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Comprehensive analysis of localization of 78 solute carrier genes throughout the subsections of the rat gastrointestinal tract

Jonathan Cedernaes [a,*], Pawel K. Olszewski [a,b], Markus Sällman Almén [a], Olga Stephansson [a], Allen S. Levine [b,c], Robert Fredriksson [a], Olof Nylander [a], Helgi B. Schiöth [a]

[a] Department of Neuroscience, Uppsala University, BMC, Uppsala SE 75124, Sweden
[b] Minnesota Obesity Center, University of Minnesota, Saint Paul, MN 55108, USA
[c] Department of Food Science and Nutrition, University of Minnesota, Saint Paul, MN 55108, USA

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ABSTRACT

Solute carriers (SLCs), the second largest super-family of membrane proteins in the human genome, transport amino acids, sugars, fatty acids, inorganic ions, essential metals and drugs over membranes. To date no study has provided a comprehensive analysis of SLC localization along the entire GI tract. The aim of the present study was to provide a comprehensive, segment-specific description of the localization of SLC genes along the rat GI tract by employing bioinformatics and molecular biology methods. The Unigene database was screened for rat SLC entries in the intestinal tissue. Using qPCR we measured expression of the annotated genes in the GI tract divided into the following segments: the esophagus, the corpus and the antrum of the stomach, the proximal and distal parts of the duodenum, ileum, jejunum and colon, and the cecum. Our Unigene-derived gene pool was expanded with data from in-house tissue panels and a literature search. We found 44 out of 78 (56%) of gut SLC transcripts to be expressed in all GI tract segments, whereas the majority of remaining SLCs were detected in more than five segments. SLCs are predominantly expressed in gut regions with absorptive functions although expression was also found in segments unrelated to absorption. The proximal jejunum had the highest number of differentially expressed SLCs. In conclusion, SLCs are a crucial molecular component of the GI tract, with many of them expressed along the entire GI tract. This work presents the first overall road map of localization of transporter genes in the GI tract.

1. Introduction

Membrane bound proteins represent about 27% of the entire human proteome and most of them belong to three major functional groups: receptors, transporters or enzymes [1]. The largest superfamily of membrane bound proteins are G protein coupled receptors (GPCRs) [2] while the second largest family is solute carriers (SLCs) comprising 384 known members [3]. SLCs outnumber by far all other transporter classes, including ion channels, water channels, pumps and ABC transporters. Amino acids, sugars, fatty acids, inorganic ions, essential metals and drugs are transported over the cell membrane by SLCs which act as exchangers, coupled transporters and passive transporters [3,4]. We have recently classified the entire repertoire of human SLC genes, classifying fifteen of the SLC subfamilies into four main groups, namely α-, β-, γ-, and δ-groups [3]. About 40% of all SLCs are still orphans without known substrates. Many of these were just recently described and thus in most cases lack biological characterization (details about SLCs can be found in the SLC tables [5]).

Mapping gene localization for the entire gastrointestinal tract is important since the different segments have such varied physiological functions while still being a part of the same organ system. Different molecules are absorbed or secreted in different parts of the GI tract's anatomical regions, such as in the proximal or distal parts of the duodenum or ileum. Common diseases such as inflammatory bowel diseases and cancers of the GI tract are also known to more often affect certain regions of the GI tract, and in some cases more frequently its proximal or distal areas. For example, Crohn's disease more often affects the terminal ileum [6].

The importance of SLCs in absorption of nutrients and pharmaceuticals in the gastrointestinal (GI) tract is well established. For example, mutations in SLC genes have been linked to Hartnup's disorder [7,8], congenital chloride diarrhea [9], glucose galactose malabsorption [10] and lysinuric protein intolerance [11]. Moreover, expression levels of SLCs change in inflammatory bowel disease (IBD) [12] and colonic cancer [13,14]. The proximodistal

Abbreviations: SLCs, Solute carriers; RT-qPCR, Real-time quantitative PCR.

* Corresponding author.
E-mail address: jonathan.cedernaes@neuro.uu.se (J. Cedernaes).

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mapping of many SLCs in the gut has not been performed in a thorough manner. There is however previous evidence indicating that SLC transporters are differentially expressed along the gut axis, even when comparing proximal and distal subsegments [15–17]. Previous studies of SLCs in the GI tract have often employed immunoblotting, in situ hybridization and immunohistochemistry [18,19]. Using RT-qPCR, SLC1a1 has been detected in the small intestine using a three- and six-segment model while SLC1a4 has been analyzed with the latter approach [20–22]. It should however be noted that SLC 1 genes have not been mapped in other parts of the GI tract. Members 5–11 of the SLC 7 family have also been identified with Real-time (RT)-qPCR in the murine stomach, duodenum, jejunum, ileum and colon, but proximal vs. distal division was disregarded [23]. Despite the large potential in RT-qPCR, providing excellent sensitivity, this method has to a limited degree been applied to study localization of genes in subsections of the GI tract. Better knowledge of SLCs' proximodistal distribution in the GI tract provides fundamental physiological information and has clinical relevance relating to absorption of substrates as well as for target drug design/delivery methods [24–26]. RT-qPCR allows for a unique opportunity for simultaneous analysis of a high number of mRNA profiles throughout complex systems, increasing the probability of linking localization and physiological roles.

In the current paper, we present a longitudinal GI tract expression profile of 78 SLCs, virtually covering all the SLC genes expressed in this region of the body. We also present a detailed description as to whether the genes have been previously studied in the GI tract and, where established, their subcellular localization. We studied all SLCs that had evidence in either the Unigene database or from an in-house tissue panel screening that they were expressed in the intestine. The list of studied SLCs was further expanded by a literature search. Expression of the SLCs was examined along the GI tract divided into 12 segments: the esophagus, the corpus and the antrum of the stomach, the proximal and distal parts of the duodenum, jejunum, ileum, and colon, and the cecum, using RT-qPCR with a validated range of house keeping genes.

2. Materials and methods

2.1. Animal handling and tissue isolation for quantitative real-time qPCR

Male Dark Agouti rats (Scanbur AB, Sweden) weighing 200–215 g, were maintained under constant conditions (12:12-h light–dark cycle; 21 °C). Before the experiments, the animals were fasted overnight with free access to water. The following morning at approximately 8 am, the animals were intraperitoneally anesthetized with Na-5-ethyl-1-(1′-methyl-propyl)-2-thiobarbituric acid (Inactin®) at a dose of 125 mg per kg of body weight. Body temperature was maintained at 37.5 ± 0.5 °C using a temperature regulator. Subsequently, a tracheotomy was performed and a cannula (PE-200) was inserted, ensuring free airways. The abdominal cavity was opened by a midline incision and the following structures, about 5–10 mm in length, were isolated and removed: Distal oesophagus (a few mm from the stomach), corpus and antrum of the stomach, proximal duodenum (1 mm from the pylorus), distal duodenum (4 cm from pylorus), proximal jejunum (9 cm from pylorus), distal jejunum (19 cm from pylorus), proximal ileum (29 cm from pylorus), distal ileum (2.5 cm from the ileocecal valve), cecum, proximal colon (5 cm from ileocecal valve) and distal colon (12 cm from the ileocecal valve). The entire GI tract wall was isolated for RT-qPCR analysis.

Following the operation, the animals were euthanized by an intravenous bolus injection of a saturated KCl solution. All protocols involving animals were approved by the Uppsala Ethic Committee and comply with all policies and regulations outlined by the Swedish Animal Protection Act.

2.2. RNA isolation and cDNA synthesis

RNA isolation and cDNA synthesis were performed as previously described [27].

2.3. RT-qPCR

In total the expression patterns of 78 SLC genes were analyzed in the abovementioned twelve different tissue segments from the rat GI tract. All primers were designed using Beacon Primer Design 7.0 software (Premier Biosoft, USA) and are documented in Supplementary file 1. The RT-qPCR experiments were done as previously described [27].

2.4. Data analysis and calculation of expression

The RT-qPCR data was analyzed with the Bio-Rad iQ5 software v2.0 software (Bio-Rad Laboratories, Sweden). The analysis was performed as previously described [27].

2.5. Data mining

Unigene is a resource that collects all available nucleotide sequences for genes and information about where they were collected. An initial screening procedure for potential intestinal SLC genes in the rat was performed by examining the expression annotation in this database. We downloaded the Unigene data for rat from NCBI's FTP-page and queried it for SLC genes, which should have a gene symbol starting with "Slc", expressed in intestinal tissues using local scripts. The representative mRNA sequences of the retrieved hits were downloaded from NCBI's genebank and used for primer design.

3. Results

Our initial selection of 83 SLC genes (for full list see Supplementary file 1) for the analysis in the rat GI tract was based on three criteria. First, we used the Unigene database as described below. Second, we utilized the in-house tissue panel of SLC genes analyzed at our laboratory (Robert Fredriksson, unpublished data). Third, we searched the relevant literature and identified other SLC genes known to be expressed in the GI tract. We included genes that had not been characterized in detail as well genes that were well characterized as they could serve as reference genes.

The screening of Unigene for rat entries containing the SLC gene symbol produced 342 positive results. We then selected entries annotated as expressed in intestinal tissues, which gave us a set of 52 Unigene entries representing potential intestinal SLC genes. Forty seven of these genes are denoted to be expressed in the small intestine and 24 in the large intestine. According to the database, many of these SLCs were also expressed in other organs and tissue types, including the brain (39 SLCs), prostate (38), kidney (37) and liver (32).

Aside from the 52 genes derived from the Unigene database, we expanded the studied transcripts by 31 additional SLCs based on the aforementioned in-house tissue panel results and a literature search.

All the studied segments, except for the esophagus and cecum, were further divided into equal-length proximal and distal parts to obtain a proximodistal expression pattern for each segment and gene. The SLC genes from the Unigene dataset for which we were able to construct working primers for (50 out of the 52), were all

detectable in our rat GI tissue using RT-qPCR. This validates this dataset as being accurate to show genes that are expressed in the GI tract. Conversely, SLC7a3, SLC7a4 and SLC17a3 were not detectable [28,29], proving that our model did not produce false positive outcomes.

Among the remaining 78 genes whose expression was detected, 44 (56%) were ubiquitously expressed, i.e. in all of the twelve studied GI tract segments (Fig. 1). Among the remaining SLC transcripts present in the GI tract, only three (SLC14a2, SLC16a7, SLC26a9) were identified in fewer than five segments. Three genes were present in five segments (SLC1a7, SLC2a7, SLC14a1), three genes in six (SLC1a2, SLC2a2, SLC5a9), two genes in seven and five genes in eight segments. Among the non-ubiquitous SLCs, more genes were expressed in the proximal and distal parts of the small intestine and colon (Supplementary file 2). When proximal and distal subsegments were compared, an equal number of non-ubiquitous genes were found in both parts of the stomach (56). In the duodenum, the proximal subsegment expressed 60 and the distal subsegment 61 SLCs. This contrasts to the jejunum (75 vs 73), ileum (74 vs 69) and colon (73 vs 68), where slightly more genes were localized to the proximal than the distal subsegments. The esophagus and cecum expressed 51 and 59 SLCs, respectively. SLC families that were consistently found throughout the GI tract were SLC27, SLC35, SLC37, SLC38 and SLC43.

Orphan genes accounted for 14% (11) of the investigated genes. The orphan genes were: SLC16a6, SLC22a17, SLC22a23, SLC25a36, SLC25a38, SLC25a39, SLC25a44, SLC25a46, SLC35f5, SLC38a10, and SLC43a3. All were found to be expressed throughout the GI tract.

In addition to our localization analysis, we reviewed the current literature (Supplementary file 3) for the initial selection of SLCs. All

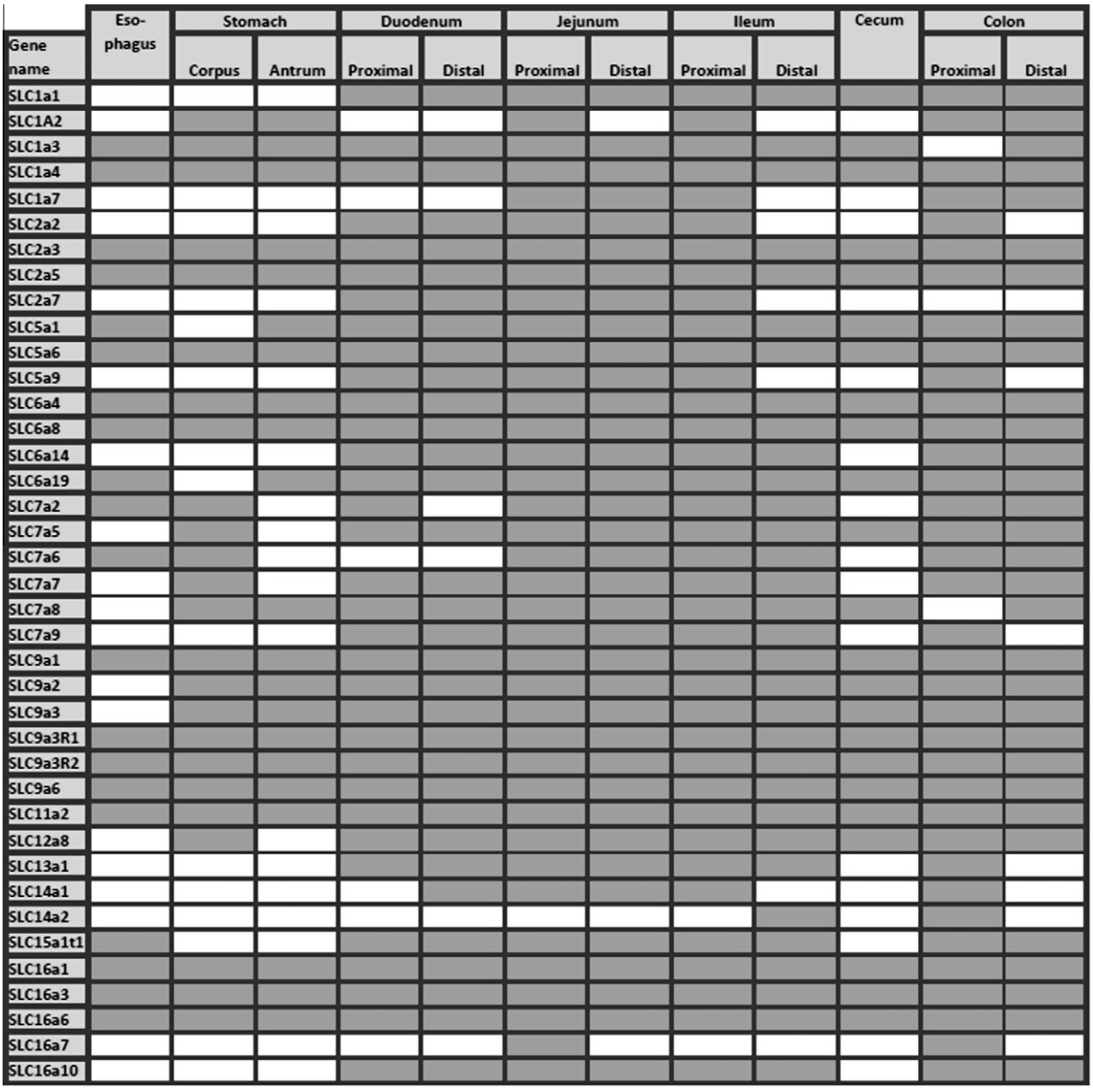

Fig. 1. Anatomical localization of SLCs along the GI tract, showing in which GI tract subsegments the genes were expressed. Grey-colored cells indicate expression; white cells indicate no expression. The GI tract was divided into twelve subsegments: esophagus, corpus and antrum of the stomach, proximal and distal parts of the duodenum, jejunum, ileum and colon, and cecum.

Gene name	Eso-phagus	Stomach		Duodenum		Jejunum		Ileum		Cecum	Colon	
		Corpus	Antrum	Proximal	Distal	Proximal	Distal	Proximal	Distal		Proximal	Distal
SLC22a1												
SLC22a5												
SLC22a17												
SLC22a23												
SLC25a1												
SLC25a3												
SLC25a10												
SLC25a20												
SLC25a22												
SLC25a28												
SLC25a36												
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SLC25a46												
SLC26a3												
SLC26a9												
SLC27a1												
SLC27a4												
SLC28a1												
SLC28a2												
SLC29a1												
SLC30a4												
SLC31a1												
SLC33a1												
SLC35a2												
SLC35c1												
SLC35f5												
SLC36a1												
SLC37a3												
SLC37a4												
SLC38a2												
SLC38a10												
SLC39a4												
SLC39a5												
SLC39a14												
SLC40a1												
SLC43a1												
SLC43a3												

Fig. 1 (*continued*)

but ten of the 81 SLCs, and all but three of the Unigene-derived genes, were found to be known to be specifically expressed in the intestine.

4. Discussion

SLCs play a crucial role in the GI tract cell function as well as ability to obtain nutritive and non-nutritive substances. The current study provides a unique, comprehensive overview of the localization of genes encoding SLCs along the GI tract. We used a detailed division of the GI tract, which took into account subtle, otherwise undetectable differences in the localization of each gene between proximal and distal GI subsegments. Using this model, mRNA levels of 78 SLCs belonging to 28 SLC gene families were analyzed (Fig. 1).

Many of the genes studied herein were found to be differently expressed, i.e. present or absent, in the proximal versus distal parts of each of the ''classical'' GI tract regions, which indicates that the GI segments should not be treated as genetically homogenous entities, but rather should be studied according to the precise localization of their molecular components. This can facilitate better understanding of the absorption processes, help in conceptualizing the function of pharmacological agents, as well as decipher pathological changes along the GI tract.

Longitudinal GI tract distribution profiles of the few SLC genes reported thus far tend to be in good agreement with our results. For example, SLC11a2, encoding the divalent metal ion transporter 1, DMT1, is expressed in the stomach and throughout the small and large intestine [30,31]. High levels of the SLC15a1 gene encoding di/tripeptide transporter PEPT1, have been shown throughout the small intestine, while the cecum and stomach were devoid of SLC15a1 mRNA [32,33].

The majority of the SLCs included in the analysis (44 out of 78, or 56%) were found to be ubiquitously expressed along the GI tract. Many of these genes were detected in parts of the GI tract where absorption occurs as well as in segments unrelated to absorption.

It shows that these SLCs may play a significant role as relay molecules allowing their substrates to enter the general circulation from the gut lumen and they may also be essential for functioning of cells within the GI tract. Some of the SLCs studied in this project transport the same type of substances and yet their localization in the GI tract overlaps, which indicates that these transporters may act concurrently and, if necessary, provide compensation for one another. An excellent example of this overlap is the triplet of genes: SLC7a2, SLC7a5 and SLC7a7.

More SLCs are expressed in gut regions with absorptive functions, such as the duodenum, jejunum, ileum and colon (see Supplementary file 2). This difference is somewhat more apparent when the data are analyzed according to the classical anatomical dissection without the proximodistal segment subdivision; in that case, the jejunum is the region with the highest number of differentially expressed SLCs. As the entire GI tract wall was used in our analysis, the ubiquitous presence of many SLC transporters may reflect gene expression in non-mucosal layers of the GI tract wall. For example, SLC5a1 encoding a protein dubbed SGLT1, has been found not in the mucosa, but in the myenteric plexus of the stomach and colon [34]. This may explain why in our study SLC5a1 expression was found not only in the small intestine but also in the stomach, colon and esophagus.

When analyzing the distribution according to our twelve-segment model, the highest number of SLCs was detected in the proximal segment of the jejunum (see Supplementary file 2). It is noteworthy that this distribution pattern differs to some extent from the bell-shaped SLC expression curve seen if the expression was divided according to the classical GI tract division, i.e. with no proximal and distal divisions. Furthermore, in the ileum, 74 SLCs were expressed in the proximal subsegment, whereas 69 transcripts were identified in the distal subsegment. This shows that gene localization patterns vary along the length of a given intestinal region, which signifies the need of applying a detailed proximodistal dissection model in future studies.

Some of our expression profiles differ somewhat from previous findings. This can be due to methodological differences, including dissection as other authors performed biopsies of only mucosa or used entire GI tract segments. Differences may also be species- or individual-specific; the latter especially in GI tract pathology. Whereas Slitt et al. report that SLC22a1 is expressed in the stomach [35], we found no expression in the corpus, but in the antrum. The mRNA expression does not always correlate with protein expression, since the protein turnover rate can vary, and translational or post-translational regulation of the genes can occur [36,37]. Future studies should therefore also study protein expression of the genes analyzed in this study.

It is known that mRNA levels of genes regulating substrate absorption may vary due to the time of the day and to the feeding state [38–40]. In the current study, gene expression levels were measured in the morning after an overnight fast and it is important to be aware that the expression could be different in the fed state or at a different time of the day. The effect of fasting on SLC gene expression in the murine small intestine has been studied and about 15% of the studied 243 SLCs were differentially expressed [41].

Finally, a large proportion of genes in this study (11 out of 78), were orphans, belonging to six SLC gene families. All were ubiquitously expressed, which suggests a potentially important role for the functioning of the entire GI tract. Most orphans belonged to the SLC25 family, known as the mitochondrial transporters [42]. Their widespread distribution could possibly suggest overlapping physiological functions. Almost all of the SLC genes found in the Unigene database were found to be expressed in our model and this was also supported by the literature, validating this database as a reliable initial screening tool.

In sum, we present the most comprehensive and detailed characterization of 78 SLC gene expression in the rat GI tract. The results show that the majority are ubiquitously expressed in the GI tract. Among the remaining genes, most are detected in more than five segments. We characterized the expression of eleven orphans. Widespread distribution of SLCs in the GI tract points out to an important role for SLCs in gut physiology. Our twelve-segment model provides a unique illustration of the intestinal SLC mRNA distribution pattern. Proximodistal differences in gene localization found in our study suggest that employing a detailed anatomical division is desirable when analyzing gene expression in the GI tract.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bbrc.2011.07.005.

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