薬物間相互作用の定量的予測および機序解明を目的とした研究

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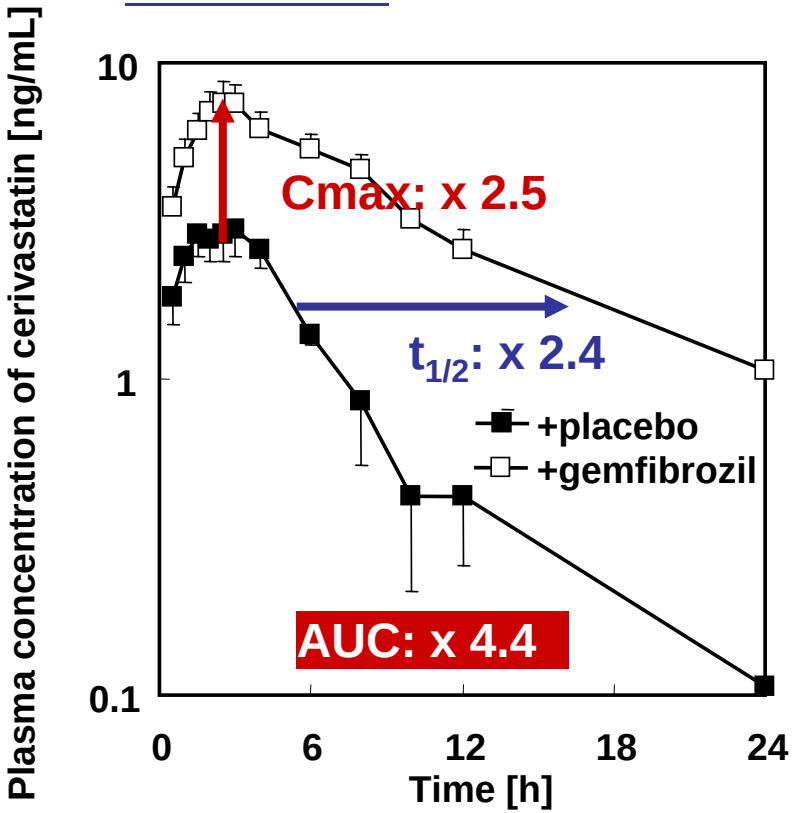
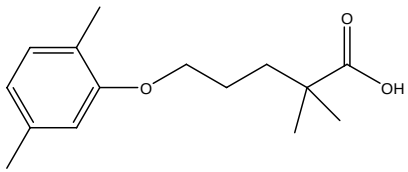
Plasma concentration of cerivastatin when coadministered with gemfibrozil and cyclosporin A.

Gemfibrozil

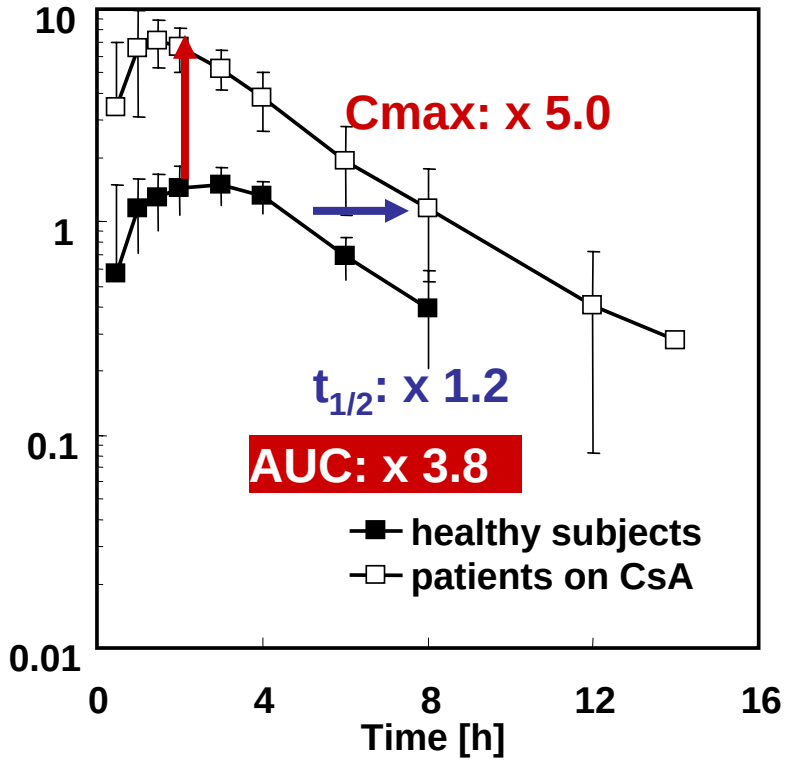


Backman JT et al. (2002) Clin Pharmacol Ther 72: 685-691

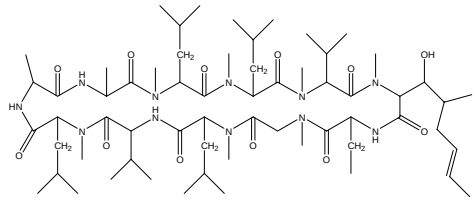


Gemfibrozil : Mw 250.3, CYP2C8 inhibitor

Cyclosporin A

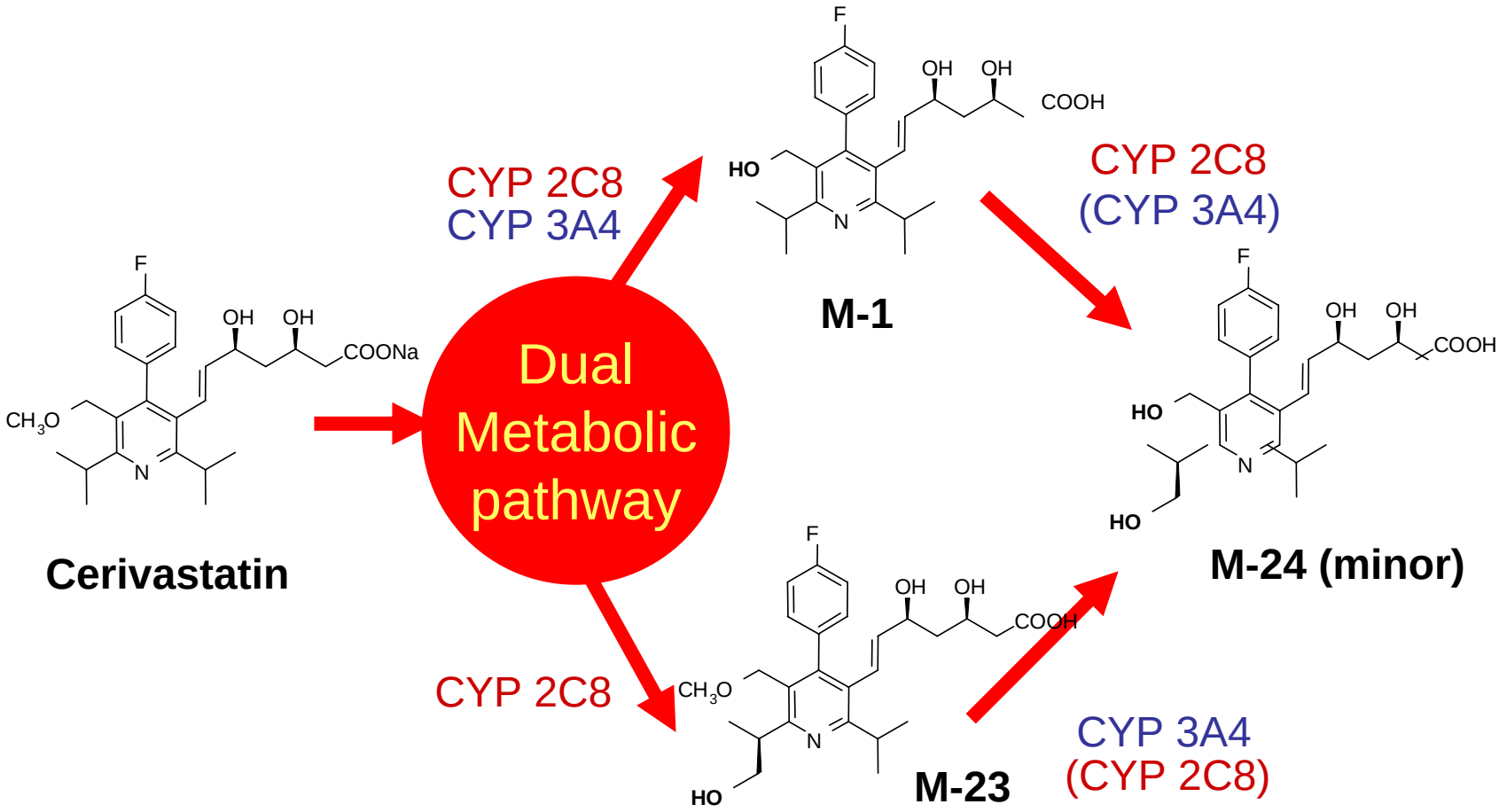


Mück W et al. (1999) Clin Pharmacol Ther 65: 251-261



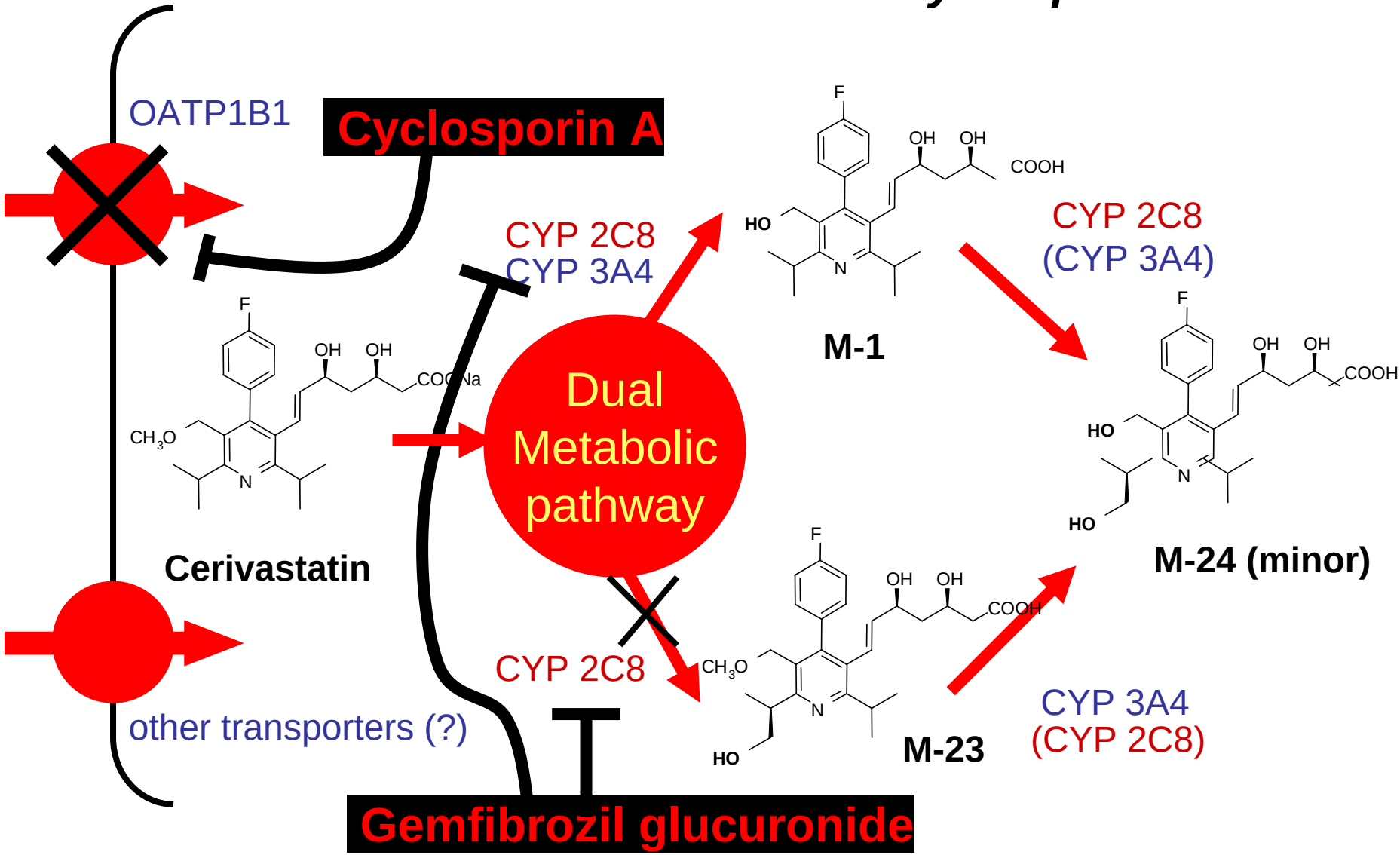
Cyclosporin A : Mw 1202.6, CYP3A4, P-glycoprotein inhibitor

Dual metabolic pathway of cerivastatin



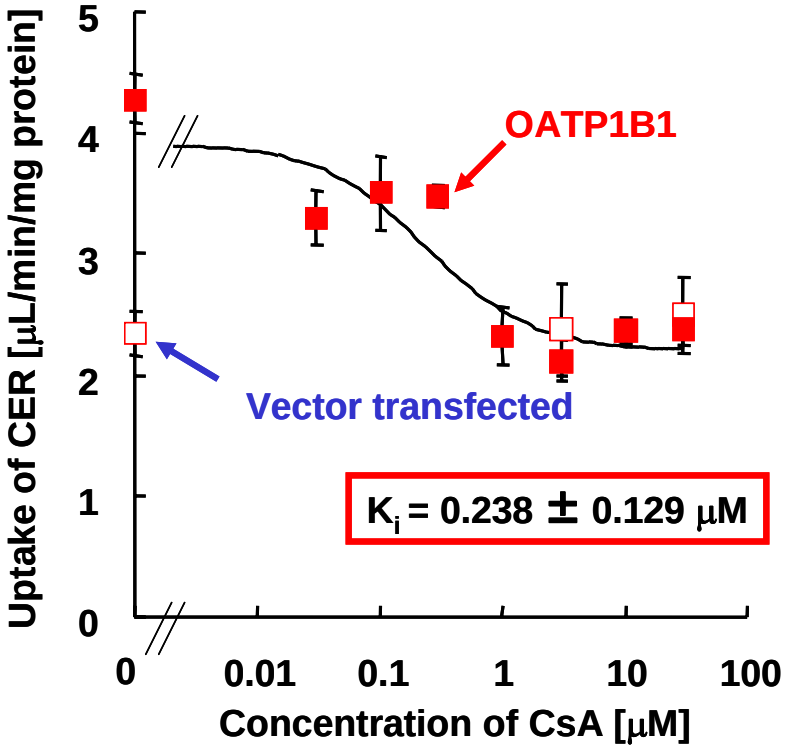
Because cerivastatin has a dual metabolic pathway mediated by CYP2C8 and 3A4, it was believed to be a safe drug with a low risk of drug-drug interactions.

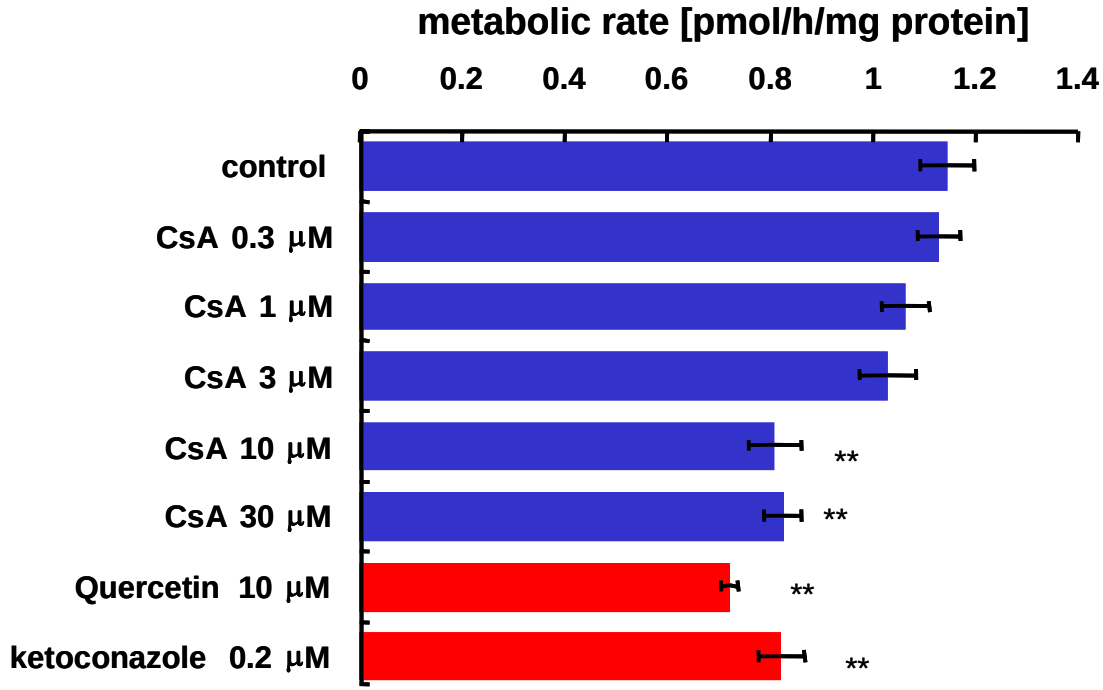
The proposed mechanism of drug-drug interaction: Cerivastatin vs. Gemfibrozil and Cyclosporin A



Cyclosporin A inhibits the OATP1B1-mediated hepatic uptake while gemfibrozil inhibits the CYP2C8-mediated metabolism as a form of gemfibrozil glucuronide.

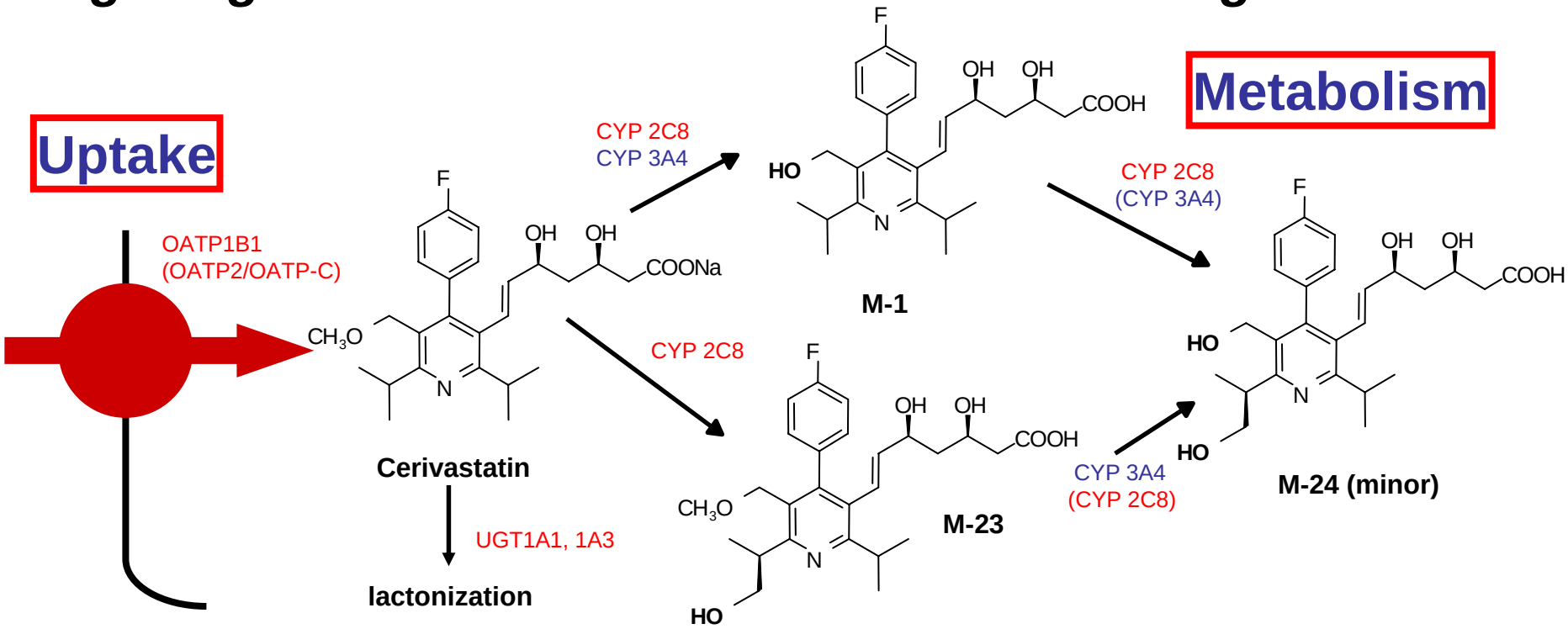
Effect of cyclosporin A on the OATP1B1 mediated hepatic uptake and metabolism of cerivastatin.





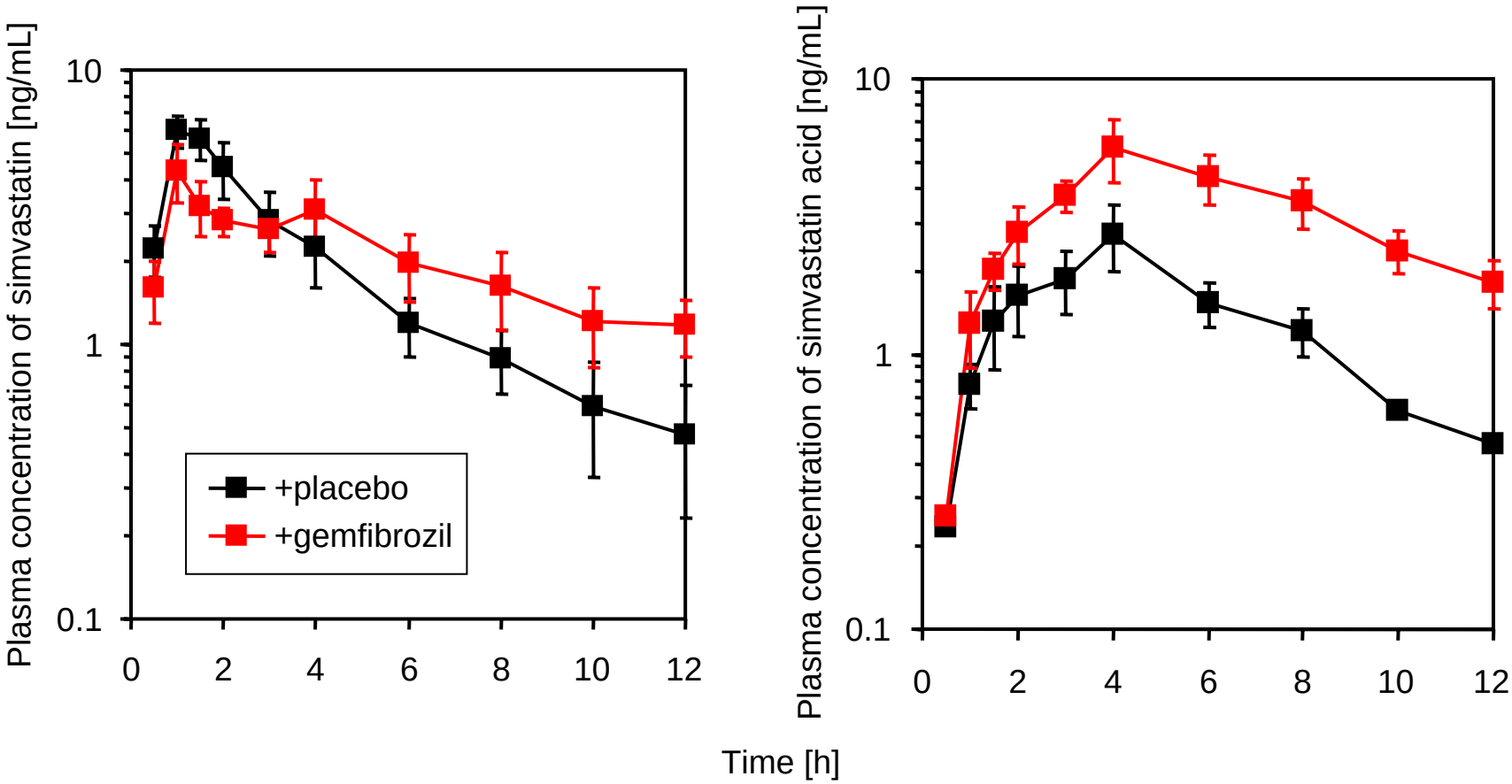
Cyclosporin A inhibits the OATP1B1-mediated hepatic uptake of cerivastatin at the therapeutic unbound concentration, with a minimal effect on its metabolism

Possible mechanism of the clinically relevant drug-drug interaction between cerivastatin and gemfibrozil



Wen X et al. (2001) *Drug Metab. Dispos.* 29, 1359-1361
Gemfibrozil does not affect CYP3A4-mediated metabolism of cerivastatin.
Wang J-S et al. (2002) *Drug Metab. Dispos.* 30, 1352-1356
Gemfibrozil inhibits the microsomal metabolism of cerivastatin.
IC_{50} … >250 μM (for M1 formulation), 95 μM (for M23 formulation, CYP2C8)
Prueksaritanont T et al. (2002) *J. Pharmacol. Exp. Ther.* 301, 1042-1051
Gemfibrozil inhibits the microsomal metabolism and UGT-mediated lactonization of cerivastatin. IC_{50} … 82 μM
**Plasma concentration of gemfibrozil: 100 - 150 μM, unbound concentration: <1 μM

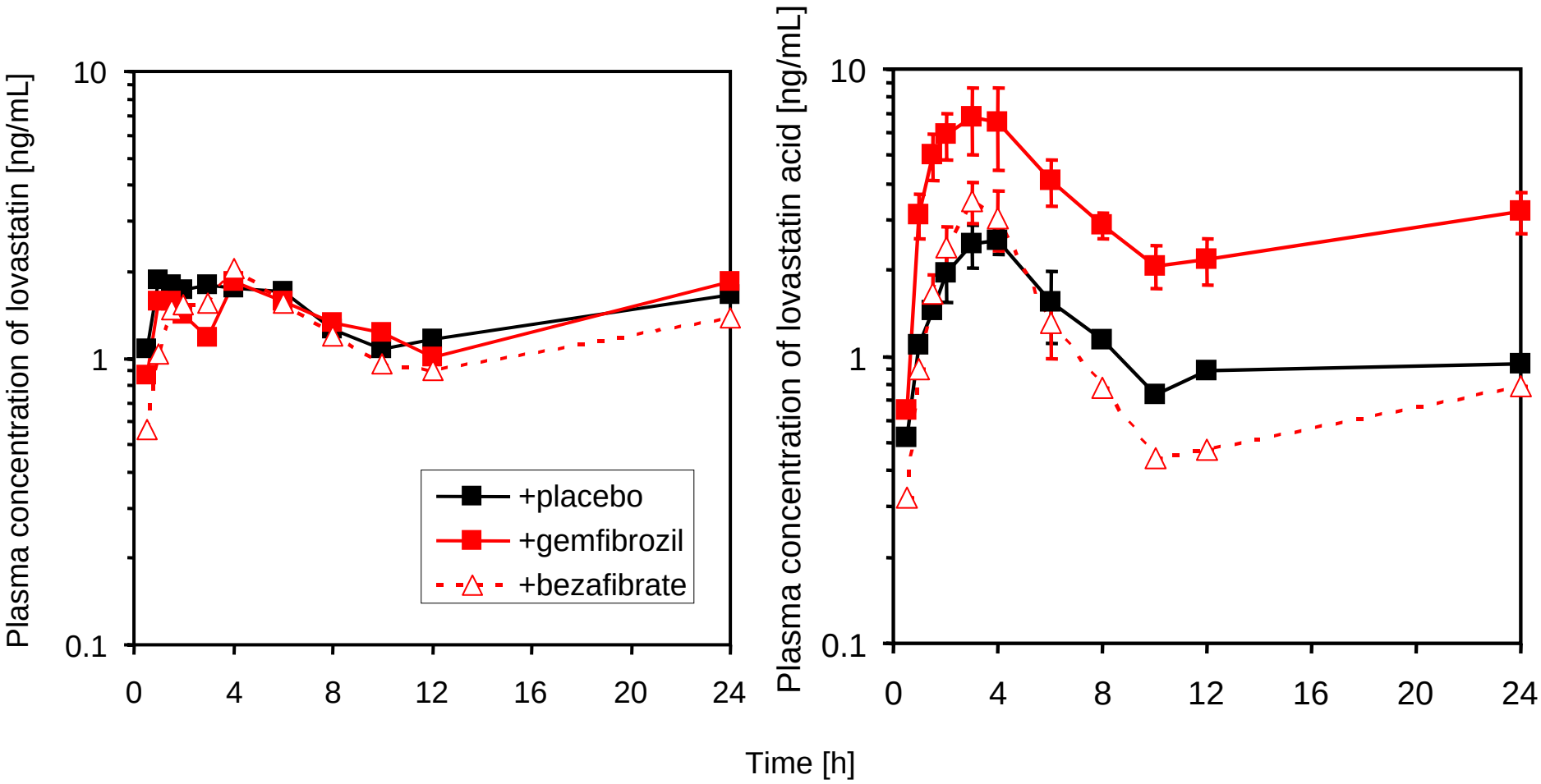
Effect of gemfibrozil on the plasma concentration of simvastatin and simvastatin acid.



Plasma concentration of simvastatin and simvastatin acid (400 mg single dose) after a 3-day preadministration of gemfibrozil (600 mg, b.i.d.).

Backman JT et al. (2000) Clin Pharmacol Ther 68: 122-129

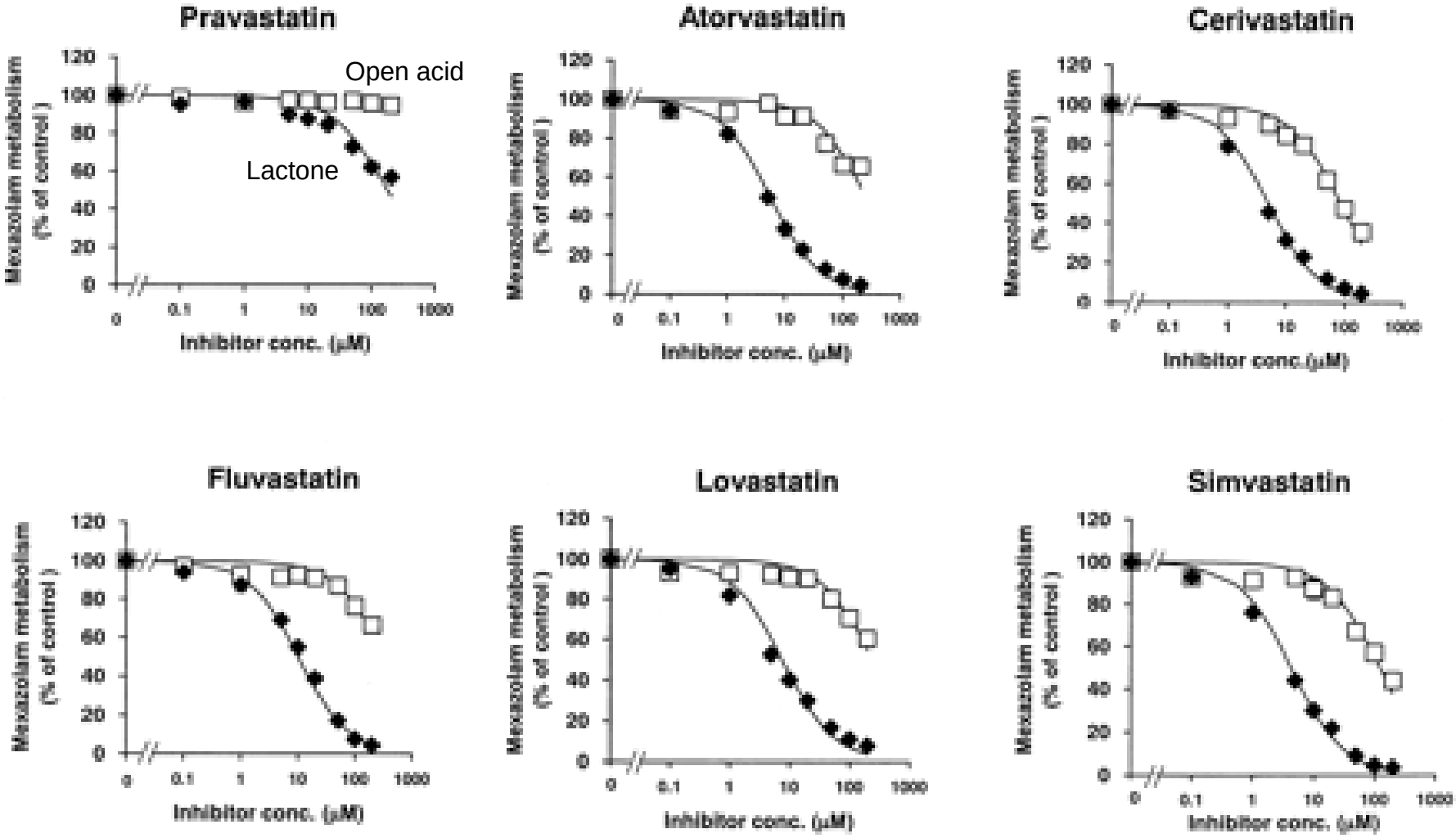
Effect of gemfibrozil on the plasma concentration of lovastatin and lovastatin acid.



Plasma concentration of lovastatin and lovastatin acid (40 mg, b.i.d.) after preadministration of gemfibrozil (1200 mg daily) or bezafibrate (400 mg daily).

Kyrklund C et al., Clin Pharmacol Ther 69: 340-345.

Affinity of different HMG-CoA reductase inhibitors for CYP3A4



Ishigami M et al. (2001) Drug Metab Disposit 29, 282-288.

The IC_{50} values of gemfibrozil and its metabolites on the OATP1B1-mediated hepatic uptake and P450-mediated metabolism.

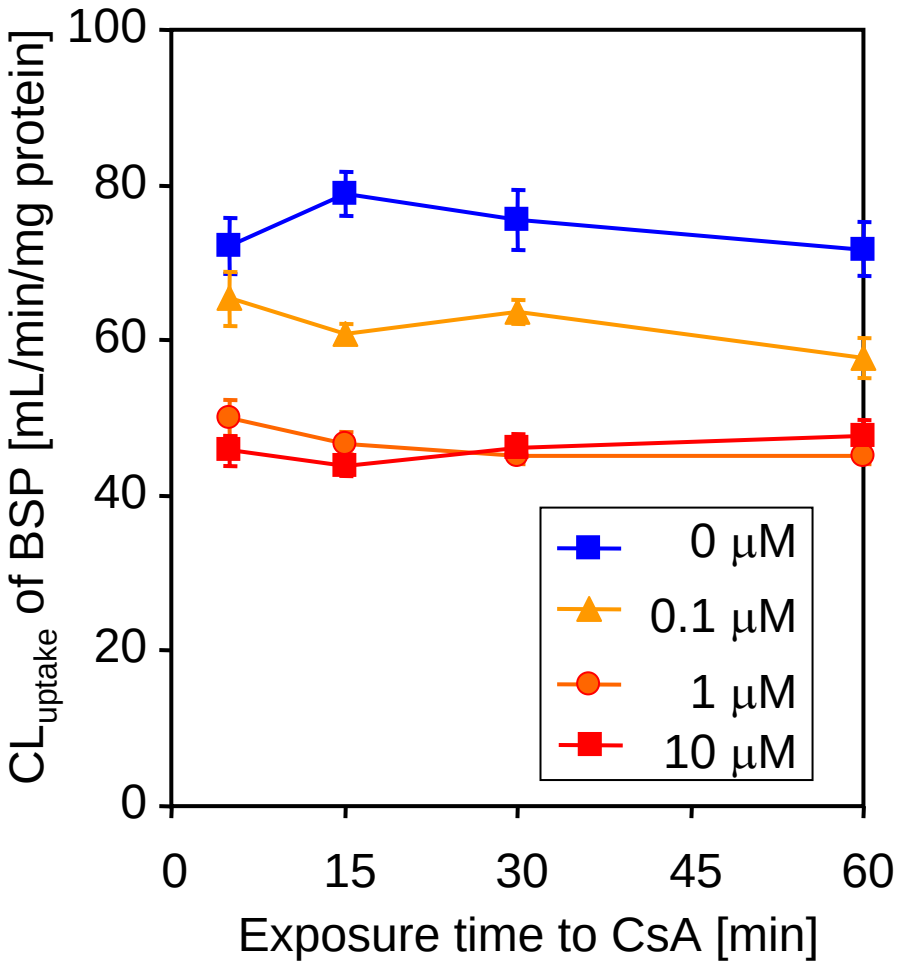
IC_{50} values

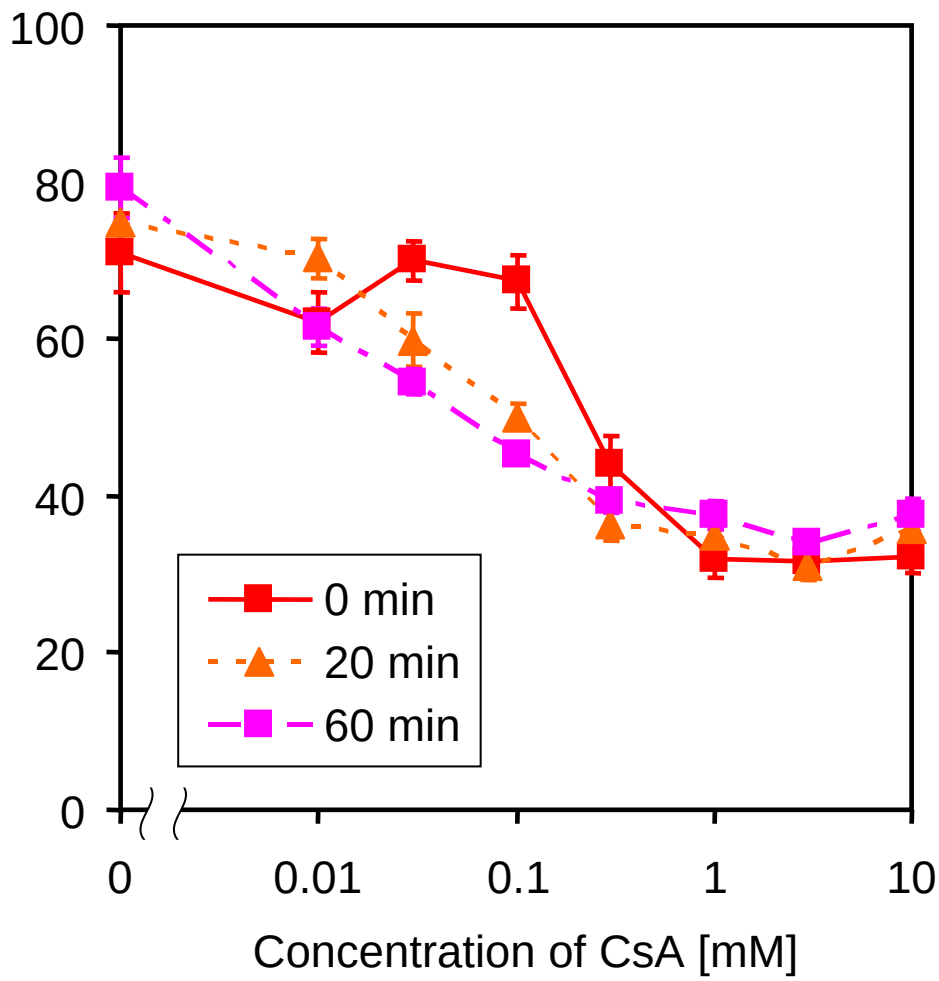
	GEM [μM]	metabolite	
		M3 [μM]	GEM-1-O-glu [μM]
OATP1B1-mediated uptake	72.4 ± 28.4	no inhibition	24.3 ± 19.8
CYP2C8-mediated metabolism (61 %)	28.0 ± 4.3	no inhibition	4.07 ± 1.23
CYP3A4-mediated metabolism (37 %)	372 ± 100	no inhibition	243 ± 59

Plasma concentration of GEM: 100 - 150 μM, unbound concentration: <1 μM
Plasma concentration of GEM-glu: 20 μM, unbound concentration: 2 μM

IC_{50} values are higher than the therapeutic concentration of GEM and its glucuronide not bound to the plasma protein
→ This clinically relevant drug-drug interaction cannot be explained!

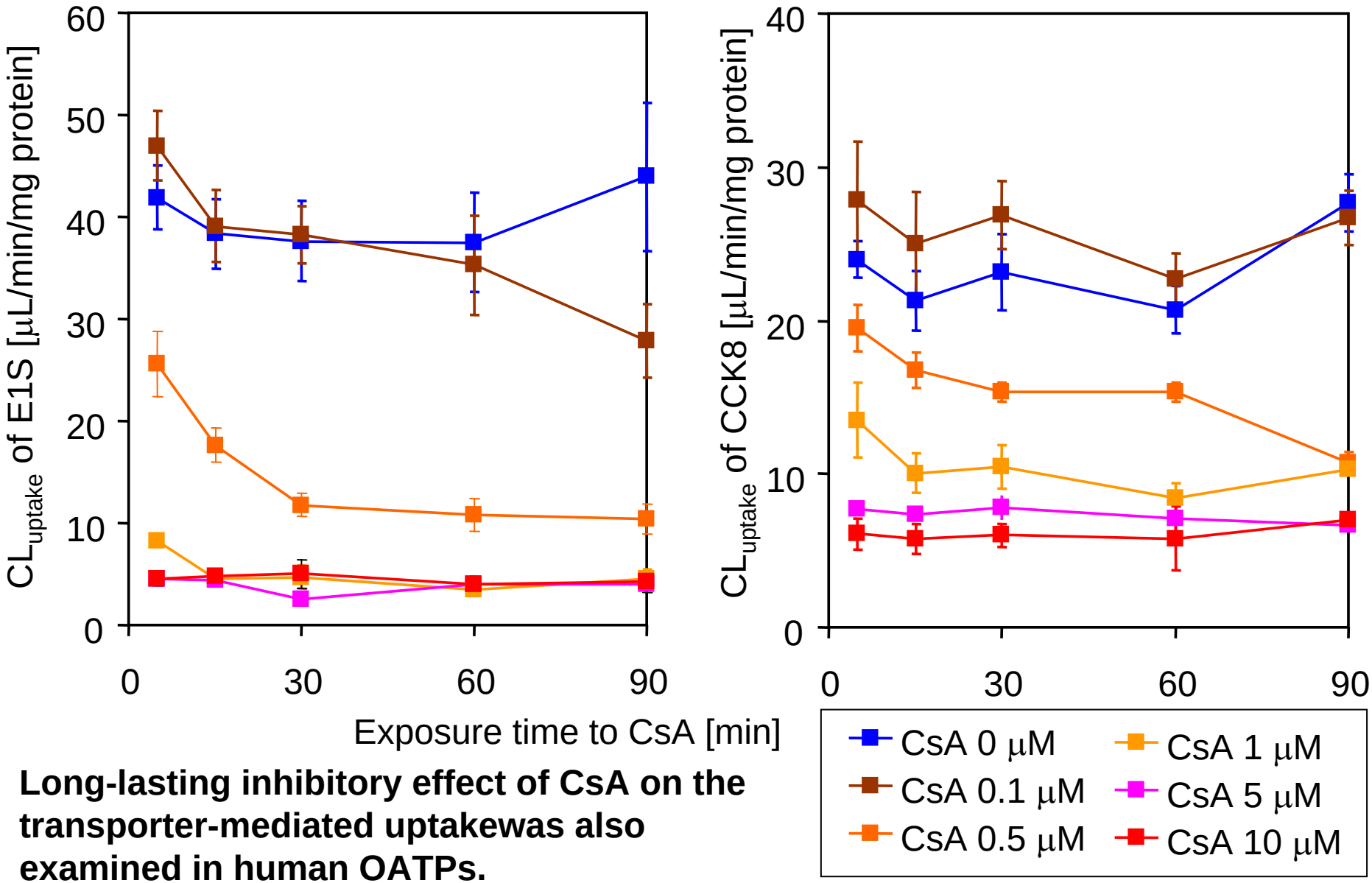
Long-lasting inhibitory effect of CsA on the transporter -mediated uptake of BSP in primary cultured rat hepatocytes.





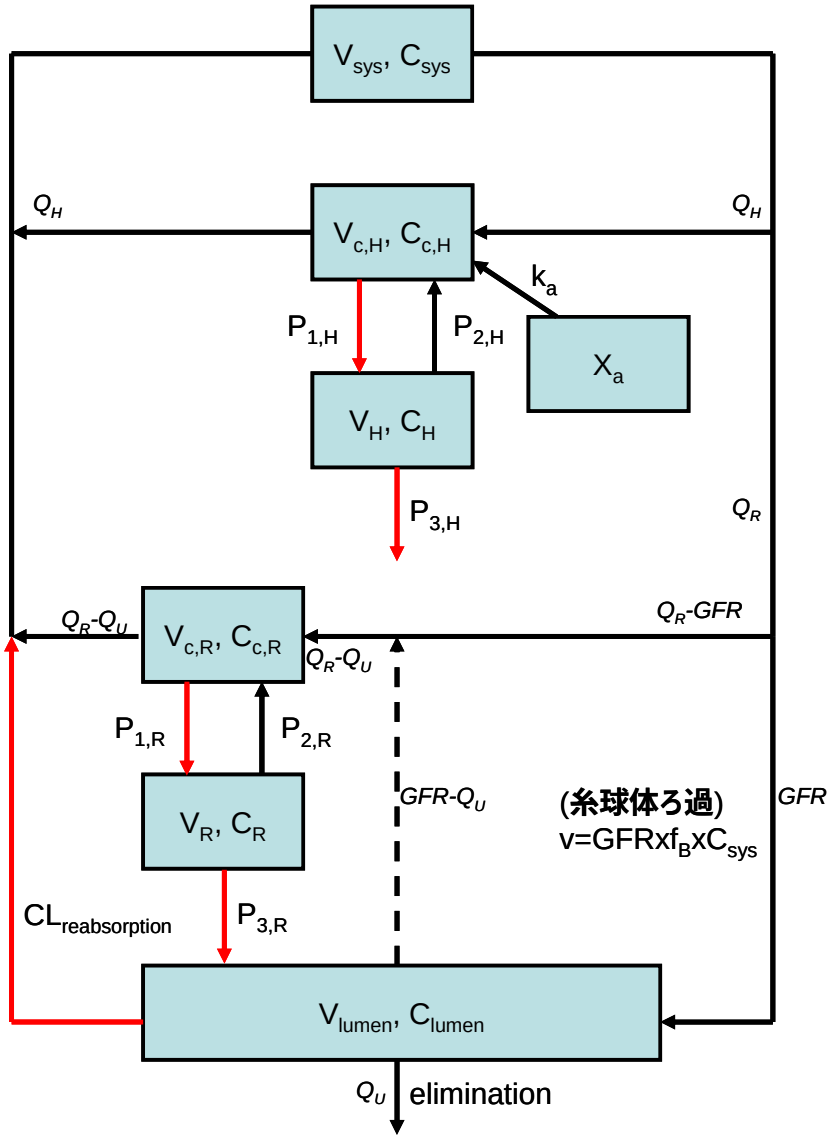
Transporter inhibition by CsA is long-lasting and exposure to CsA reduced the IC_{50} value.

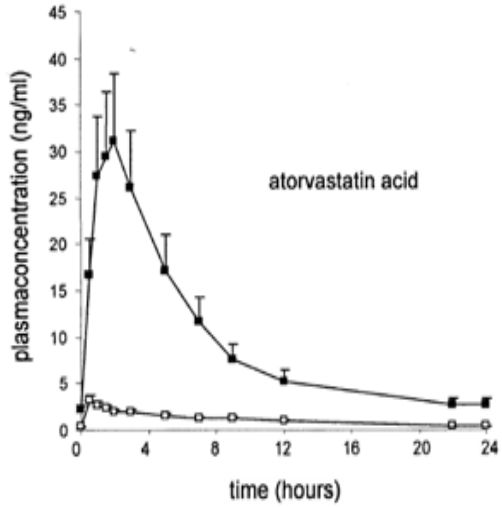
Long-lasting inhibitory effect of CsA on the human OATP1B1 and 1B3-mediated uptake.



Long-lasting inhibitory effect of CsA on the transporter-mediated uptakewas also examined in human OATPs.

Model-based simulation of transporter-mediated drug-drug interactions





Lau YY et al., Clin Pharmacol Ther 81, 194-204, 2007

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