BACKGROUND

Organic anion transporter 7 (OAT7, SLC22A9) was identified in 2007 as a novel member of the SLC22 transporter family and is the first liver-specific functional OAT member in humans to date.

Hepatic uptake transporters have been shown to play a significant role in the absorption, distribution, toxicity and excretion of various xenobiotics, including HMGC-CoA reductase inhibitors (statins).

Though several transporters have been implicated in the hepatic uptake of statins, they seem to have only a partial contribution to the disposition of statins.

RESULTS

SLC22A9 mRNA Expression

Investigation of normalized cDNAs from 20 normal and tumor human tissues showed predominant expression of SLC22A9 in the liver.

Other tissues, including kidney and pancreas, expressed approximately 60-fold lower SLC22A9 mRNA levels.

Across the 126 liver samples, SLC22A9 mRNA expression was not normally distributed and showed 16-fold variability.

OAT7 Protein Expression

OAT7 protein expression measured across the 126 liver samples was a 25-fold variability and was not normally distributed.

OAT7 expression was investigated in cryosections of human liver in high- and low-expansivity individuals (B). Staining of sinusoidal hepatocyte membrane (green) was observed, whereas, canalicular membrane staining (red) did not show co-staining with the OAT7 signal.

No correlation was observed between SLC22A9 mRNA and OAT7 protein expression in the human liver samples, likely due to post-transcriptional/translational regulation.

OBJECTIVE AND METHODS

1. To investigate the potential contribution of OAT7 to the hepatic uptake of statins.

2. To identify factors that may contribute to variability in SLC22A9/OAT7 expression and function.

RESULTS (cont’d)

OAT7 Transport Function

The uptake of simvastatin, fluvastatin, atorvastatin and pravastatin was tested in vector-transfected (o) and OAT7-transfected (Δ) cells – of these, only pravastatin showed significantly higher accumulation (~2x) in OAT7 compared to vector-transfected cells.

Determination of kinetic properties of pravastatin uptake showed that OAT7 is a high-capacity, low-affinity transporter of pravastatin with:

\[ V_{\text{max}} = 2.3 \pm 0.3 \text{nmol/mg.min} \quad \text{and} \quad K_m = 1.0 \pm 0.3 \text{mM} \]

REFERENCES


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