Abundance & Relative Segmental Expression of Intestinal Transporters in Caucasians: A Meta-Analysis

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Abstract

A database of available region-specific gut transporter expression data was collated from the literature based on a combination of absolute & relative quantification approaches. Weighted mean absolute and relative gut segmental expression was calculated for 16 transporters from 28 studies. The highest jejunum transporter abundance was for SLC15A1 (PepT1), with SLC10A2 (IBAT) showing the greatest variability between gut regions. This systematic analysis of gut regional transporter abundances is expected to be useful for gut transporter *In Vitro*-to-*In Vivo* Extrapolation (IVIVE).

Background & Objectives

Physiological-Based Pharmacokinetic (PBPK) models use IVIVE scaling factors that account for inter-individual variability in expression based on quantitative protein abundance. At present, the region-specific gut transporter expression levels are described within IVIVE-PBPK models based on relative expression, *i.e.,* relative to a reference gene or protein approaches *via* PCR or immunoblotting[1]. However, absolute transporter abundances are increasingly quantified using standards of known concentration by proteomic methods. The key objective of this study is to compile available region-specific gut transporter expression data to enable robust values to be used for scaling purposes in IVIVE-PBPK modelling.

Methods

Original articles quantifying intestinal transporter expression were retrieved on PubMed through a keyword search (*e.g.* 'Human', 'Intestinal', 'Transporter', 'Absolute' 'Relative', 'Protein', 'Expression', 'Abundance'. Studies were excluded where quantification took place in non-Caucasians, and subjects <18 years old; diseased tissue; the sample was reported in more than one study; a non-total membrane or pooled matrices and cDNA expression systems. The GetData Graph Digitizer was used to obtain numerical values from graphical data in publications. The weighted mean absolute and relative expression in each of 8 gut segments, including 7 small intestine segments (duodenum, 2 jejunum, and 4 ileum segments), and the colon was calculated. Relative expression data was normalised to the expression level in the proximal jejunum.

Results

Of the 2640 transporter expression measurements, 1767 were included from 28 studies in the final database, that did not breach the exclusion criteria. This included 16 transporters; 6 solute carriers (SLC) and 10 ATP-dependent (ABC) transporters. However, suitable absolute abundance data was not found for: SLC16A1 (MCT1), SLC2A2 (GLUT2), SLCO4C1 (OATP4C1), SLC22A4 (OCTN2), ABCC1 (MRP1) and ABCC4 (MRP4). No between study heterogeneity was found.

Table 1. Proximal jejunum transporter abundance in Caucasians obtained *via* meta-analysis. The mean, geometric mean (GM), coefficient of variation (CV) and sample number (N) is given.

Transporter	Proximal Jejunum Abundance (pmol transporter/mg membrane protein)			
	Mean	GM	CV(%)	N
ABCB1 (P-gp)[2, 3, 4]	0.4	0.37	65	11
ABCC2 (MRP2)[2, 3 ,4]	0.86	0.71	79	11
ABCC3 (MRP3)[2, 4]	0.58	0.49	64	7
ABCG2 (BCRP)[2, 3, 4]	0.34	0.29	63	11
SLC10A2 (ASBT/IBAT)[4]	0.01	0.01	43[a]	6
SLC15A1 (PepT1)[2, 3, 4]	3.69	3.41	41	11
SLCO2B1 (OATP2B1)[2, 3, 4]	0.4	0.32	74	11
SLC22A1 (OCT1)[4]	0.65	0.58	49	6
SLC22A3 (OCT3)[4]	0.06	0.83	74	6
SLC51A/B (OST-α/β)[5]	0.47[b]	0.47	99[c]	1

[a] Taken from mRNA data[6], [b] α-subunit used; [c] taken from α-subunit mRNA data[4]

Results (continued)

A simulation run using the Simcyp Simulator (V17, Sheffield, UK) in 2000 North European Caucasian virtual individuals was able to replicate the reported abundance values and the reported population variability for the 10 intestinal transporters **(Fig. 1).**

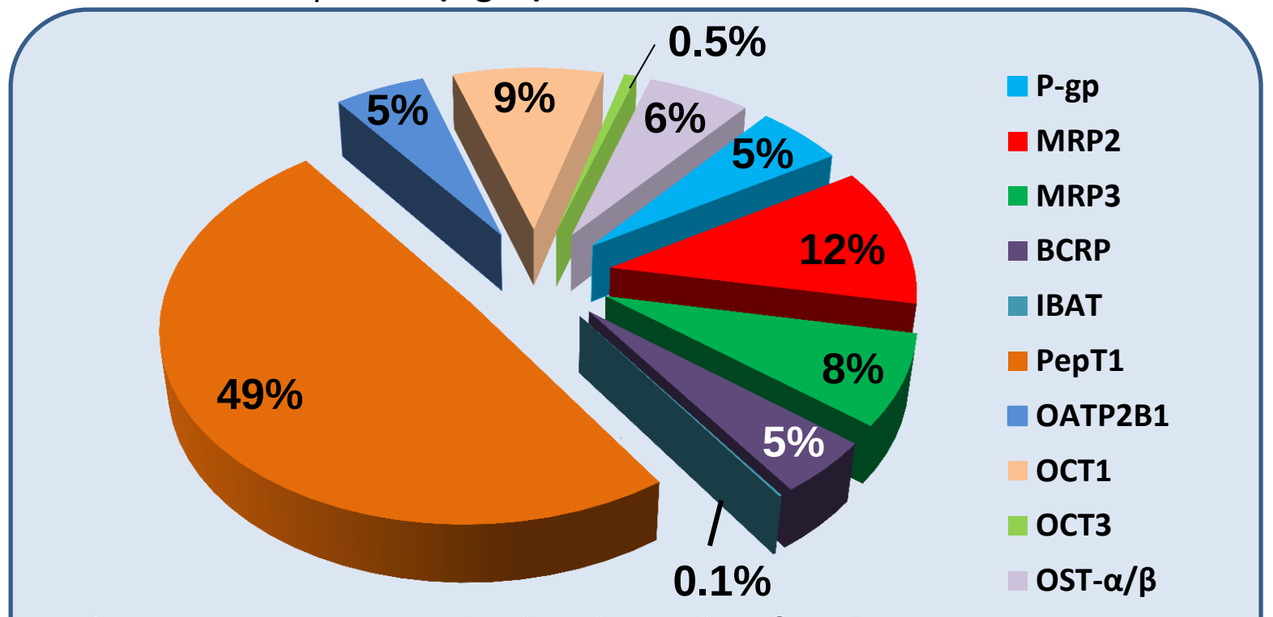

Fig. 1. Transporter protein abundance data for 10 gut transporters as a percentage of the total abundance following a simulation of 2000 virtual individuals using the Simcyp Simulator (V17 build 66).

The IBAT showed the greatest regional expression difference, with 18-fold higher expression in distal ileum *versus* proximal jejunum, while OATP2B1 showed the most uniform expression (**Fig. 2**). Relative quantification approaches yielded quite different segmental expression results from absolute for IBAT (**Fig. 2A**), which was not apparent for OATP2B1 (**Fig. 2B**).

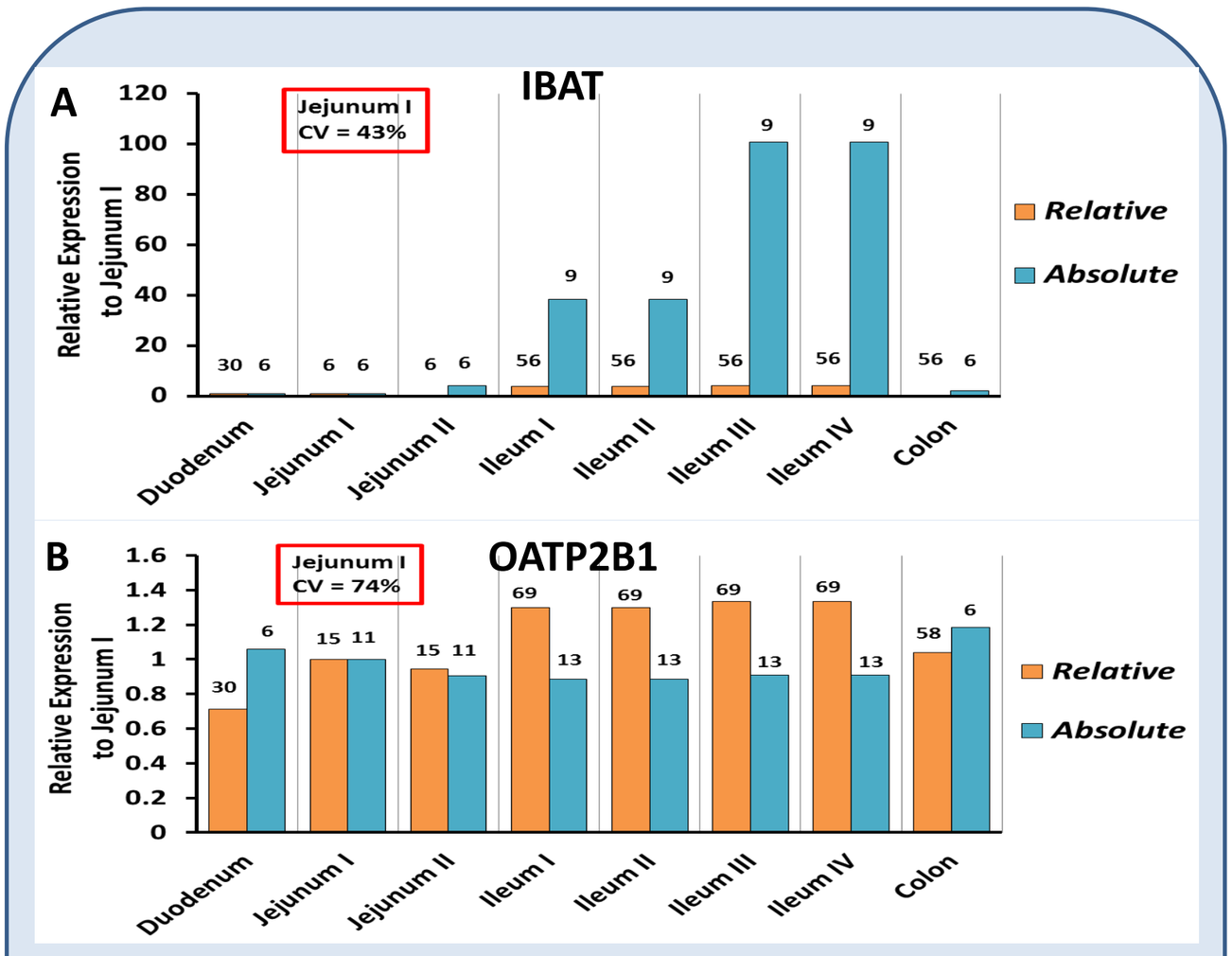

Fig. 2. IBAT (A) and OATP2B1 (B) expression relative to the proximal jejunum when meta-analysis was performed using 'Relative' or 'Absolute' quantification approaches. Values above bars are sample n.

Conclusions

This is the first in-depth analysis reporting region-specific intestinal transporter expression obtained *via* absolute and relative approaches and collated in a database. Therefore, this data can be expected to be useful for IVIVE in healthy adult Caucasian subjects. However, similar analyses are required for other ethnicities and disease states.

References

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