Changes in mRNA expression levels of solute carrier transporters in inflammatory bowel disease patients

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Running title: Expression of SLC transporters in IBD

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Number of text pages: 14
Number of tables: 4
Number of figures: 2
Number of references: 27
Number of words in:
- Abstract: 219
- Introduction: 723
- Discussion: 1128

Abbreviations: IBD, inflammatory bowel disease; SLC, solute carrier; RT-PCR, real time polymerase chain reaction; SERT, serotonin transporter; ENT, equilibrative nucleoside transporter; OATP, organic anion transporting polypeptide; ASBT, apical sodium-dependent bile acid transporter; OCTN, organic zwitterion/cation transporter; CNT, concentrative nucleoside transporter; PEPT, peptide transporter; CD, Crohn's disease; UC, ulcerative colitis; OCT, organic cation transporter; OAT, organic anion transporter; E-3-S, estrone-3-sulfate; DHEAS, dihydroepiandrosterone
Abstract

Inflammatory bowel disease (IBD) is an inflammatory condition that affects gastrointestinal tract. Solute carrier superfamilly of transporters (SLC) comprise proteins involved in the uptake of drugs, hormones, and other biologically active compounds. The purpose of this study was to determine the mRNA expression levels of 15 solute carrier transporters in two regions of the intestine in IBD patients. Endoscopic biopsies were taken from two locations (terminal ileum and colon) for histological examination and RNA extraction. We quantitatively measured the mRNA expression of 15 SLC transporters in 107 IBD patients (53 Crohn's disease and 54 ulcerative colitis) and 23 control subjects. Messenger RNA expression was evaluated using the quantitative reverse transcription-PCR technique. We observed that in ileum of IBD patients, mRNA levels for SERT, ENT1, ENT2, and OATP2B1 were significantly elevated while for ASBT and OCTN2 they were significantly lower. In colon, mRNA levels for ENT1, ENT2, CNT2, OATP2B1, and OATP4A1 were significantly higher, while mRNA levels for OCTN2 were significantly decreased. In inflamed colon of IBD patients the mRNA expression levels of ENT1, ENT2, CNT2, OATP2B1, OATP4A1, and PEPT1 were significantly higher. We conclude that intestinal SLC mRNA levels are dysregulated in IBD patients, which may be linked to the inflammation of the tissue and provides an indication about the role of inflammatory signalling in regulation of SLC expression.
Introduction

Solute carrier superfamily of transporters (SLC) consists of over 300 members subdivided into 47 families. They are expressed in most tissues, but primarily in the liver, lung, kidney, and intestine. Most solute carrier transporters are localized at either basolateral or apical plasma membrane of polarized cells, but some are expressed in mitochondria and other organelles. The expression levels of SLCs are modulated by cytokines, hormones, growth factors, extracellular signals, and changes in the metabolic state of the cell. Typical SLC transporters consist of several transmembrane α-helices connected by intra- and extracellular loops and function as either monomers or hetero- or homodimers. SLC transporters are responsible for the uptake of amino acids, peptides, ions, xenobiotics, drugs, and other biologically active compounds (Koepsell et al., 2007). The driving force of SLCs is mostly ion-dependent, but some of them function as equilibrative transporters.

Inflammatory bowel disease (IBD) is a disease affecting the inner lining of the gut and it can be divided into two entities: Crohn’s disease (CD) and ulcerative colitis (UC). Until now, there are only a few studies implicating the involvement of SLC family members in the pathophysiology of IBD and/or other inflammatory conditions. For example, the expression and activity of the peptide transporter 1 (PEPT1; gene symbol SLC15A1) has been shown to be increased by pro-inflammatory cytokines, such as tumour necrosis factor-α (TNF-α) and interferon-γ (IFN-γ) (Vavricka et al., 2006). This observation was proposed to be linked with the PEPT1-mediated uptake of muramyl dipeptide, a degradation product of bacterial outer wall, followed by activation of the intracellular receptor NOD1 and consequently of the transcription factor NF-κB. PEPT1 was also reported to be involved in the suppression of inflammation in mouse models of colitis due to the uptake of the therapeutic tripeptide DMD 23767.
Another SLC transporter implicated in IBD is the organic cation/zwitterion transporter 2 (OCTN2; gene symbol SLC22A5). It has been reported that SLC22A5s are high susceptibility genes in IBD, located at the so-called IBD locus 5 (IBD5), and that genetic polymorphisms within this region contribute to the inflammatory phenotype (Cucchiarai et al., 2007; Silverberg et al., 2007; Waller et al., 2006). These observations are consistent with a mouse study showing that homozygous inactivation of Octn2 resulted in spontaneous development of colitis (Shekhawat et al., 2007). Decreased expression of Octn2 and another carnitine transporter Atb0+ were also shown to be associated with development of inflammatory condition in rats (D’Argenio et al., 2006). Recently, the mRNA expression levels of OCTN1 and OCTN2 were reported to be significantly decreased in UC patients (Noble et al., 2008). Another SLC member implicated in pathogenesis of IBD is the apical sodium-dependent bile acid transporter (ASBT; gene symbol SLC10A2). It has been shown that the protein levels of this transporter are lower in CD patients than in control individuals (Jung et al., 2004). It has been proposed that ASBT mRNA levels are decreased by pro-inflammatory cytokines via a mechanism that involves the c-Fos transcription factor in human, rat, and mouse intestinal epithelium (Neimark et al., 2006). In addition, the expression and function of another SLC superfamily member, serotonin transporter (SERT; gene symbol SLC6A4), is affected by 2,4,6-trinitrobenzenesulfonic acid (TNBS) -induced inflammation in mice (Linden et al., 2005). In concert with this, it has been reported that function and expression of SERT are decreased by the pro-inflammatory cytokines TNF-α and IFN-γ in human intestine-derived cells (Foley et al., 2007). These observations suggest that certain SLC transporters are affected in inflammatory conditions, such as IBD. Given the physiological function of SLCs they might contribute to the
pathology of this disease, or their function may be affected as a consequence of inflammation.

Recently, we have described the distribution of 15 SLC transporters along the human intestinal tract (Meier et al., 2007). This group included PEPT1, OCTN1, and OCTN2, the concentrative nucleoside transporters (CNTs; gene family SLC28), ASBT, the organic anion transporting polypeptides (OATPs; gene family SLCO), the equilibrative nucleoside transporters (ENTs; gene family SLC29), the organic cation transporter 1 (OCT1; gene symbol SLC22A1), the organic anion transporter 2 (OAT2; gene symbol SLC22A7), and SERT. In the present study we have determined the expression levels of these 15 SLC transporters in terminal ileum and colon of IBD patients, in comparison with non-IBD control patients. Localisation, function, and implicated association with IBD of these transporters are summarized in Table 1.
Materials and Methods

Patients and colonoscopy

In this study, 53 patients with ulcerative colitis (UC) and 49 patients with Crohn’s Disease (CD), as well as 23 control subjects were enrolled after having given their informed consent. Diagnosis of patients with UC and CD was based on clinical history, laboratory findings, as well as endoscopic and histological criteria. Tissue biopsies were sampled by experienced gastroenterologists. From patients with active disease (newly diagnosed patients and patients with refractory disease) biopsies were taken both from the inflamed and from the unaffected region (paired biopsies). Unaffected areas were defined as mucosa regions without any macroscopic/endoscopic signs of inflammation (ulceration, edema, discoloration, hemorrhagic appearance, or mucinous/fibrinous coating); these biopsies were obtained at least 10-15 cm distant from the inflamed area. Control subjects had an indication for a gastrointestinal tract endoscopy for reasons not related to IBD. Biopsy specimens were obtained during routine endoscopy, submerged in RNAlater solution (Ambion, Austin, USA) and stored at –80°C until further processing. The summary of patients’ characteristics is presented in Table 2. Additional patient information is shown in supplementary material (supplementary tables 1 and 2).

Isolation of RNA from biopsies

For RNA isolation from biopsies obtained from IBD patients, intestinal biopsies were homogenized for 30 seconds (Polytron PT 2100, Kinematika AG, Switzerland) and RNA was extracted using the RNeasy Mini Kit (Qiagen GmbH, Hilden, Germany) following the instructions provided by the manufacturer. Control biopsies were syringed in TRIzol reagent and RNA was extracted in according to the manufacturer’s
protocol (Invitrogen, Carlsbad, USA). RNA was quantified with a GeneQuant spectrophotometer (Pharmacia, Uppsala, Sweden) and NanoDrop ND-1000 spectrophotometer (NanoDrop Technologies, Wilmington, USA).

Synthesis of cDNA and quantitative real-time PCR

Complementary DNA (cDNA) was produced using the reverse transcription kit (Promega, Madison, USA) with 1.2 μg RNA as a template and random hexamers as primers. The product was diluted with H₂O to a total volume of 120 μl. For each PCR reaction 2 μl of the cDNA was used in the final reaction volume of 10 μl. SLC expression levels were determined by TaqMan real-time PCR and absolute quantification. The cycling conditions were identical to those used in our previous study: stage 1 (50°C, 2min); stage 2 (95°C, 10min); stage 3: 40 repeats (95°C, 15s; 60°C, 1min). Based on our previous observations, for detectable targets each PCR was performed in duplicate, for targets below detection limit PCR was performed as a single measurement. PCR for villin was performed in triplicate. For each assay, a dilution series (12; 120; 1’200; 12’000; 120’000, and 12’000’000 copies) of the cloned PCR product was quantified in parallel. The expression levels of the target genes in each sample were determined by the ratio of cDNA copies of a target gene vs. cDNA copies of villin. The samples below the cut-off limit (<0.01 ratio of target cDNA copies vs. villin cDNA copies) were considered undetectable. All the TaqMan Gene Expression Assays (Applied Biosystems, Foster City, USA) used in this study were the same as used in our previous study (Meier et al., 2007).

Statistical analysis
Basic statistical analysis was performed using the GraphPad Prism 5 software. Statistical significance of the differences in mRNA expression levels between the patient subgroups was determined by performing ANOVA analysis (Kruskal-Wallis test) with Dunn’s Multi Comparison Test. For paired biopsies analysis statistical significance was determined using a paired t-test. The effect of steroid therapy, age, gender, and smoking on expression levels was analyzed using mixed models of ANOVA with patients as random factors. Here, the values of mRNA expression levels were logarithmically transformed prior to an analysis performed using SPSS 13 (SPSS Inc., Chicago, USA) (supplementary table 3).

**Ethical considerations**

The study protocol and consent forms were approved by the State Ethical Committee of Basel (EKBB) and University Hospital Zurich (EK-837) prior to the start of the study. The sample collection was carried out at the University Hospital Basel and the University Hospital Zurich between 2001 and 2007.
Results

The mRNA expression of SLC transporters in terminal ileum of IBD patients

Despite considerable individual variation between patients within each subgroup, we observed clear and significant differences in SLC mRNA expression levels in IBD patients compared to the control group. We found that in terminal ileum, mRNA expression levels of ASBT and OCTN2 were significantly decreased in IBD patients (Table 3). Also the mRNA expression levels of CNT2 were decreased in IBD patients, but it was not statistically significant. The elevation of mRNA levels of SERT, ENT1, ENT2, and OATP2B1 in ileum of IBD patients was statistically significant, but the increase in mRNA levels of PEPT1 and OCTN1 was not. The increase in the expression levels of CNT1 was only significant in CD patients. We observed statistically significant elevation of mRNA expression of OATP4A1, but its levels in IBD patients remained on the border of detection limit. The mRNA levels of CNT3, OAT2, OATP1A2, and OCT1 were below detection limit.

The mRNA expression of SLC transporters in colon of IBD patients

In colon, we observed that OCTN2 mRNA levels were significantly decreased in IBD patients (Table 3). The mRNA levels of ENT1, ENT2, OATP2B1, OATP4A1, and CNT2 were significantly increased, while the increase in the mRNA expression of OCTN1 was statistically significant only in UC patients, and the increase of mRNA expression levels of PEPT1 was significant only in CD patients. The mRNA levels of ASBT, SERT, CNT1, CNT3, OAT2, and OATP1A2 in colon of IBD patients were below detection limit. The OCT1 mRNA was detected, but its levels were not altered in IBD patients. Among 15 targets tested, only two exhibited significant differences
between CD and UC patients, namely OATP2B1 and OATP4A1. Both OATP2B1 and OATP4A1 expression were higher in UC patients.

**Changes in mRNA expression levels of SLC transporters in inflamed tissues of CD patients**

Analysis of the biopsies based on the inflammatory status of the tissue revealed that changes in mRNA expression levels of certain SLC transporters in CD patients were correlated with the inflammation (Fig. 1). In terminal ileum, expression levels of ENT1 and ENT2 in the inflamed tissues were higher than in non-inflamed tissues, but this difference was not statistically significant (Fig. 1A). The mRNA expression levels of OATP2B1 and OATP4A1 were not changed, while the expression of CNT2 was decreased, but not significantly. To exclude the influence of individual variation in basal mRNA levels of SLC transporters we next analysed only paired biopsies from terminal ileum of CD patients. We observed that the increase in mRNA expression levels of ENT2, and OATP2B1 between the non-inflamed and inflamed tissues became significant (Fig. 1B). The changes in mRNA expression levels of ENT1, OATP4A1, and CNT2 were still apparent, but did not reach statistical significance in paired samples. Similarly, compared to non-inflamed tissues mRNA levels of ENT1, ENT2, CNT2, OATP2B1, OATP4A1, and PEPT1 were higher, but not significantly, in the inflamed colonic tissues of all CD patients (Fig. 1C). The expression levels of OCTN1 and OCTN2 were not changed upon inflammation. When only paired biopsies were analysed, the mRNA levels of ENT2, OATP2B1, and PEPT1 were significantly increased in colon of CD patients. Interestingly, we observed a significant increase in mRNA levels of OCTN1, but not OCTN2, when only paired biopsies were included in the analysis. The mRNA levels of ENT1, CNT2, and OATP4A1 were increased, but not significantly (Fig. 1D).
Changes in mRNA expression levels of SLC transporters in inflamed colon of UC patients

In colon of UC patients, the inflamed tissues expressed significantly higher mRNA levels of ENT1, ENT2, CNT2, OATP4A1, and PEPT1. Similarly to the colon of CD patients, the levels of OCTN1 and OCTN2 in UC patients were not changed upon inflammation (Fig. 2A). When paired biopsies were analysed, the mRNA levels of ENT1, ENT2, CNT2, OATP2B1, OATP4A1, and OCTN1 were significantly higher. Despite the strong increase tendency, the elevation of the mRNA levels of PEPT1 in inflamed tissue did not reach statistical significance, when paired biopsies were analyzed (Fig. 2B).

Changes in mRNA expression levels of SLC transporters in IBD patients on steroid therapy

Next, we examined, whether SLC mRNA levels in IBD patients were influenced by any medication taken. We found a strong correlation between colonic mRNA expression levels of OCTN2 and steroid therapy in male patients (Table 4): we observed approximately 2.5-fold increase in OCTN2 expression in both CD (from 0.02 to 0.05) and UC (from 0.04 to 0.09) in male patients. Also, in CD males, steroid therapy decreased mRNA levels of ASBT in terminal ileum, but this was not statistically significant. The mRNA levels of OATP4A1 in UC patients taking steroids were increased 2-fold, but this change was not statistically significant. All the changes in mRNA expression levels of SLCs in IBD patients taking steroids are summarized in Table 4.
Discussion

SLC transporters play an important role in the absorption of drugs and biologically active compounds in the intestine. Determining expression levels of SLC transporters in IBD intestine provides an indication about the role of inflammatory signalling cascades on regulation of SLC expression. Since we did not observe any significant gender- or age-dependent changes in mRNA expression levels in either of two intestinal regions of IBD patients (supplementary table 3), we propose that these differences in mRNA expression levels may be attributed to inflammation and/or therapy. We observed certain small, but significant, differences in the expression levels of some SLCs in both regions of control group, compared to the control levels reported in our previous study (Meier et al., 2007). Significant differences in mRNA levels were detected for four out of nine detectable target genes in terminal ileum (PEPT1, ASBT, CNT1, and CNT2) and three out of nine detectable target genes in colon (OCT1, CNT2, and ENT2). These differences may derive from individual variation in mRNA levels of these transporters amongst the patients in each subgroup, and be dependent on variables such as individual differences in medication.

We observed significantly decreased ASBT mRNA levels in IBD patients - an observation that has previously been reported for CD patients at the ASBT protein level (Jung et al., 2004). Although we did not observe any changes in ASBT mRNA levels in the inflamed tissues, steroid therapy seems to be associated with a tendency of decreased ASBT mRNA levels in terminal ileum of male CD patients. This is in apparent disagreement with the previous observation that CD patients undergoing steroid treatment exhibit increased levels of ASBT (Jung et al, 2004). This contradiction may be explained by the small numbers of patients employed in
the previous study, and larger heterogeneity of the dose- and time-dependent treatment of IBD population tested in the present study.

We also observed a significant decrease in mRNA levels of the carnitine transporter OCTN2 in IBD patients. The OCTN2 protein is encoded by the IBD5 locus and polymorphisms in the SLC22A5 coding regions have been linked to IBD pathology (Cucchiara et al., 2007; Silverberg et al., 2007; Waller et al., 2006; Russell et al., 2006). In rats, a decrease in Octn2 expression levels triggers inflammation of the gastrointestinal tract (Shekhawat et al., 2007), possibly due to an aberration of carnitine transport and fatty acid metabolism (D’Argenio et al., 2006). Interestingly, a decrease in mRNA expression of OCTN2 was recently reported in sigmoid region of UC colon (Noble et al., 2008), although to a lesser extent than to the decrease observed here in colon and terminal ileum (Table 3). Low levels of OCTN2 even in non-inflamed tissues from IBD patients could result from either specific genetic background, e.g. polymorphisms/mutations in OCTN2 gene and/or its promoter sequence, or it could be due to suppression by circulating pro-inflammatory cytokines. Interestingly, we observed a slight, but not statistically significant decrease in OCTN2 mRNA levels in all inflamed tissues compared to all non-inflamed biopsies (Fig. 1C and Fig. 2A). Moreover, a closer examination of paired biopsies reveals that 50% of CD patients, and 82% of UC patients, express lower mRNA levels of OCTN2 in paired inflamed tissues (data not shown). In addition, we demonstrated higher mRNA expression levels of OCTN2 in patients taking steroids (Table 4). Moreover, in patients in remission of the disease, colonic OCTN2 mRNA levels of were slightly, but not significantly, higher than in non-remission CD patients (data not shown) suggesting that elevation of the mRNA levels of OCTN2 might be correlated with overall therapeutic effect. All these observations support the idea of OCTN2 being
associated with IBD and/or inflammation. The exact mechanisms, by which the OCTN2 protein contributes to the pathogenesis of IBD, remain unclear.

We observed an increase in mRNA levels of most intestinal nucleoside transporters in colon and in terminal ileum. It has been reported that altered expression levels of certain nucleoside transporters are associated with pathological states, such as ampullary cancer (Santini et al., 2008) and HIV infection (Guallar et al., 2007). The relevance of the observed increase in nucleoside transporter expression in IBD intestine remains unclear. Elevated levels of nucleoside transporters may trigger an influx of nucleosides, such as adenosine, and be responsible for inflammation of the tissue - similarly to the mechanism proposed for inflammatory lung diseases (Hirsh et al., 2007). In support of this, mRNA levels of nucleoside transporters are elevated in the inflamed tissues of IBD patients (Fig. 1 and 2). This observation may also imply a role for pro-inflammatory cytokines in transcriptional regulation of nucleoside transporter genes in intestinal cells, as already reported in the context of liver parenchymal cells (Fernández-Veledo et al., 2004) and macrophages (Soler et al., 2001). While we did not observe any changes in nucleoside transporter mRNA levels in patients taking standard therapies, it would be interesting to measure mRNA levels of nucleoside transporters in IBD patients taking anti-TNF-α medications, such as infliximab or adalimumab.

Another group of target genes exhibiting increased mRNA levels in IBD patients is the family of organic anion transporting polypeptides. In both terminal ileum and colon, we observed an increased mRNA expression of OATP2B1 and OATP4A1 in IBD patients. This elevation is correlated with the inflammatory status of the tissue in both intestinal regions, and is most significant in colon of UC patients (Fig. 2). It has been reported that the mRNA levels of murine hepatic Oatp2 are sensitive to pro-inflammatory signalling (Hartmann et al., 2002), but until now there
has been no clear indication that OATP transporters may be involved in the pathology of IBD in humans.

We also observed increased mRNA expression of PEPT1 in both regions of the intestine in IBD patients. This elevation was statistically significant in colon of both CD and UC patients and was correlated with the inflammation of the tissue. Elevated expression of PEPT1 has already been previously implicated in inflammation and the pathology of IBD (Vavricka et al., 2006).

The intestinal SLC mRNA levels are dysregulated in IBD patients, which may be linked to the inflammatory status of the affected tissue. Determining expression levels of SLC transporters in inflamed and non-inflamed intestine provides an indication about the role of inflammatory signalling cascades on regulation of SLC expression. While it is important to bear in mind that changes in mRNA levels may not fully correlate with such alterations in the corresponding protein levels, we believe that the expression levels of SLCs may help to assess the severity of the disease and/or serve as prognostic factor for patients taking certain medications and that this information may help to optimize drug therapies for IBD patients.
Acknowledgements

We would like to acknowledge Christian Hiller and Dr. Christa Wenger for providing additional cDNA of control samples and helping with the analysis of patients' medication. We would also like to thank Martin Moser for helping with the data collection, Ursula Behrens for helping with the transfer of the samples, and Prof. Burkhardt Seifert for performing additional statistical analysis. We would also like to acknowledge Dr. Sarah Haile for helping with the choice of the suitable statistical analysis.
References


and ethnic differences observed for the IBD5 association with Crohn's disease. Eur J Hum Genet 15: 328-335.


Footnotes

This study was supported by project grants from the Swiss National Science Foundation (320000-114009/1, S. R. Vavricka; 32-120463/1, G. A. Kullak-Ublick and J. J. Eloranta; 3347CO-108792, Swiss IBD Cohort) and a collaborative project grant from the Zurich Center of Integrative Human Physiology (ZIHP; G. A. Kullak-Ublick and J. J. Eloranta). P. Hruz is supported by the Swiss National Science Foundation (PASMA 114623).
Figure legends

**Fig. 1.** The changes in mRNA expression levels of SLCs in the inflamed tissues of CD patients. (A) The mRNA expression levels of ENT1, ENT2, but not OATP2B1 and OATP4A1, are elevated in inflamed tissues of terminal ileum of all CD patients of the study. Mean values of mRNA expression levels are presented. Error bars indicate SD values. (B) Paired analysis of inflamed and non-inflamed tissues from the same patients shows a significant increase of ENT2, and OATP2B1, in terminal ileum. The mRNA expression levels in non-inflamed tissues were set to 1. (C) The mRNA expression levels of ENT1, ENT2, CNT2, OATP2B1, OATP4A1 and PEPT1 are increased in inflamed colon of CD patients. Averages of mRNA expression levels are presented. (D) Paired comparison of inflamed and non-inflamed tissues shows a significant increase in ENT2, CNT2, OATP2B1, OCTN1, and PEPT1 mRNA levels. The mRNA expression levels in non-inflamed tissues were set to 1. P value: * < 0.05; ** <0.01; *** <0.001. Error bars indicate SD values.

**Fig. 2.** The changes in mRNA expression levels of SLCs in the inflamed colon of UC patients. (A) The mRNA expression levels of ENT1, ENT2, CNT2, and OATP4A1, and PEPT1 are significantly higher in the inflamed tissues. mRNA levels of OCTN1 and OCTN2 are not significantly changed. Mean values of mRNA expression levels are presented. Error bars indicate SD values. (B) Paired comparison of inflamed and non-inflamed tissues from the same patients shows a significant increase in mRNA levels of ENT1, ENT2, CNT2, OATP2B1, OATP4A1 and OCTN1. Elevation of mRNA levels of OCTN2 and PEPT1 is not significant. The mRNA expression levels in non-inflamed tissues were set to 1. P value: * < 0.05; ** <0.01; *** <0.001.
Table 1. The characteristics of 15 solute carrier transporters investigated in this study.

<table>
<thead>
<tr>
<th>Full name</th>
<th>Acronym</th>
<th>SLC code</th>
<th>Tissue expression</th>
<th>Substrate specificity</th>
<th>Reported/implicated association with inflammation in:</th>
<th>Reported/implicated association with IBD</th>
<th>References</th>
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<td>Apical sodium-dependent bile acid transporter</td>
<td>ASBT</td>
<td>SLC10A2</td>
<td>Small intestine, biliary epithelium, kidney</td>
<td>Bile acids</td>
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<td>Jung et al., 2004; Neimark et al., 2006</td>
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<td>Concentrative nucleoside transporter 1</td>
<td>CNT1</td>
<td>SLC28A1</td>
<td>Jejunum, kidney, liver, small intestine, brain</td>
<td>Nucleosides, nucleoside analogues</td>
<td>Rat hepatocytes</td>
<td>No</td>
<td>Fernández-Veledo et al., 2004; Podgórska et al., 2005</td>
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<td>CNT2</td>
<td>SLC28A2</td>
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<td>Nucleosides, nucleoside analogues</td>
<td>Human primary epithelial cells</td>
<td>No</td>
<td>Hirsh et al., 2007; Podgórska et al., 2005</td>
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<td>SLC28A3</td>
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<td>No</td>
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<td>SLCO1A2</td>
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<td>Organic cations, carnitine</td>
<td>Experimental colitis in mice and rats</td>
<td>Yes</td>
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<td>Intestine, kidney</td>
<td>Di- and tripeptides</td>
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<td>Brain, small intestine</td>
<td>Serotonin</td>
<td>Experimental colitis in mice; human intestine-derived cell line</td>
<td>No</td>
<td>Coates et al., 2006; Foley et al., 2007; Linden et al., 2005</td>
</tr>
</tbody>
</table>
Table 2. Summary of patients included in the study.

<table>
<thead>
<tr>
<th></th>
<th>IBD</th>
<th>control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (CD/UC)</td>
<td>102 (49/53)</td>
<td>23</td>
</tr>
<tr>
<td>Number of biopsies (CD/UC)</td>
<td>193 (97/96)</td>
<td>43</td>
</tr>
<tr>
<td>Males/Females/Unknown</td>
<td>40/61/1</td>
<td>7/16/0</td>
</tr>
<tr>
<td>Average age (SD)</td>
<td>48 (15)</td>
<td>60 (10)</td>
</tr>
<tr>
<td>Average BMI (SD)</td>
<td>24.9 (5.0)</td>
<td>24.0 (4.0)</td>
</tr>
<tr>
<td>Number of patients on therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Steroids</td>
<td>28</td>
<td>0</td>
</tr>
<tr>
<td>• Azathioprine</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>• Mesalazine</td>
<td>29</td>
<td>0</td>
</tr>
<tr>
<td>• None</td>
<td>29</td>
<td>19</td>
</tr>
<tr>
<td>• Other</td>
<td>36</td>
<td>4</td>
</tr>
<tr>
<td>Smokers/non-smokers/unknown</td>
<td>26/64/12</td>
<td>-</td>
</tr>
<tr>
<td>Patients in remission</td>
<td>29</td>
<td>-</td>
</tr>
<tr>
<td>Inflamed/non-inflamed (biopsies total)</td>
<td>73/120</td>
<td>-</td>
</tr>
<tr>
<td>Inflamed/non-inflamed (paired biopsies)</td>
<td>53/53</td>
<td>-</td>
</tr>
<tr>
<td>Patients excluded</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 3. The relative mRNA expression levels of 15 SLC transporters. The expression level of the target genes in each sample was evaluated based on the ratio of cDNA copies of a target gene vs. cDNA copies of villin. Numbers represent mean values (±SD). Targets with detectable mRNA expression levels and statistical significant changes are marked in bold (ns: not significant).

<table>
<thead>
<tr>
<th>SLC</th>
<th>Control</th>
<th>CD</th>
<th>p- value (vs control)</th>
<th>UC</th>
<th>p- value (vs control)</th>
<th>p- value (CD vs UC)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PEPT1</strong></td>
<td>7.44 (±4.33)</td>
<td>10.02 (±6.39)</td>
<td>ns</td>
<td>10.16 (±6.79)</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td><strong>OCNT1</strong></td>
<td>2.00 (±1.28)</td>
<td>2.32 (±1.39)</td>
<td>ns</td>
<td>2.76 (±2.16)</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td><strong>ASBT</strong></td>
<td>0.96 (±0.85)</td>
<td>0.12 (±0.12)</td>
<td>&lt; 0.001</td>
<td>0.21 (±0.19)</td>
<td>&lt; 0.05</td>
<td>ns</td>
</tr>
<tr>
<td><strong>CNT2</strong></td>
<td>0.85 (±0.63)</td>
<td>0.76 (±0.57)</td>
<td>ns</td>
<td>0.39 (±0.27)</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td><strong>CNT1</strong></td>
<td>0.15 (±0.09)</td>
<td>0.25 (±0.15)</td>
<td>&lt; 0.01</td>
<td>0.22 (±0.13)</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td><strong>OCTN2</strong></td>
<td>0.1 (±0.05)</td>
<td>0.02 (±0.01)</td>
<td>&lt; 0.001</td>
<td>0.02 (±0.02)</td>
<td>&lt; 0.001</td>
<td>ns</td>
</tr>
<tr>
<td><strong>SERT</strong></td>
<td>0.05 (±0.04)</td>
<td>0.16 (±0.09)</td>
<td>&lt; 0.001</td>
<td>0.15 (±0.12)</td>
<td>&lt; 0.05</td>
<td>ns</td>
</tr>
<tr>
<td><strong>OATP2B1</strong></td>
<td>0.01 (±0.01)</td>
<td>0.07 (±0.07)</td>
<td>&lt; 0.001</td>
<td>0.04 (±0.02)</td>
<td>&lt; 0.05</td>
<td>ns</td>
</tr>
<tr>
<td><strong>ENT2</strong></td>
<td>0.01 (±0.01)</td>
<td>0.04 (±0.03)</td>
<td>&lt; 0.001</td>
<td>0.05 (±0.03)</td>
<td>&lt; 0.01</td>
<td>ns</td>
</tr>
<tr>
<td><strong>ENT1</strong></td>
<td>0.008 (±0.01)</td>
<td>0.02 (±0.02)</td>
<td>&lt; 0.001</td>
<td>0.02 (±0.01)</td>
<td>&lt; 0.05</td>
<td>ns</td>
</tr>
<tr>
<td><strong>OCT1</strong></td>
<td>0.004 (±0.007)</td>
<td>0.003 (±0.002)</td>
<td>ns</td>
<td>0.004 (±0.005)</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td><strong>OATP4A1</strong></td>
<td>0.002 (±0.003)</td>
<td>0.01 (±0.009)</td>
<td>&lt; 0.001</td>
<td>0.01 (±0.009)</td>
<td>&lt; 0.001</td>
<td>ns</td>
</tr>
<tr>
<td><strong>OATP1A2</strong></td>
<td>0.002 (±0.006)</td>
<td>0.00006 (±0.0001)</td>
<td>-</td>
<td>0.00005 (±0.00005)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>CNT3</strong></td>
<td>0.001 (±0.001)</td>
<td>0.003 (±0.004)</td>
<td>-</td>
<td>0.001 (±0.001)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>OAT2</strong></td>
<td>0.0009 (±0.0002)</td>
<td>0.001 (±0.002)</td>
<td>-</td>
<td>0.003 (±0.008)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Colon**

<table>
<thead>
<tr>
<th>SLC</th>
<th>Control</th>
<th>CD</th>
<th>p- value (vs control)</th>
<th>UC</th>
<th>p- value (vs control)</th>
<th>p- value (CD vs UC)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OCTN1</strong></td>
<td>0.53 (±0.53)</td>
<td>0.76 (±0.8)</td>
<td>ns</td>
<td>0.91 (±0.78)</td>
<td>&lt; 0.05</td>
<td>ns</td>
</tr>
<tr>
<td><strong>OCTN2</strong></td>
<td>0.26 (±0.14)</td>
<td>0.05 (±0.04)</td>
<td>&lt; 0.001</td>
<td>0.04 (±0.05)</td>
<td>&lt; 0.001</td>
<td>ns</td>
</tr>
<tr>
<td><strong>PEPT2</strong></td>
<td>0.18 (±0.23)</td>
<td>0.58 (±0.63)</td>
<td>&lt; 0.05</td>
<td>0.67 (±1.14)</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td><strong>ENT2</strong></td>
<td>0.09 (±0.11)</td>
<td>0.17 (±0.07)</td>
<td>&lt; 0.001</td>
<td>0.2 (±0.17)</td>
<td>&lt; 0.001</td>
<td>ns</td>
</tr>
<tr>
<td><strong>CNT2</strong></td>
<td>0.05 (±0.05)</td>
<td>0.35 (±0.42)</td>
<td>&lt; 0.001</td>
<td>0.6 (±0.79)</td>
<td>&lt; 0.001</td>
<td>ns</td>
</tr>
<tr>
<td><strong>ENT1</strong></td>
<td>0.02 (±0.02)</td>
<td>0.08 (±0.06)</td>
<td>&lt; 0.001</td>
<td>0.07 (±0.07)</td>
<td>&lt; 0.001</td>
<td>ns</td>
</tr>
<tr>
<td><strong>OATP2B1</strong></td>
<td>0.01 (±0.01)</td>
<td>0.08 (±0.07)</td>
<td>&lt; 0.001</td>
<td>0.13 (±0.13)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td><strong>OATP4A1</strong></td>
<td>0.01 (±0.01)</td>
<td>0.03 (±0.06)</td>
<td>&lt; 0.01</td>
<td>0.08 (±0.11)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td><strong>OCT1</strong></td>
<td>0.01 (±0.01)</td>
<td>0.01 (±0.07)</td>
<td>ns</td>
<td>0.008 (±0.008)</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td><strong>ASBT</strong></td>
<td>0.007 (±0.008)</td>
<td>0.0002 (±0.0005)</td>
<td>&lt; 0.001</td>
<td>0.0005 (±0.001)</td>
<td>&lt; 0.001</td>
<td>-</td>
</tr>
<tr>
<td><strong>OAT2</strong></td>
<td>0.003 (±0.006)</td>
<td>0.0008 (±0.001)</td>
<td>-</td>
<td>0.001 (±0.003)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>SERT</strong></td>
<td>0.002 (±0.003)</td>
<td>0.002 (±0.004)</td>
<td>-</td>
<td>0.003 (±0.005)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>CNT3</strong></td>
<td>0.001 (±0.001)</td>
<td>0.002 (±0.004)</td>
<td>-</td>
<td>0.008 (±0.017)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>CNT1</strong></td>
<td>0.001 (±0.001)</td>
<td>0.001 (±0.006)</td>
<td>-</td>
<td>0.001 (±0.0006)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>OATP1A2</strong></td>
<td>0.0003 (±0.001)</td>
<td>0.00006 (±0.0001)</td>
<td>-</td>
<td>0.00007 (±0.0001)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Table 4. Changes in the mRNA expression levels of SLCs in IBD patients on steroid therapy.

Statistical significance was estimated using unpaired t-test with two tailed p-value.

<table>
<thead>
<tr>
<th>SLC</th>
<th>Region</th>
<th>Disease</th>
<th>Group</th>
<th>Fold change</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCTN2</td>
<td>Colon</td>
<td>CD</td>
<td>males</td>
<td>2.88</td>
<td>0.0003</td>
</tr>
<tr>
<td>OCTN2</td>
<td>Colon</td>
<td>UC</td>
<td>males</td>
<td>2.28</td>
<td>0.0115</td>
</tr>
<tr>
<td>ASBT</td>
<td>Terminal ileum</td>
<td>CD</td>
<td>males</td>
<td>-7.23</td>
<td>0.0708</td>
</tr>
<tr>
<td>OATP4A1</td>
<td>Colon</td>
<td>UC</td>
<td>females</td>
<td>1.99</td>
<td>0.1276</td>
</tr>
<tr>
<td>OATP4A1</td>
<td>Colon</td>
<td>UC</td>
<td>males</td>
<td>2.00</td>
<td>0.1416</td>
</tr>
<tr>
<td>OATP2B1</td>
<td>Colon</td>
<td>CD</td>
<td>females</td>
<td>-1.86</td>
<td>0.144</td>
</tr>
<tr>
<td>ENT1</td>
<td>Terminal ileum</td>
<td>CD</td>
<td>females</td>
<td>-1.78</td>
<td>0.1494</td>
</tr>
</tbody>
</table>
Fig. 2

A

Relative mRNA expression

<table>
<thead>
<tr>
<th></th>
<th>control</th>
<th>UC non-inflamed</th>
<th>UC inflamed</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENT1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ENT2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNT2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OATP2B1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OATP4A1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OCTN1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OCTN2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEPT1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

B

mRNA level (fold change)

<table>
<thead>
<tr>
<th></th>
<th>UC non-inflamed</th>
<th>UC inflamed</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENT1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ENT2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNT2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OATP2B1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OATP4A1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OCTN1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OCTN2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEPT1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:** The figure illustrates the relative mRNA expression and mRNA level (fold change) for different genes in control, UC non-inflamed, and UC inflamed conditions. Significant differences are indicated by asterisks (*) and triple asterisks (***).
### Supplementary table 1. Summary of the control group used in the study.

<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Sex</th>
<th>BMI</th>
<th>Reason for colonoscopy/Diagnosis</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>66</td>
<td>0</td>
<td>25</td>
<td>Sigma diverticulitis with abscess</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>72</td>
<td>0</td>
<td>29</td>
<td>Diverticulosis, psoriasis</td>
<td>Calcipotriol creme, irbesartan</td>
</tr>
<tr>
<td>3</td>
<td>59</td>
<td>1</td>
<td>-</td>
<td>Hyperplastic polyp, hemorrhoids</td>
<td>Esomeprazol</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>0</td>
<td>28</td>
<td>Diverticulitis, sigma polyp</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>68</td>
<td>1</td>
<td>19</td>
<td>Elevated CRP-level, emphysema</td>
<td>Estradiol, ibuprofen, lornoxicam</td>
</tr>
<tr>
<td>6</td>
<td>51</td>
<td>0</td>
<td>-</td>
<td>Hemorrhoids</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>55</td>
<td>1</td>
<td>-</td>
<td>Multiple polyps, primary biliary cirrhosis, Billroth-I operation, GERD, adipositas</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>66</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>60</td>
<td>0</td>
<td>21</td>
<td>Polyps, angiodysplasia of the stomach, anemia, paraproteinemia</td>
<td>Mercaptopurine, azathioprine, abecarnil, alendronate, estradiol, ibuprofen, lornoxicam</td>
</tr>
<tr>
<td>10</td>
<td>73</td>
<td>0</td>
<td>24</td>
<td>GERD, polyps</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>73</td>
<td>1</td>
<td>22</td>
<td>Tumor screening</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>78</td>
<td>1</td>
<td>21</td>
<td>Diverticulosis, heart disease, hypertension, hypercholesterinemia</td>
<td>Metoprolol, amlodipine, phenprocoumon, alendronate, estradiol, ibuprofen, lornoxicam, hydrochlorothiacid, calcium, vitamin D</td>
</tr>
<tr>
<td>13</td>
<td>56</td>
<td>1</td>
<td>-</td>
<td>Tumor of the mammary gland</td>
<td>-</td>
</tr>
<tr>
<td>14</td>
<td>42</td>
<td>1</td>
<td>-</td>
<td>Healthy</td>
<td>-</td>
</tr>
<tr>
<td>15</td>
<td>70</td>
<td>1</td>
<td>-</td>
<td>Healthy</td>
<td>-</td>
</tr>
<tr>
<td>16</td>
<td>45</td>
<td>1</td>
<td>-</td>
<td>Healthy</td>
<td>-</td>
</tr>
<tr>
<td>17</td>
<td>53</td>
<td>1</td>
<td>-</td>
<td>Healthy</td>
<td>-</td>
</tr>
<tr>
<td>18</td>
<td>63</td>
<td>1</td>
<td>-</td>
<td>Healthy</td>
<td>-</td>
</tr>
<tr>
<td>19</td>
<td>67</td>
<td>1</td>
<td>-</td>
<td>Healthy</td>
<td>-</td>
</tr>
<tr>
<td>20</td>
<td>52</td>
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<td>-</td>
<td>Healthy</td>
<td>-</td>
</tr>
<tr>
<td>21</td>
<td>68</td>
<td>1</td>
<td>-</td>
<td>Healthy</td>
<td>-</td>
</tr>
<tr>
<td>22</td>
<td>45</td>
<td>1</td>
<td>-</td>
<td>Healthy</td>
<td>-</td>
</tr>
<tr>
<td>23</td>
<td>69</td>
<td>1</td>
<td>-</td>
<td>Healthy</td>
<td>-</td>
</tr>
</tbody>
</table>

**Abbreviations:**

GERD: gastroesophageal reflux disease
CRP: C-reactive protein
**Supplementary table 2. Summary of IBD patients used in the study.**

<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Sex</th>
<th>BMI</th>
<th>IBD</th>
<th>Medication</th>
<th>smoker (pw)</th>
<th>CDAI score</th>
<th>CAI score</th>
<th>Quality of life</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>0</td>
<td>27.7</td>
<td>CD</td>
<td>Steroids, azathioprine</td>
<td>0</td>
<td>170</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>2</td>
<td>56</td>
<td>1</td>
<td>-</td>
<td>UC</td>
<td>-</td>
<td>0</td>
<td>7</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>79</td>
<td>1</td>
<td>-</td>
<td>UC</td>
<td>-</td>
<td>0</td>
<td>7</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>35</td>
<td>1</td>
<td>25.6</td>
<td>UC</td>
<td>-</td>
<td>0</td>
<td>5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>46</td>
<td>1</td>
<td>30.4</td>
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<td>64</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>6</td>
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Supplementary table 2 (continued)

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**Abbreviations:**

PG: pyoderma gangrenosum  
0: male  
1: female
**Supplementary table 3.** Summary of p values obtained with statistical analysis between subgroups of IBD patients with respect to region, age, gender, steroid therapy and smoking prevalence.

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