Molecular mechanisms governing different pharmacokinetics of ginsenosides and potential for ginsenoside-perpetrated herb-drug interactions on OATP1B3

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- Supporting Information Appendix S4 -

Rifampin inhibition of human OATP1B3- and rat Oatp1b2-mediated uptakes of the ppt-type ginsenosides, plasma pharmacokinetics of rifampin in rats and rifampin-perpetrated drug-drug interactions

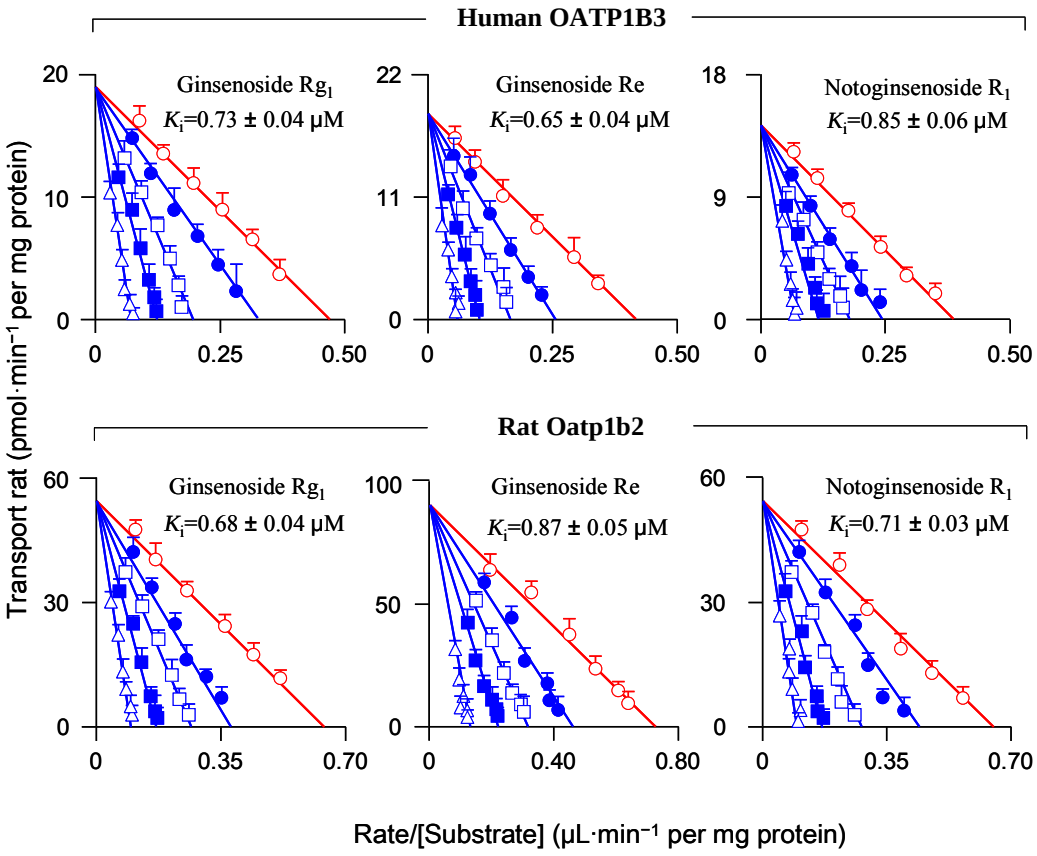

Figure 1

Eadie-Hofstee plots for rifampin inhibition of human OATP1B3- and rat Oatp1b2-mediated uptakes of the ppt-type ginsenosides. The rifampin concentrations for the inhibition of ginsenosides were 0 (red ○), 0.5 (blue ●), 1 (blue □), 2 (blue ■) and 4 μM (blue △).

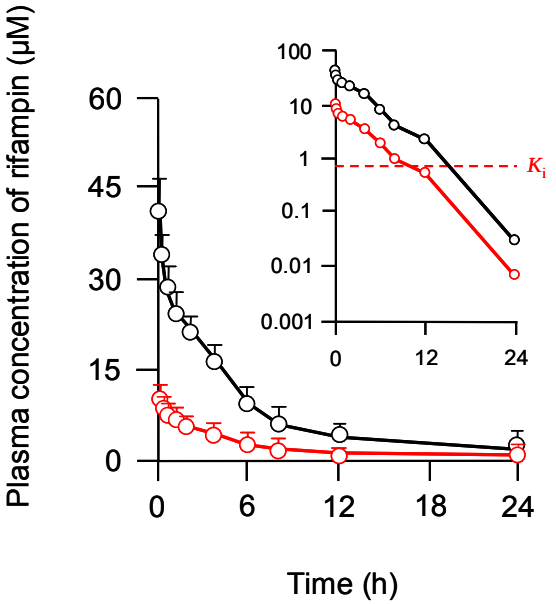

Figure 2

Total concentrations (bound + unbound; black line) and unbound concentrations (red line) of rifampin in plasma over time after a bolus i.v. dose at 20 mg·kg^{-1} in rats. The unbound plasma concentrations of rifampin, during 0–8 h after dosing, exceeded its K_i values for inhibition of rat Oatp1b2-mediated transports of the ppt-type ginsenosides (0.7–0.9 μM).

Table 1

Plasma PK parameters of rifampin after a bolus i.v. dose at 20 mg·kg^{-1} in rats

PK parameters	Rifampin
C_{5min} (μM)	42.2 ± 4.1
AUC_{0-t} (h·μM)	138 ± 29
$AUC_{0-\infty}$(h·μM)	139 ± 29
$t_{1/2}$ (h)	3.33 ± 0.37
MRT (h)	4.58 ± 0.5
V_{SS} (mL·kg^{-1})	821 ± 31
$CL_{tot,p}$ (mL·h^{-1}·kg^{-1})	182 ± 40
f_U (%)	23.1 ± 1.0

Rifampin-perpetrated drug-drug interactions

Effects of rifampin on drug metabolism and transport are broad and of established clinical significance (Niemi *et al.*, 2003). Rifampin induces intestinal and hepatic CYP3A4-mediated metabolism of drugs (including midazolam, triazolam, simvastatin, antimycotics, itraconazole, cyclosporin and most dihydropyridine calcium channel antagonists) and also induces hepatic CYP2C-mediated metabolism of drugs [including (*S*)-warfarin and the sulfonylurea antidiabetic drugs]. In addition, rifampin induces intestinal MDR1 and can reduce the plasma concentrations of drugs that are substrates of MDR1 (including veripamil and digoxin). Recent research has demonstrated that induction of the P450 enzymes and P-gp by rifampin is mediated by activation of the nuclear PXR (Chen and Raymond, 2006).

Because rifampin is an OATP/Oatp-inhibitor and substrate (Zaher *et al.*, 2008; Vavricka *et al.*, 2002), this compound was used in the current study to estimate the role of Oatp1b2 in regulation of rat systemic exposure to the ppt-type ginsenosides Rg_1 and Re and notoginsenoside R_1 via impairment of hepatobiliary excretion of these saponin compounds. The ppt-type ginsenosides are very poorly oxidized by P450 enzymes (Liu *et al.*, 2009). Therefore, induction of P450 enzymes by

rifampin is not considered to have significant effect on the systemic exposure to the ginsenosides in rats, particularly when rats were treated with a single i.v. dose of rifampin. Although the ppt-type ginsenosides Rg_1 and Re and notoginsenoside R_1 were found to be substrates of human MDR1, but its rat ortholog appeared not to transport these ginsenosides. Therefore, induction of Mdr1 by rifampin probably has no effect on the systemic exposure to the ginsenosides in rats. It was also found that both the human BSEP and rat Bsep could be inhibited by rifampin. However, rifampin treatment of rats was found to result in decreased liver concentrations of ginsenosides (Supplemental Data 4). This suggested that rifampin-based inhibition of Oatp1b2 had more significant effect than rifampin-based inhibition of Bsep. In addition, reduced function of Bsep by rifampin in the liver could be compensated by function of hepatic Mrp2 and Bcrp, which were not affected by rifampin. Taken together, despite its broad effects on drug metabolism and transport, rifampin was a useful tool compound for estimation of the role of Oatp1b2 in regulation of rat systemic exposure to the ppt-type ginsenosides.

References

Chen J, Raymond K. (2006) Roles of rifampicin in drug-drug interactions: underlying molecular mechanisms involving the nuclear pregnane X receptor. Ann Clin Microbiol Antimicrob 5: 3.

Liu H-F, Yang J-L, Du F-F, Gao X-M, Ma X-T, Huang Y-H (2009). Absorption and disposition of ginsenosides after oral administration of Panax notoginseng extract to rats. Drug Metab Dispos 37: 2290–2298.

Niemi M, Backman JT, Fromm MF, Neuvonen PJ, Kivistö KT. (2003). Pharmacokinetic interactions with rifampicin: clinical relevance. Clin Pharmacokinet 42: 819–850.

Vavricka SR, Montfoort JV, Ha HR, Meier PJ, Fattinger K (2002). Interactions of rifamycin SV and rifampicin with organic anion uptake systems of human liver. Hepatology 36: 164–172.

Zaher H, zu Schwabedissen HEM, Tirona RG, Cox ML, Obert LA, Agrawal N et al. (2008). Targeted disruption of murine organic anion-transporting polypeptide 1b2 (Oatp1b2/Slco1b2) significantly alters disposition of prototypical drug substrates pravastatin and rifampin. Mol Pharmacol 74: 320–329.