## S39-3 Transporter-mediated drug-drug interactions

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Transporters as well as metabolizing enzymes have been increasingly recognized as a determinant of pharmacokinetics. Hepatic uptake transporters determine not only the biliary excretion rate but also metabolic rate of drugs. Previously, we have reported that the clinically-reported drug-drug interaction between cerivastatin and cyclosporin A (CsA) is caused by the inhibition of hepatic uptake transporter(s). Following this report, a number of drug-drug interactions including other HMG-CoA reductase inhibitors, bosentan and repaglinide vs CsA have been reported to be caused by the inhibition of hepatic uptake transporter(s) including OATP1B1. Recently, we have shown that CsA has a long-lasting inhibitory effect on the hepatic uptake transporter(s) for sulfobromophthaleine in rats. After exposure to CsA, the transporter function remained low even in the absence of CsA. This long-lasting inhibition was also observed in the rat Oatp1a1-expressing cells and human OATP1B1- and OATP1B3-expressing cells. By this mechanism, more severe drug-drug interactions should occur comparing to those assuming a simple competitive inhibition. Now, we are investigating a long-lasting inhibition by other inhibitor drugs.