. P < 0.05 or less was considered statistically significant.

**RESULTS**

**SST increases butyrate uptake in Caco2 cells.** SST is known to function as a proabsorptive peptide by stimulating NaCl absorption (13, 18) and inhibiting Cl− secretion (15, 16, 45) in the intestine. Therefore, we examined the possible role of SST in the regulation of butyrate uptake in Caco2 cells. Confluent Caco2 cells grown on 24-well plastic supports at 10–12 days postplating were treated with SST (25 nM or 50 nM) for 30 min, and pH-driven 14C butyrate uptake was measured as described in MATERIALS AND METHODS. Figure 1 shows that SST treatment to Caco-2 cells significantly increased the butyrate uptake at 25 nM and 50 nM (~60–70%; P < 0.05).

**Effect of luminal and serosal SST on butyrate uptake in Caco2 cells.** Our initial studies showed that SST1, 2, and 5 receptor mRNA is present in both human small intestine and colon as well as in differentiated Caco2 cells (data not shown). Because SST receptors 1, 2, and 5 in the intestine are expressed on both the apical and basolateral membranes (7, 45, 46), we examined the effects of luminal or serosal SST (25 nM, 30 min) on apical butyrate uptake in Caco2 cells grown on permeable supports. Figure 2 shows that luminal SST significantly stimulated apical butyrate uptake, whereas the basolateral addition of SST on butyrate uptake was slightly more (~2.5 vs. 2.0-fold) compared with control. For all subsequent experiments the effects of only luminal SST were examined.

**Effect of SST receptor agonists on butyrate uptake in Caco2 cells.** SSTR1 and 2 receptor subtypes have been shown to be involved in mediating the inhibitory effects of SST on ion secretion in animal and cell culture models (27, 44, 45). The involvement of SSTR1 and 2 receptors in SST-stimulated effects on butyrate uptake in Caco2 cells was examined. Because SSTR1 agonist L-797,591 was commercially unavailable, we used the selective SSTR2 receptor agonist, seglitide. As shown in Fig. 3, apical addition of the seglitide (25–50 nM) for 30 min resulted in a significant increase in butyrate uptake. These observations suggest that SSTR2 receptor agonist mimicked the effects of SST in stimulating butyrate uptake in Caco2 cells.

**Role of p38 MAPK in SST-induced stimulation of butyrate uptake in Caco2 cells.** SST is well known to trigger a number of intracellular pathways including activation of MAPKs (24, 29). Therefore, we next determined the role of MAPKs in the SST-mediated stimulation of butyrate uptake in Caco2 cells. The effects of PD98059 (a specific inhibitor of Erk1/2, 30 μM, 1 h) and SB203580 (a specific p38 MAPK inhibitor, 30 μM, 1 h) on butyrate uptake in response to SST were examined. Specific p38 MAPK inhibitor, SB203580, blocked the SST-mediated stimulation of butyrate uptake in Caco2 cells (Fig. 4), suggesting the involvement of p38 MAPK on the effects of SST on butyrate uptake. However, PD98059 failed to show any effect indicating that Erk 1/2 are not involved (data not shown).

![Fig. 1. Effect of somatostatin (SST) on butyrate uptake in Caco2 cells. Overnight serum-starved postconfluent Caco2 cells were treated with 25 and 50 nM concentrations of SST in serum-free cell culture medium for 30 min. 14C Butyrate uptake (5 mM) was measured as described in MATERIALS AND METHODS. Results are expressed as a percentage of control and represent means ± SE of 6 separate experiments performed in triplicate. *P < 0.05 compared with control.

![Fig. 2. SST treatment from apical or basolateral side stimulates butyrate uptake in Caco2 cells. Overnight serum-starved postconfluent Caco2 cells grown on permeable supports were treated with 25 nM SST in serum-free cell culture medium from either the apical or basolateral side for 30 min. 14C Butyrate uptake (5 mM) was measured as described in MATERIALS AND METHODS. Results represent means ± SE of 3 separate experiments performed in triplicate. *P < 0.05 compared with control.](http://ajpgi.physiology.org/)

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Effect of SST on kinetics of butyrate uptake in Caco2 cells.

To understand the mechanisms by which SST stimulates butyrate uptake, we evaluated its effect on the kinetic parameters of butyrate uptake in Caco2 cells. Butyrate uptake was measured at increasing concentrations of butyrate ranging from 0.5–15 mM in response to SST treatment to Caco-2 cells. MCT1 activity exhibited saturation with increasing butyrate concentrations in both control and SST-treated cells as analyzed by GraphPad Prism software (Fig. 5). Incubation with SST significantly increased the maximal velocity (V_{max}) of the transport process (14.86 ± 1.14 compared with untreated cells) without significant changes in the apparent Michaelis-Menten constant (K_m) for butyrate (control: 3.34 ± 0.95 mM compared with SST: 4.54 ± 1.33 mM).

These results suggest that SST treatment alters either the number of active transporters on the membrane or the turnover rate of the transporter but not the affinity of the transporter for butyrate.

Surface levels of MCT1 are increased by SST.

The observed increase in the value of V_{max} of MCT1 in response to SST suggested that SST might increase MCT1 activity via recycling of the transporter from the intracellular pools to the apical compartment. We, therefore, examined the effects of SST on the surface levels of MCT1 in Caco2 cell membranes. Cell surface biotinylation studies were performed to determine the changes in cell surface levels of MCT1 protein or the biotin-treated fraction of total cellular protein. Biotinylated proteins from control and SST-treated cells were separated from the cell lysate by avidin, and proteins were probed with human MCT1 antibody. As shown in Fig. 6A, cell surface biotinylation studies demonstrated an increase (2.8-fold increase compared with control, Fig. 6B) in the apical membrane levels of MCT1 parallel to a decrease in the intracellular pool.

SST induces association of MCT1 with CD147.

Previous studies have shown that coexpression of accessory protein, CD147 (also known as basigin) not only improved trafficking of MCT1 to the plasma membrane but also influenced its catalytic activity (47). The interaction between MCT1 and CD147 is required for proper targeting of MCT1 from the endoplasmic reticulum/Golgi apparatus to the plasma membrane (23). Moreover, studies have shown that luminal leptin enhanced butyrate uptake via an increased translocation of CD147/MCT1 to the apical plasma membrane of Caco2-brush border-expressing (BBE) cells (6). To elucidate the potential role of CD147 in the stimulatory effects of SST on butyrate uptake in Caco2 cells, we examined the association of MCT1 with CD147 in SST-treated Caco2 cells. Cells were treated with SST (25 and 50 nM) at 30 or 60 min, lysed and immunoprecipitated with anti-CD147-specific antibody, and probed with anti-MCT1 antibody. As shown in Fig. 7A, immunoprecipitation analysis showed an enhanced association of MCT1 with CD147 in response to SST (25 nM) at both 30 and 60 min (2.2-fold increase compared with control, Fig. 7B). Interest-
ingly, the enhanced MCT1/CD147 association at both 30 and 60 min was abolished in the presence of SB203580. These results indicate that CD147 plays an important role in the regulation of MCT1 activity by SST.

SST increases CD147 membrane levels. As SST enhanced the association of MCT1 with CD147, we next determined whether SST also increases CD147 levels in membranes of Caco2 cells. Western blot analysis was performed in the biotinylated samples of untreated and SST-treated CD147-GFP transfected Caco2 cells using monoclonal mouse GFP antibody. Figure 8A shows that SST significantly increased the membrane levels of CD147 compared with control (2.2-fold increase compared with control, Fig. 8B). These results demonstrate that, similar to an increase in surface MCT1 levels, SST also increased the membrane levels of CD147 in Caco2 cells.

DISCUSSION

We and others have previously shown the involvement of MCT1 in the luminal absorption of butyrate in human intestinal epithelial cells (6, 10, 21, 36). Butyrate is known to play an important role in maintaining colonic epithelial integrity and function (37). The present studies were designed to investigate the mechanisms underlying the regulation of butyrate uptake by the proabsorptive peptide hormone, SST, in the human intestine. SST has been shown to exert antisecretory effects in intestinal epithelial T84 and HT29–C119A cells (14, 44). The SST analog, lanreotide (BIM 23014), has been shown to reduce ion secretion in vivo under basal and PGE1-stimulated conditions in the human jejunum (40). Also, SST infusion has been reported to inhibit watery diarrhea in patients with carcinoid syndrome (11). Present studies for the first time demonstrated that luminal SST stimulated butyrate uptake in Caco2 cells. The concentration of SST used in our present study is in the physiological range (25–50 nM) and is in agreement with previous studies showing that SST at physiological nanomolar concentrations (1–100 nM) markedly inhibited both basal- and agonist-stimulated ion secretion in animal models (27, 45) and cultured intestinal epithelial cells (14, 44).

SST is known to exhibit diverse physiological functions via G protein-coupled receptors (SSTRs) (8, 30). Our receptor mRNA expression studies utilizing real-time PCR have shown that SSTR1, 2, and 5, but not 3 and 4, are expressed in the...
Intracellular pool.

Apical membrane levels of MCT1 parallel to a decrease in the number of MCT1 molecules on the apical membrane in Caco2 cells. Our present studies also demonstrated that SST-mediated modulation of MCT1 occurs via a recycling mechanism in response to entero-pathogenic Escherichia coli infection (3) and serotonin (19) in Caco2 cells. These data are in accordance with previous studies in murine heart plasma membranes (23), epithelial cells of kidney, retina (12), and thyroid (17) in which CD147 was found to be tightly associated with MCT1 to facilitate proper targeting of MCT1 to cell surface.

Previous studies have demonstrated that CD147 plays an important functional role in butyrate transport activity. For example, MCT1/CD147 association in Caco2-BBE cells was found to be critical for butyrate uptake as butyrate uptake was decreased in antisense CD147 transfected Caco2-BBE cells when compared with empty vector or nontransfected cells (6). Disruption of MCT1/CD147 association by covalent modification of CD147 with the cell impermeant organomercurial reagent, p-chloromercuribenzenesulfonate, inhibited transport activity (47). Moreover, enhanced association of MCT1 and CD147 by leptin was shown to increase butyrate uptake in Caco2-BBE cells (6). However, previous studies failed to address the possible signaling mechanisms involved in increasing MCT1/CD147 association. Our studies provided novel evidence on the involvement of p38 MAPK in SST-induced association of CD147 with MCT1, as this association was abolished in the presence of the specific p38 MAPK inhibitor, SB203580. Because SST-mediated effects on butyrate uptake are dependent on p38 MAPK pathway, these results further suggested that SST-induced MCT1/CD147 association may be crucial for butyrate transport in the human intestine. Also, our low stringent analysis of both MCT1 and CD147 using in silico analysis by Scansite 2.0 (28) identified potential phosphorylation sites for p38 MAPK. We speculate that these sequence motifs may play an important role in the direct or indirect phosphorylation of MCT1 and CD147 that could result in the enhanced association of MCT1 and CD147. Further studies are needed to address this important issue.

In summary, our results demonstrated that SST stimulates butyrate uptake in Caco2 cells via the activation of p38 MAPK involving SST receptor 2, which subsequently results in an increase in the membrane levels of both MCT1 and CD147. Increased MCT1 and CD147 then associate at the membrane leading to the stimulation of apical butyrate uptake process in Caco2 cells. Our findings provide novel mechanistic insights into the hormonal regulation of MCT1 and CD147 in the human intestine. We speculate that SST secreted in the intestinal lumen during inflammation might play a protective role in maintaining colonic epithelial integrity by increasing the activity, surface levels, and association of MCT1/CD147 for enhanced SCFA absorption.

GRANTS

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