Concordance Analysis of Renal Transporter Expression Changes in Human Nonalcoholic Steatohepatitis to Established Rodent NASH Models

Kayla L. Frost1, Joseph L. Jilek2, Erica L. Toth1, Michael J. Goedken2, Nathan J. Cherrington1
1Department of Pharmacology & Toxicology, University of Arizona, Tucson, AZ
2Rutgers Translational Sciences, Rutgers University, Piscataway, NJ

ABSTRACT

Interindividual alterations to renal elimination processes can lead to adverse drug reactions. Nonalcoholic steatohepatitis (NASH) is known to alter hepatic drug transport but may also affect renal transporters as well. This study investigates renal physiological changes in rodent and human NASH for identification of a model that recapitulates human alterations. Clinical chemistry and quantitative protein expression of drug transporters by surrogate peptide LC-MS/MS were used to characterize each rodent model relative to human NASH. MCD, Athero and AIOS exhibit an increase in blood urea nitrogen while all models, except Athero, demonstrate a decrease in GFR coinciding with human NASH. A significant decrease in renal basolateral uptake transporter OATP4C1 in mouse models (from 0.67 to 0.35 db/db; 0.27 FFDTH; 0.34 AIOS pmol/mg protein, respectively) coincides with the decrease in human OATP4C1 expression. Similarly, renal apical uptake transporter OAT1 exhibits a significant decrease in mouse models (from 4.59 to 0.45 db/db; 1.59 FFDTH; 2.83 AIOS, respectively) but a significant increase in MCD rats (1.67 to 4.17 pmol/mg protein) suggesting the mouse models are most appropriate to extrapolate to human values. Multiple renal apical efflux transporters are altered including an increase in expression of MRPI in MCD (0.17 to 0.30) but decreases of BCAP in db/db and AIOS (from 0.25 to 0.14, 0.13, respectively) and of MRP4 in mouse models (from 0.87 to 0.34 db/db; 0.29 FFDTH; 0.18 AIOS pmol/mg protein). Of these alterations, only the decrease in MRP4 recapitulates human expression. The renal basolateral efflux transporter MRPI3 was decreased in MCD and Athero rats (from 2.71 to 1.53, 1.68, respectively), and in each mouse model (from 9.49 to 8.33 db/db; 8.82 FFDTH, 8.44 AIOS pmol/mg protein, respectively), where the human trend was also decreased. These data exemplify alterations in renal physiology during NASH and identify corresponding rodent models, FFDTH and AIOS, for future pharmacokinetic studies.

METHODS

Human Samples: Quantitative proteomic analysis of human transporters obtained from human kidney FFPE needle biopsy samples

RESULTS

Concordance analysis of rodent renal transporter models against human renal drug transporters. FFDTH and AIOS models recapitulate some of the alterations observed in human.

CONCLUSIONS

These data suggest variations in renal drug transporter expression in response to altered renal physiology elicited by NASH. While individual transporters may differ, the FFDTH and AIOS mouse models most closely recapitulate the various alterations in clinical chemistry and human transporter protein expression changes in kidneys of NASH patients. These models provide a valuable resource to identify human interindividual variability in renal elimination.

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