

Rodent Models for Renal Disposition in Nonalcoholic Steatohepatitis

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Nonalcoholic steatohepatitis (NASH) has the ability to alter drug disposition through the disruption of drug transporters leading to potential adverse drug reactions. While disruption of hepatic drug transporters is well characterized in NASH, little is known about alterations in renal drug transporters caused by potential hepato-renal cross talk. Compensatory physiological changes by the kidney during liver disease is suggested to occur during NASH causing an alteration in renal disposition. The current study was designed to determine alterations in renal drug transporter expression in widely used rodent models of NASH. Clinical chemistry and transcriptional expression of renal drug transporters was determined to identify the model most representative of human NASH. NASH models include Sprague Dawley rats fed a methionine and choline deficient (MCD), atherogenic, or control diets, or C57 mice fed a fast food diet with thrice weekly thioacetamide injections (FFDTH), American lifestyle induced obesity syndrome (ALIOS), or control diet, and genetically defective leptin receptor mice fed an MCD diet (db/db). The MCD, atherogenic and ALIOS models exhibited a significant increase in blood urea nitrogen. However, only the MCD and ALIOS models had a significant increase in alanine transaminase relative to control mice. The FFDTH model experienced no significant changes in clinical chemistry for the liver or kidney. The db/db, FFDTH, and ALIOS models all presented a significant decrease in renal Oatp1a1 to 3, 22 and 44% of control, respectively. The FFDTH and ALIOS models expressed a reduction to 73 and 38% of control in Oat2. However, Oat3 was significantly increased to 184% of control in the db/db model. For the efflux transporters, Mrp2 and Mate1 presented a decrease to 65 and 69% of control in the FFDTH model. Interestingly, there is a downward trend of expression for both uptake and efflux renal transporters across the mouse models except for Oat3. Conversely, none of the rat models presented significant alterations in renal xenobiotic transporters. These data suggest alterations in renal drug transporters are associated with NASH in db/db and ALIOS models and demonstrate the potential for renal disposition changes during liver disease. Importantly, this provides a mechanistic basis for variability in the fate of drugs and environmental toxicants eliminated through renal clearance.