Fundamentals of Membrane Transporters and their Role in In Vivo PK/PD of Drugs - II

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Fundamentals of Drug Transporters

Regulation of P-gp expression

- **PXR binds to DR4(1) motif in the distal XREM**
- **PXR binds to both proximal promoter region and distal XREM of CYP3A**

Fundamentals of Drug Transporters

- **P-gp and CYP based induction drug interactions are likely :**
  - If the drug is a PXR ligand/activator as these drugs will induce the expression of P-gp and CYP3A4 as well as other CYPs (e.g. CYP2C9) and transporters (e.g. MRP2).

Note: other receptors such as VDR and CAR may also play a role in regulating P-gp and CYP expression

Fundamentals of Drug Transporters

- **Pharmacogenetics of MDR1**
  - Controversial area - needs clarification of genotype-phenotype relationship
  - G2677T (Ala893Ser) in exon 21 leads to enhanced activity of MDR1, *in vitro* (digoxin) and *in vivo* (fexofenadine).
  - G2677T, and synonymous mutations at C1236T in exon 12 and C3435T in exon 26 (collectively MDR1*2) occurs in 62% of European Americans, 13% African Americans

Fundamentals of Drug Transporters

- **Pharmacogenetics of MDR1**

Genotype	Race	P-gp substrate	AUC(0-4h) ng.h/ml
MDR1*1	Caucasian	Fexofenadine	1316±543
MDR1*2	Caucasian	Fexofenadine	837±311*
3435C/C	Japanese	Digoxin	4.11±0.57
3435T/T	Japanese	Digoxin	3.27±0.58*

Fundamentals of Drug Transporters

- **Pharmacogenetics of MDR1**
  - **Others have found no association between C3435T and digoxin, talinolol or fexofenadine pharmacokinetics**
    1. **Gerloff et al. MDR1 genotypes do not influence the absorption of a single oral dose of 1 mg digoxin in healthy white males. Br J Clin Pharmacol 2002 Dec;54(6):610-6**
    2. **Siegmund et al The effects of the human MDR1 genotype on the expression of duodenal P-glycoprotein and disposition of the probe drug talinolol. Clin Pharmacol Ther 2002 Nov;72(5):572-83**
    3. **Drescher et al. MDR1 gene polymorphisms and disposition of the P-glycoprotein substrate fexofenadine. Br J Clin Pharmacol 2002 May;53(5):526-34**

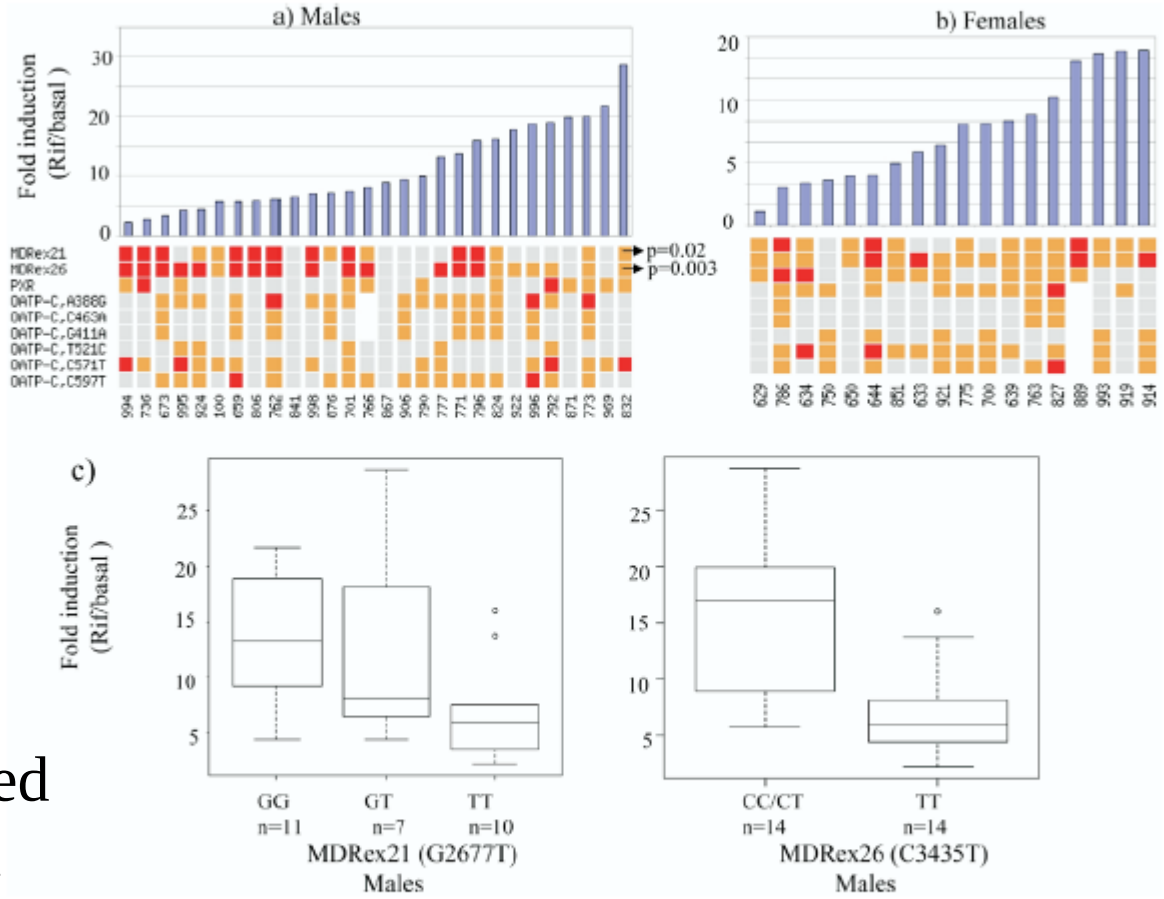


Fig 2. Relationship between *MDR1*, PXR, and *OATP-C* genotypes and rifampin (Rif) inductive phenotype in primary human hepatocytes in cohort I. The CYP3A4 inductive phenotype measured as testosterone 6β-hydroxylation (in picomoles per minute per milligram protein) in hepatocytes after treatment with rifampin/vehicle control activity is shown (fold induction). In men $P = .03$ for *MDR1* 2677 GG versus GT versus TT, $P = .012$ for 2677 GG + GT versus TT, $P = .0015$ for 3435 CC + CT versus TT, and $P = .004$ for 3435 CC versus CT versus TT.

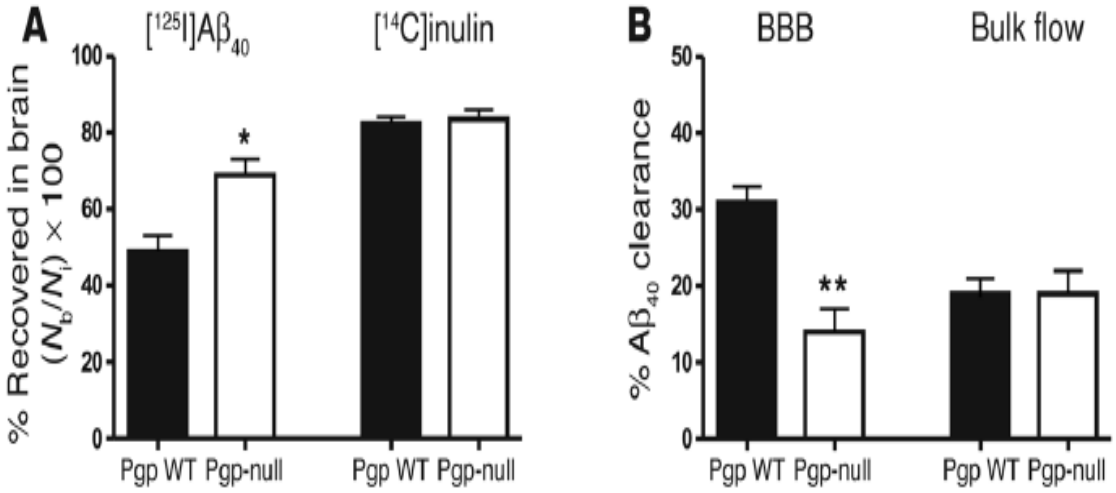
MDR2677TT associated with decreased hepatic CYP3A4 induction

Courtesy Dr. Kelly

Fundamentals of Drug Transporters

Alzheimer's Disease

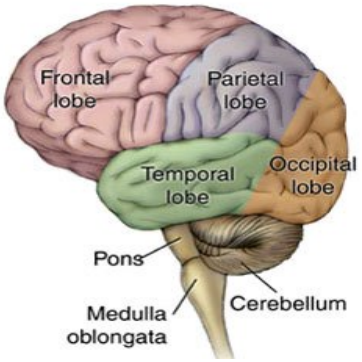
Increased brain recovery and reduced clearance after 30 min of $A\beta_{1\text{-}40}$ injection in brain of P-gp null mice



Similar increased recovery and reduce clearance in P-gp null mice was shown for $A\beta_{1\text{-}42}$

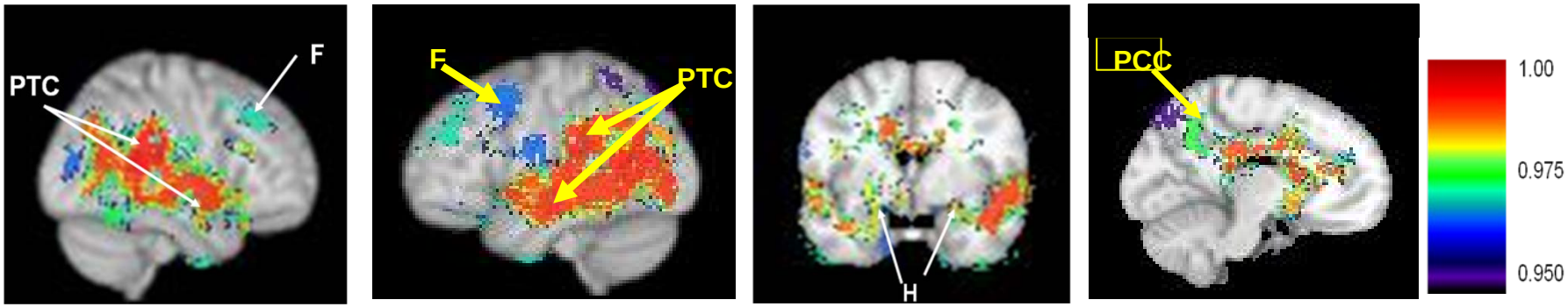
Cirrito et al. The Journal of Clinical Investigation 115, 11, 3285-3290

P-gp Activity and Regional Cerebral Blood Flow is Reduced in AD



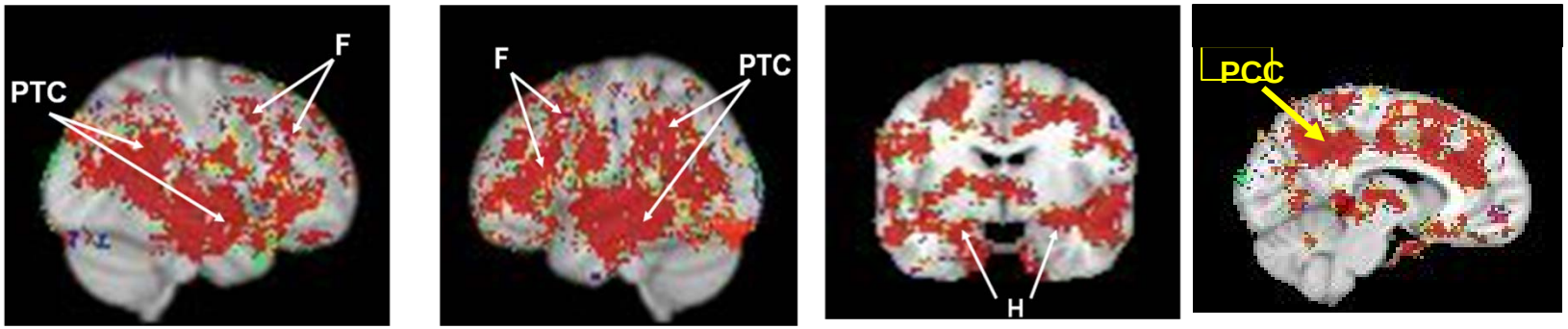
Regional cerebral blood flow (rCBFc)

Right side **Left side**



Sagittal **Coronal** **Mid-Sagittal**

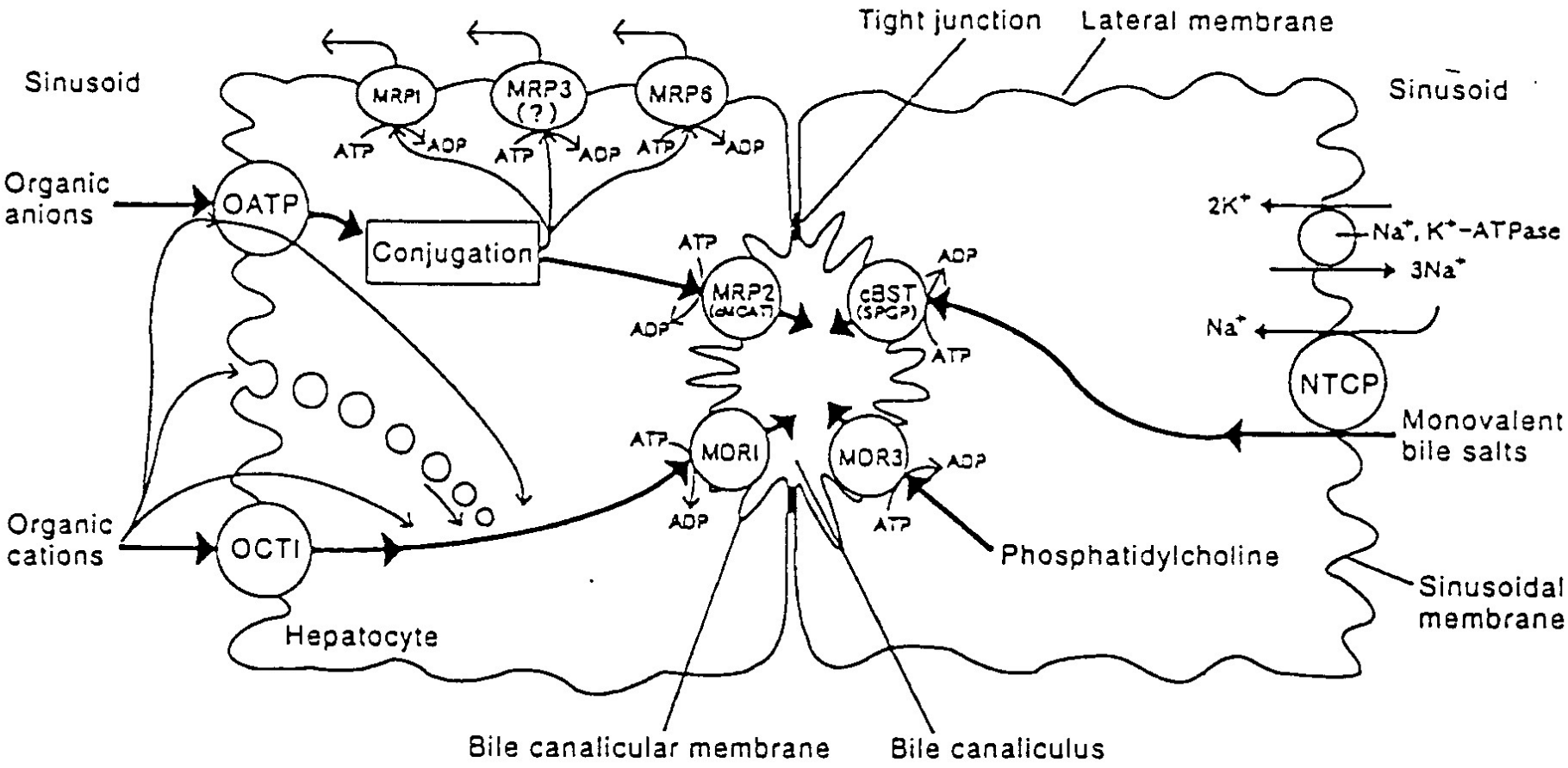
ERc



JD Unadkat, Ph.D. ***Deo et al., In Preparation***

Organic Anion Transporting Polypeptides (OATPs)

A Model of Hepatobiliary Transport Of Organic Anions and Cations



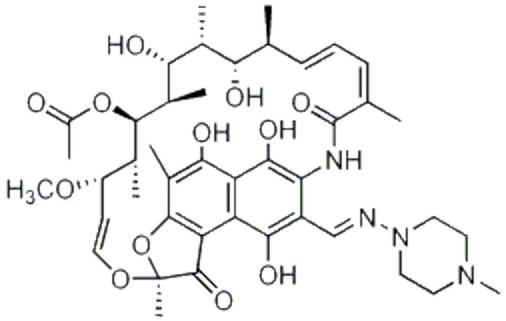
Courtesy Dr. Wang

Transport Mode

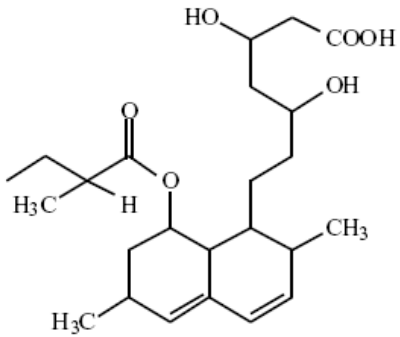
- Na+-independent transport systems.
- Mechanism appears to be anion exchange, coupling the cellular uptake of organic compounds with the efflux of GSH, or bicarbonate, and/or glutathione-S-conjugates. (only demonstrated for rat Oatp1a1 and Oatp1a4)
- bidirectional organic substrate transport, with overall directionality of transport dependent on substrate and counter-ion gradients.

Courtesy Dr. Wang

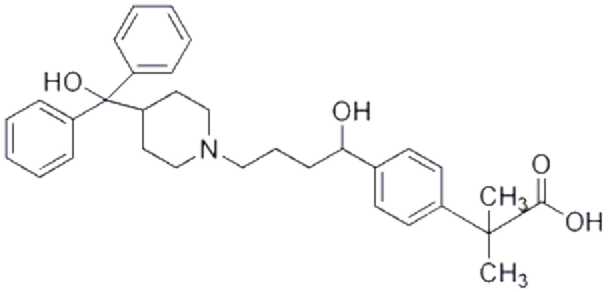
Human OATP Substrates



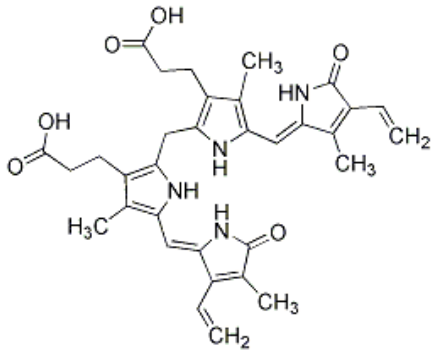
Rifampin
OATP1B1,1B3



Pravastatin
OATP1B1,2B1
Not sig. metabolized



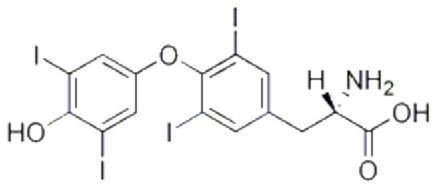
Fexofenadine
OATP1A2,2B1
Not sig. metabolized



Bilirubin
OATP1B1?

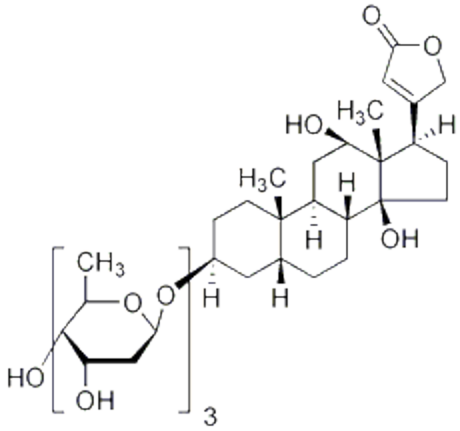
Courtesy Dr. Wang

CCK-8
OATP1B3



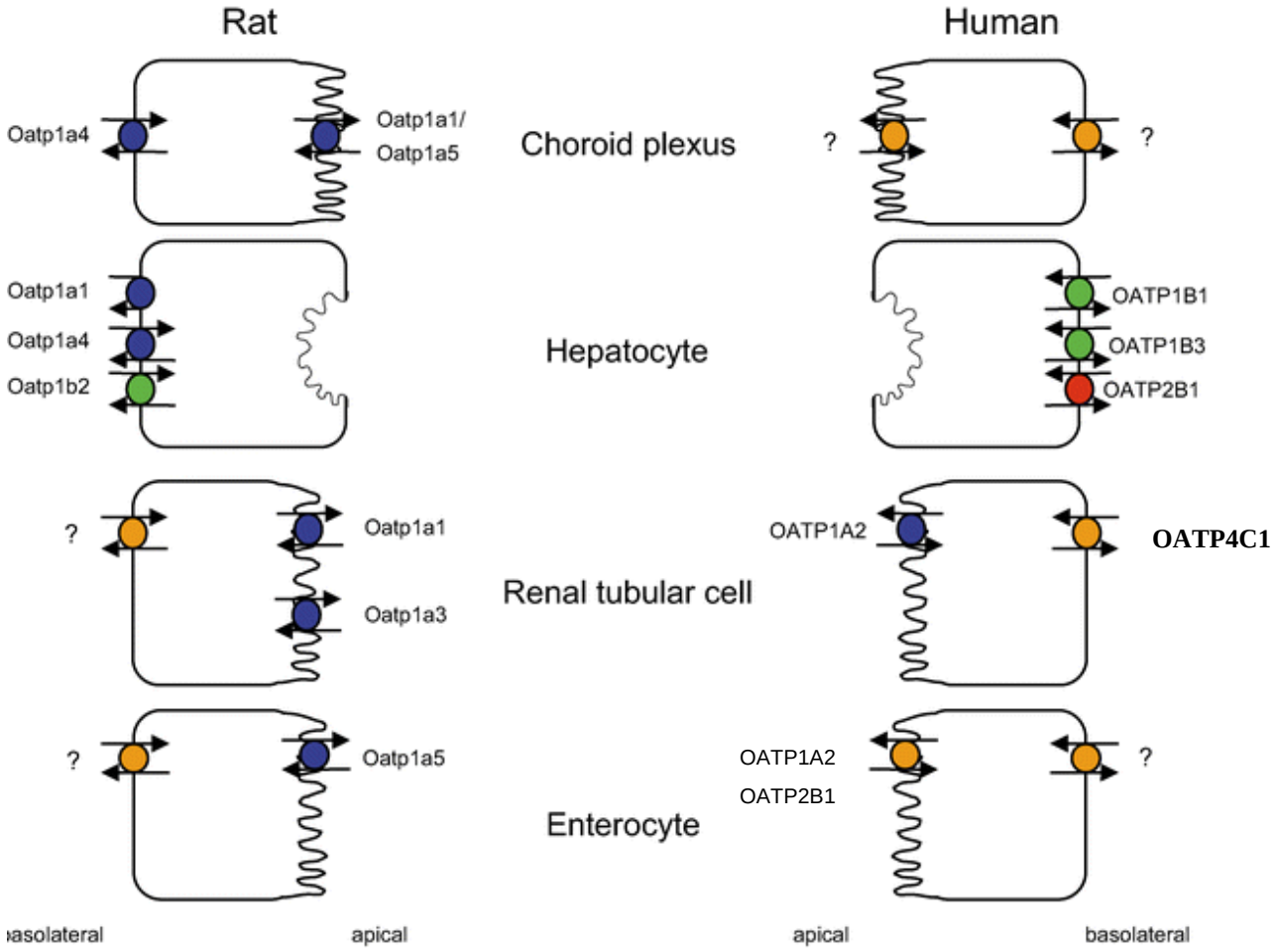
Thyroxine

OATP1A2,1B1,1B3,1C1,4A1,4C1



Digoxin
OATP1B3,4C1
Not extensively metabolized

Expression of Oatps/OATPs in Epithelial Tissues



Courtesy Dr. Wang

(Hagenbuch and Meier, Pflugers Arch 2004)

OATP1A2 – Fexofenadine

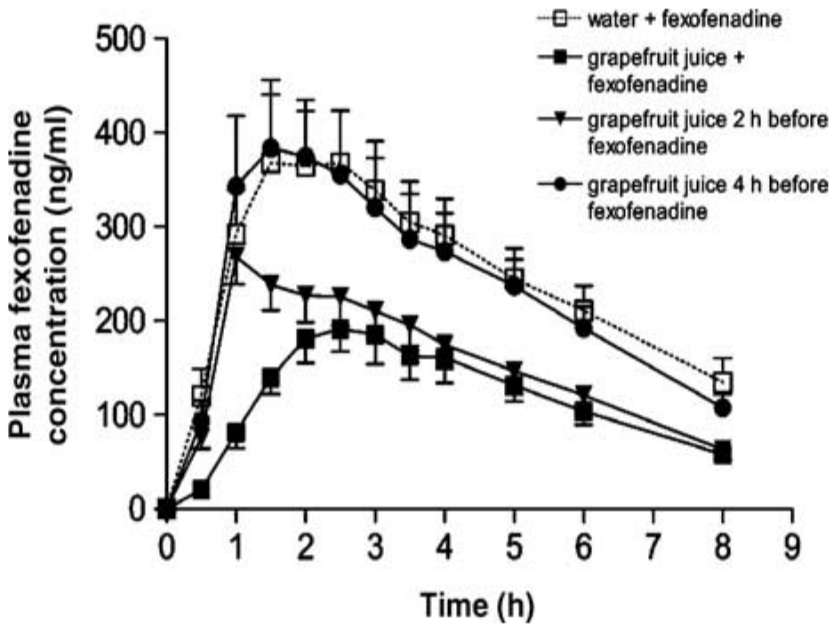
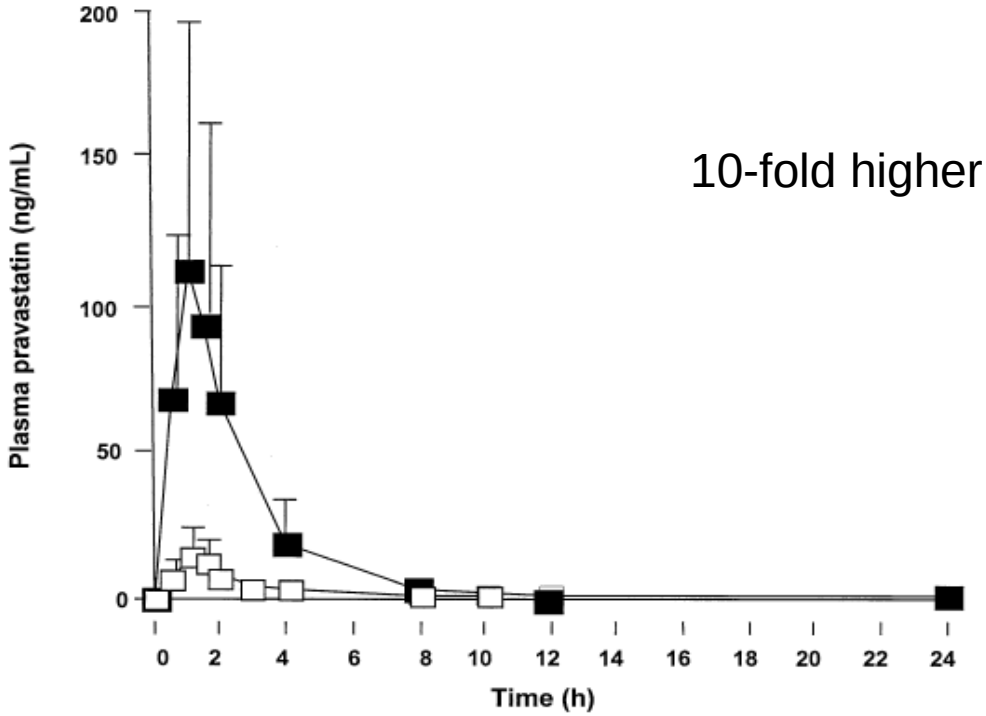


Figure 5 Mean plasma drug concentration–time profiles for healthy volunteers ($n = 12$) administered water 300 ml with (open squares) or grapefruit juice 300 ml with (filled squares), 2 h before (filled triangles) or 4 h before (filled circles) fexofenadine 120 mg. Error bars represent SEM.

Effect of cyclosporin-containing immunosuppression therapy on pravastatin PK in cardiac transplant patients



10-fold higher AUC!

Fig 1. Mean plasma pravastatin concentrations (±SD) in 19 pediatric transplant recipients on a regimen of triple immunosuppression after a single oral dose of 10 mg pravastatin (*solid squares*) and corresponding values in 20 control patients with familial hypercholesterolemia receiving pravastatin monotherapy (*open squares*).

Courtesy Dr. Wang

Hedman et al. Clin Pharmacol Ther. 2004 Jan;75(1):101-9

HMG-CoA Reductase Inhibitor-Cyclosporin Interaction

Some interactions have been reported to cause the severe side effect of myotoxicity of statins, including lethal rhabdomyolysis

TABLE 1 Kinetic parameters of HMG-CoA reductase inhibitors coadministered with cyclosporin A

HMG-CoAreductase inhibitors	Cyclosporin A (+/−) Cmax [ng/mL]	Ratio	AUC [ng · h/mL]	Ratio	Major clearance mechanism	Reference
Simvastatin	18.9/2.5**	7.56	78.1/9.8**	7.97	CYP3A4	193
	20.6/9.9*	2.08	101/39.6*	2.55		194
Pravastatin	223/28.0	7.95	1300/ 57.1***		OATP-C	143
Fluvastatin	155/119	1.30	373/192	1.94	CYP2C9	195
Cerivastatin	7.82/1.56	5.01	36.2/9.53	3.80	CYP2C8/ 3A4OATP-C	142
Atorvastatin	58.0/8.8#*	6.59	595/79.9#*	7.45	CYP3A4-OATP-C	145
Pitavastatin	179/27.6***	6.49	347/76.9***	4.51	OATP-C	144

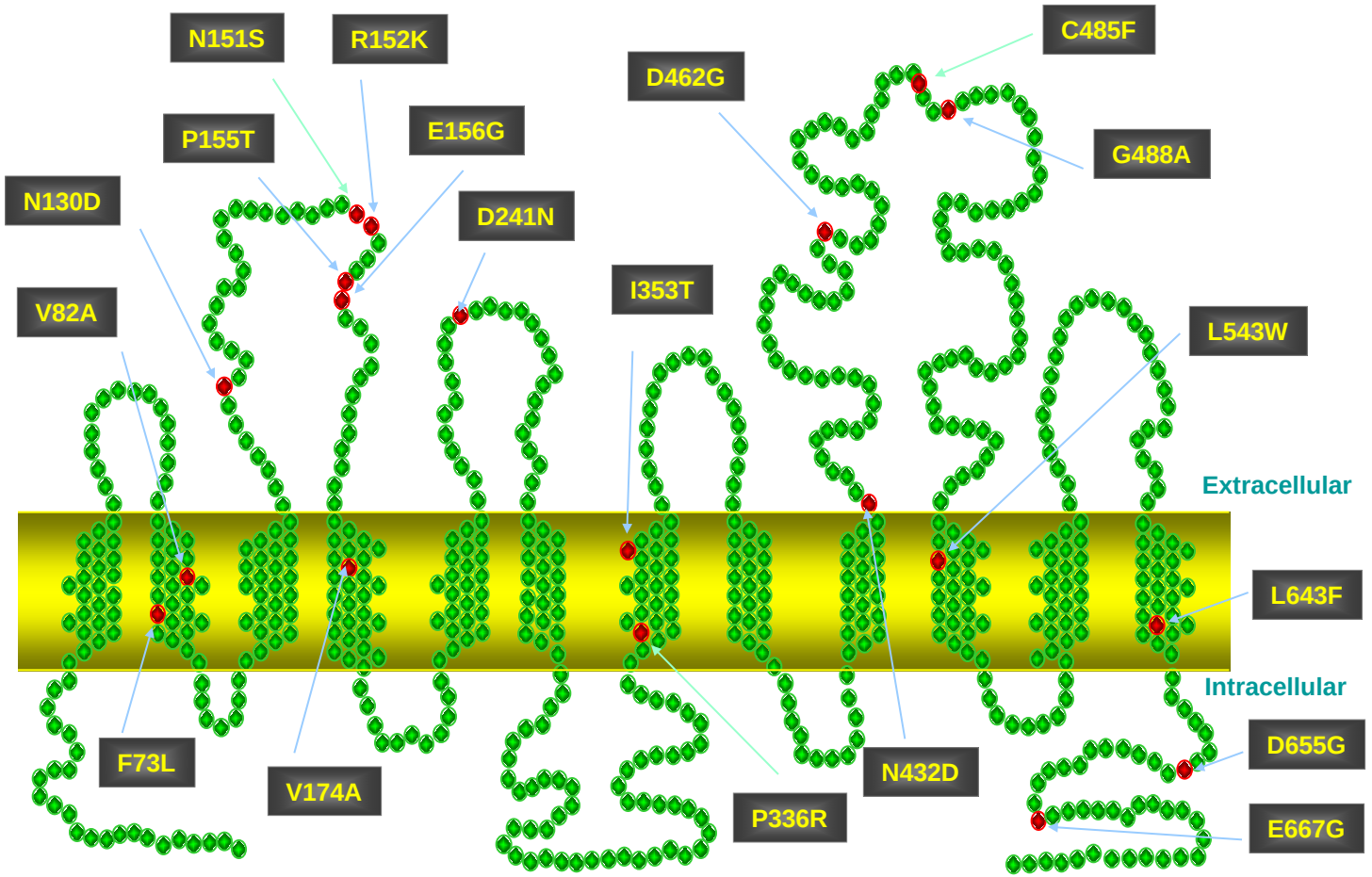
#ng eq./mL or ng eq. · h/mL
*p<0.05, **p<0.01, ***p<0.001

OATP1B1 is inhibited by cyclosporin A with a Ki value of less than 0.2 μM

Courtesy Dr. Wang

Shitara Y et al. Annu Rev Pharmacol Toxicol. 2005;45:689-723

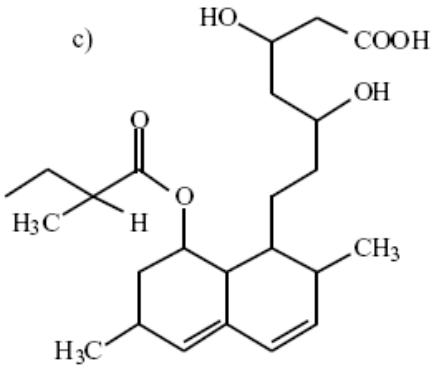
Genetic Variants of OATP1B1



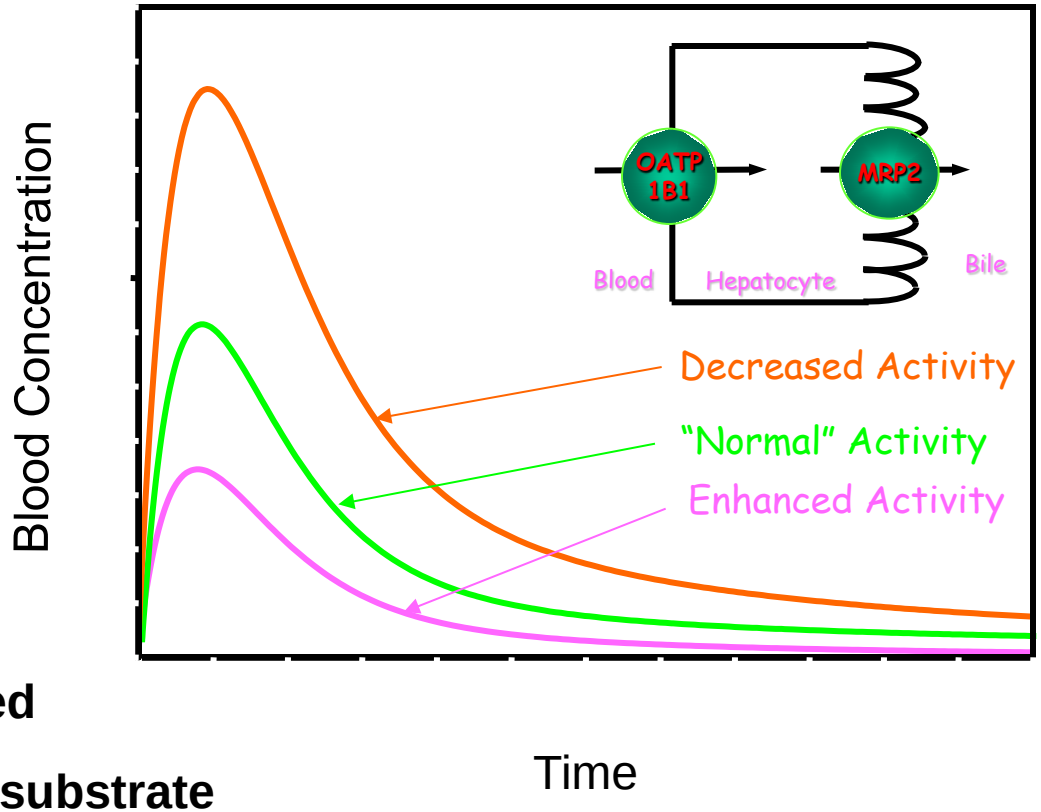
Courtesy Dr. Wang

Tirona et al., JBC 2001; Nozawa et al., JPET 2002; Nishizato et al., 2003;
Niemi et al., Pharmacogenetics 2004; Morimoto et al., Drug Metab Pharmacokinet 2004

Pravastatin as a Probe Drug to Study the Impact of OATP1B1 Genetic Variation in Vivo

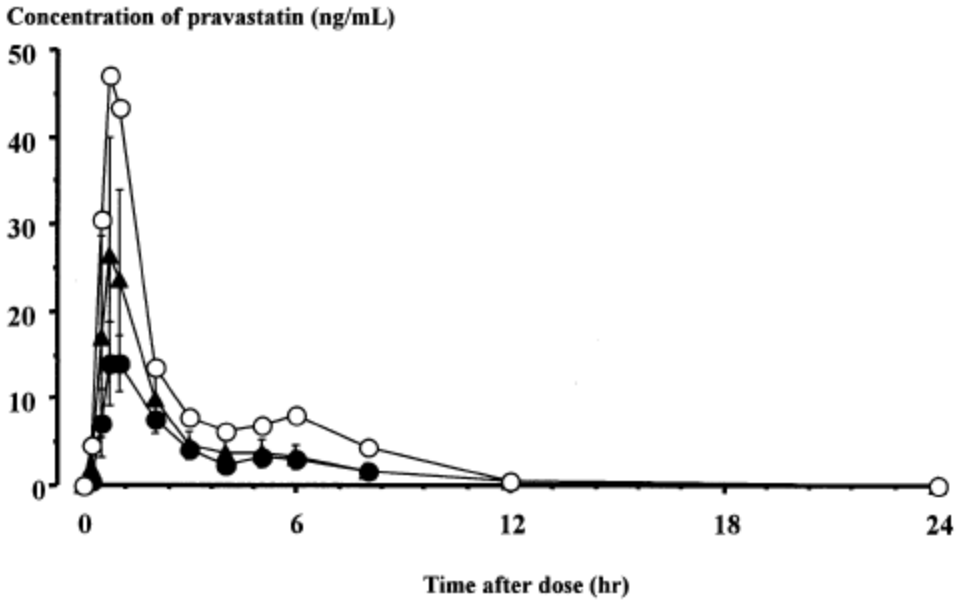


- **hydrophillic “statin”**
- **HMG-CoA reductase inhibitor**
- **not metabolized**
- **Clearance is uptake rate-limited**
- **OATP1B1, OATP2B1and OAT3 substrate**



Courtesy Dr. Wang

OATP1B1 Genotype and Pravastatin Pharmacokinetics In Vivo



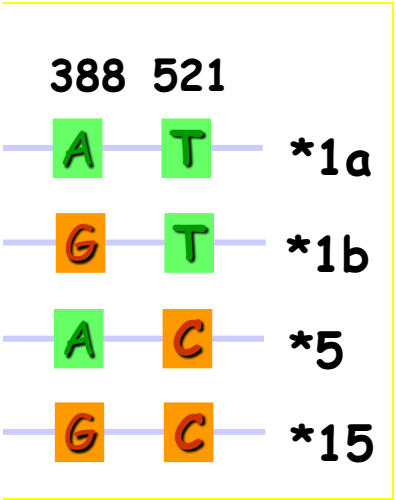


Fig 1. Mean serum concentration over time after a single oral pravastatin dose of 10 mg in 3 organic anion transporting polypeptide C (OATP-C) genotypic groups. *Solid circles*, *OATP-C*1b/*b* subjects (n = 4); *triangles*, **1b/*15* subjects (n = 9); *open circles*, **15/*15* subject (n = 1).

Non-renal clearance:

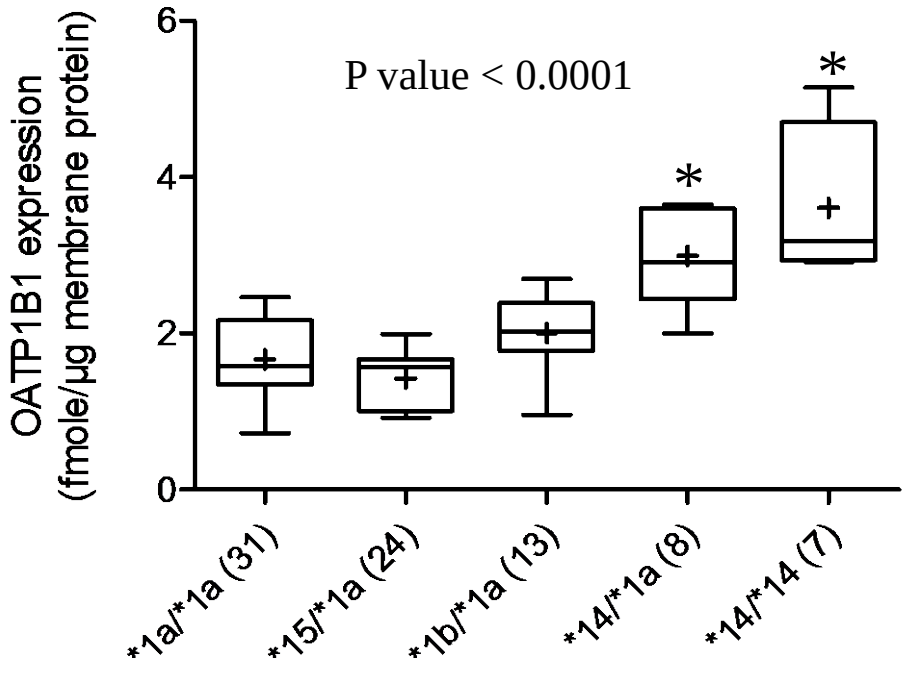
*1b/*1b (n = 4)	2.01 ± 0.42 L/ kg*h
*1b/*15 (n = 9)	1.11 ± 0.34 L/ kg*h
*15/*15 (n = 1)	0.29 L/ kg*h

Courtesy Dr. Wang

Nishizato et al., Clin Pharmacol Ther 2003

Genotype dependent OATP1B1 expression

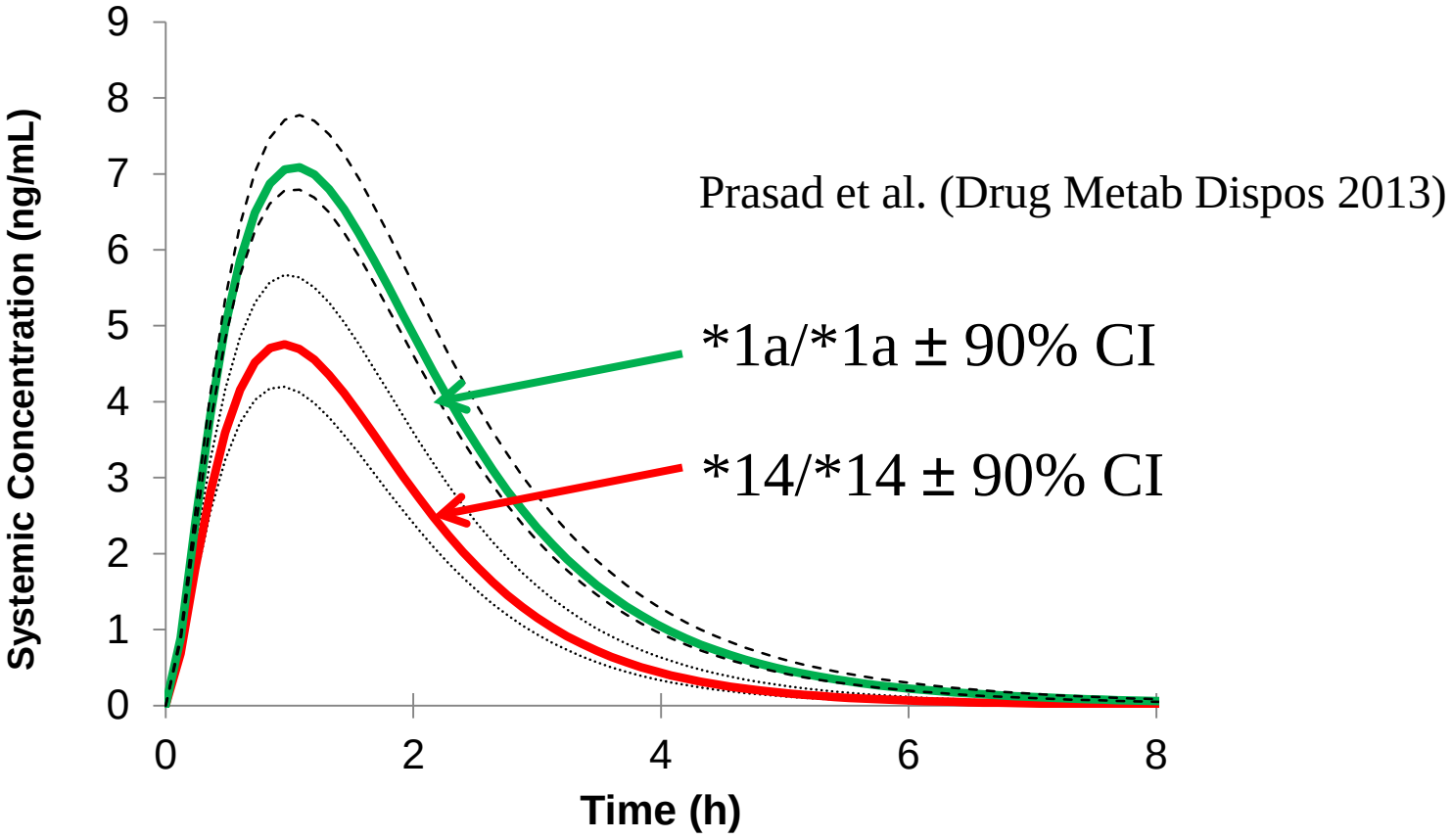
SLCO1B1 haplotype	c.388A>G (N130D)	c.463C>A (P155T)	c.521T>C (V174A)
*1a			
*1b	■		
*4		■	
*5			■
*14	■	■	
*15	■		■



- ↑ statin response and tolerance (Rodrigues et al., 2011, Donnelly et al., 2011)
- ↓ pravastatin AUC (Mwinyi et al., 2004)
- ↑ risk of methotrexate toxicity (Trevino, et al. 2009)

Prasad et al. (Drug Metab Dispos 2013)

Expression Data Predict Genotype-Dependent Changes in Repaglinide PK



32%↓in $AUC_{0-\infty}$ of repaglinide in individuals with 388GG (Kalliokoski et al., 2008)

OATP1B1 – Pravastatin Efficacy

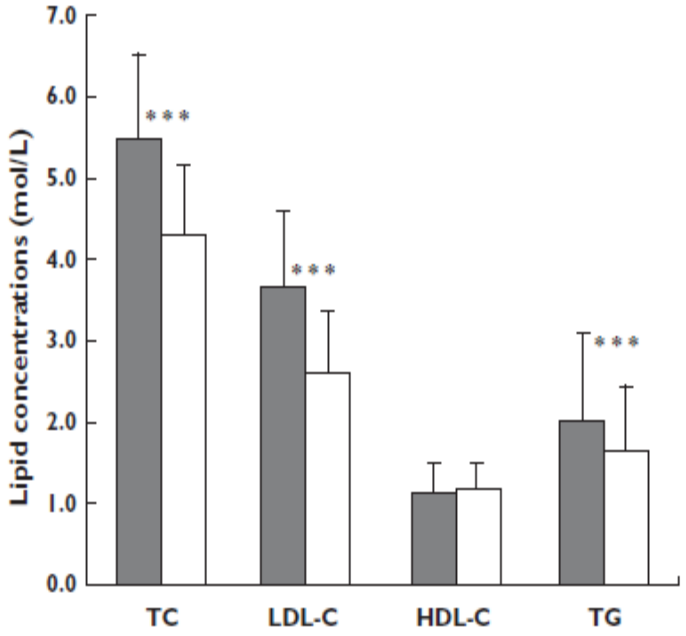


Figure 1

Total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C) and triglyceride (TG) concentrations (mmol l^{-1}) at baseline (■) and after treatment with 20 mg pravastatin daily for 30 days (□) in 45 patients with coronary heart disease. Data are shown as mean ± SE. ***P-value < 0.05

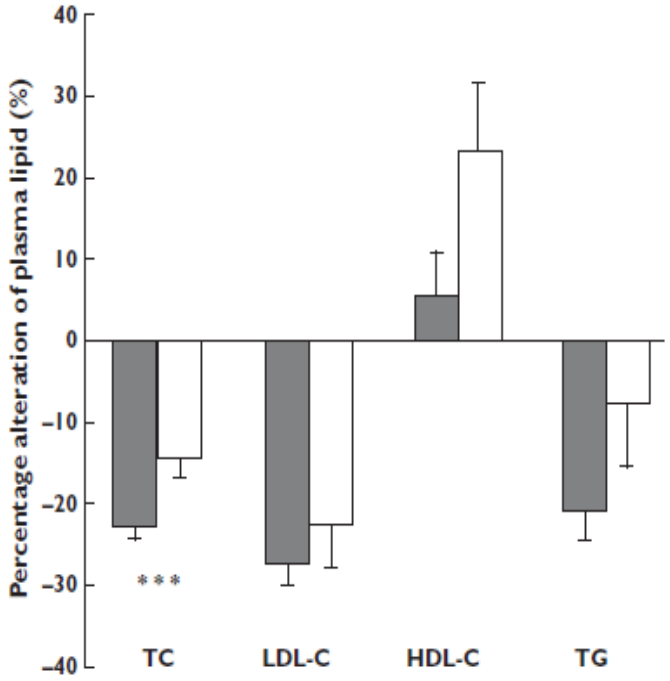


Figure 2

Comparison of percentage changes from baseline in total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C) and triglyceride (TG) between the SLCO1B1 reference genotype group (521TT, ■) and those who carry the 521C allele (521TC genotype, □). Data are shown as mean ± SE. ***P-value < 0.05

Impact of OATP1B1 Polymorphisms on Drug Pharmacokinetics

Table 3 Impact of *SLCO1B1* polymorphisms on drug disposition and effects in humans

Drug	Subjects / study design	Result	Reference
Pravastatin	41 healthy Caucasians / 1×40 mg p.o.	AUC: −11187GG<GA; AUC: 521TT<TC; AUC: *15B non-carriers<carriers; AUC: *17 non-carriers<carriers	Niemi et al. (2004)
Pravastatin	30 healthy Caucasians / 1×40 mg p.o.	AUC: *1a/*1b or *1b/1b<*1a/*1a<*1a/*5	Mwinyi et al. (2004)
Pravastatin	23 healthy Japanese / 1×10 mg p.o.	CLnr: *1b/*15<*1b/*1b	Nishizato et al. (2003)
Pravastatin	41 healthy Caucasians / 1×40 mg p.o.	effect of pravastatin on rate of cholesterol synthesis: *17 carriers<non-carriers	Niemi et al. (2005c)
Pravastatin/ atorvastatin	10 Japanese patients with plasma creatinine kinase elevation or severe muscle complaints vs control patients, who received statins	risk for pravastatin- or atrovastatin induced myopathy: *15 non-carriers<carriers	Morimoto et al. (2004)
Fexofenadine	20 healthy Caucasians / 1×180 mg p.o.	AUC: 521TT<TC< CC	Niemi et al. (2005b)
Repaglinide	56 healthy volunteers / 1×0.25 mg p.o.	AUC: 521TT<TC< CC (+ CYP2C8 genotype) change in blood glucose concentration: −11187GG<GA	Niemi et al. (2005a)
Repaglinide	12 healthy volunteers / 1×0.25 mg p.o.	Increase in repeglinide AUC caused by cyclosporine: 521TT>TC	Kajosaari et al. (2005)
Pitavastatin	24 healthy Koreans / 1×1–8 mg p.o.	AUC: *1b/*1b<*1a/*1a or *1a/*1b<*1a/*15 or *1b/*15	Chung et al. (2005)
Rosuvastatin	36 white, 36 Chinese, 35 Malay and 35 Asian-Indians / 1×40 mg p.o	Whites AUC: 521TT<TC<CC; other ethnic groups AUC: no effect of 521 polymorphism	Lee et al. (2005b)

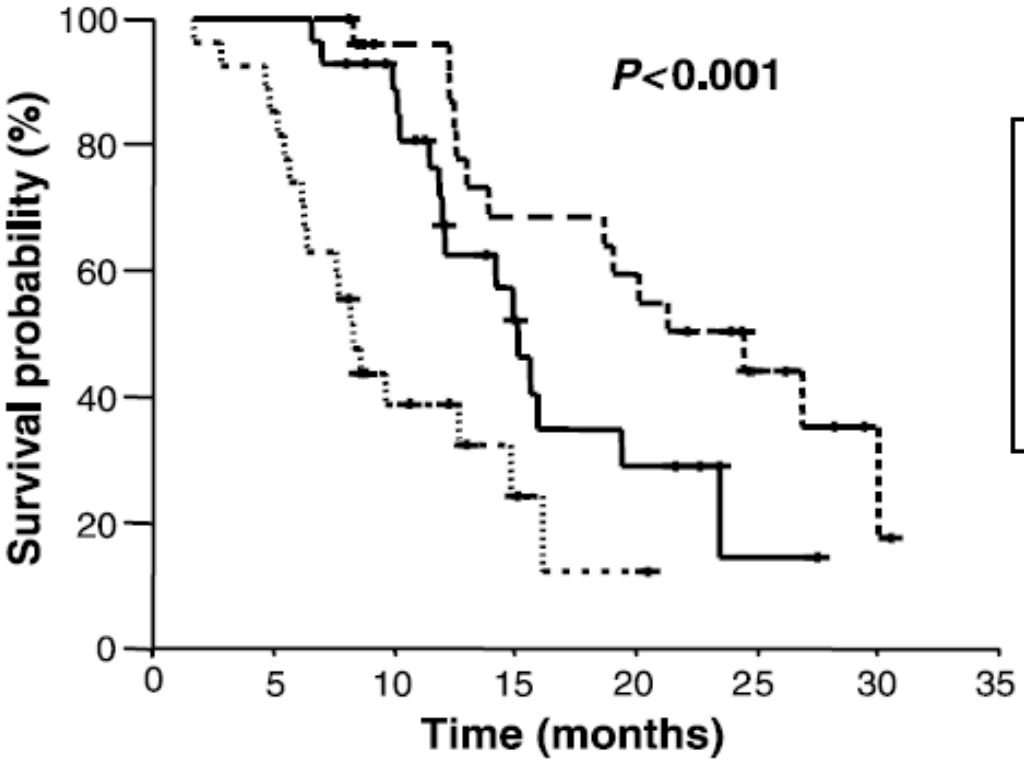
AUC: area under the plasma-concentration-time curve; CL_{nr}: non-renal clearance

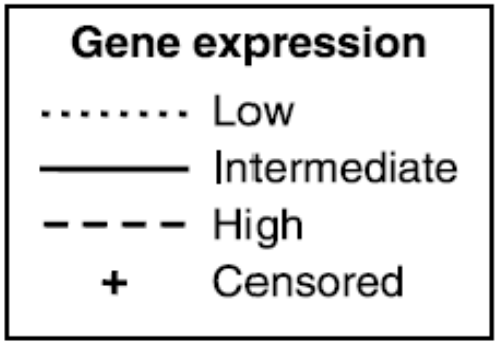
Courtesy Dr. Wang

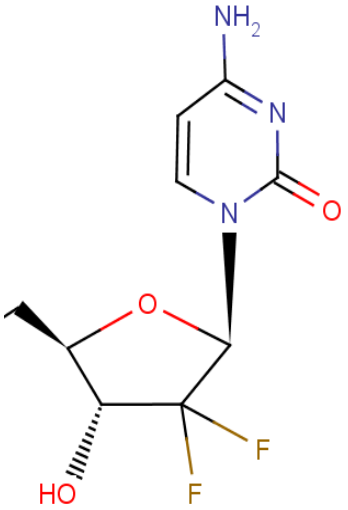
Naunyn Schmiedebergs Arch Pharmacol. 2006 Mar;372(6):432-43.

Role of Other Transporters in Drug Efficacy, Toxicity and Delivery

Gemcitabine Efficacy





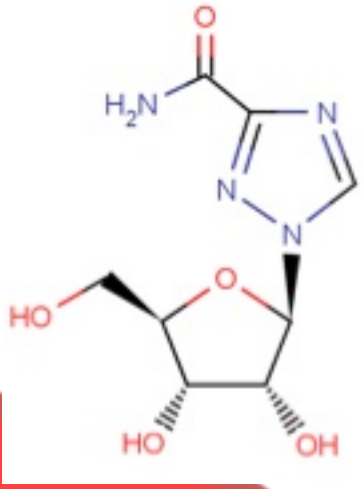


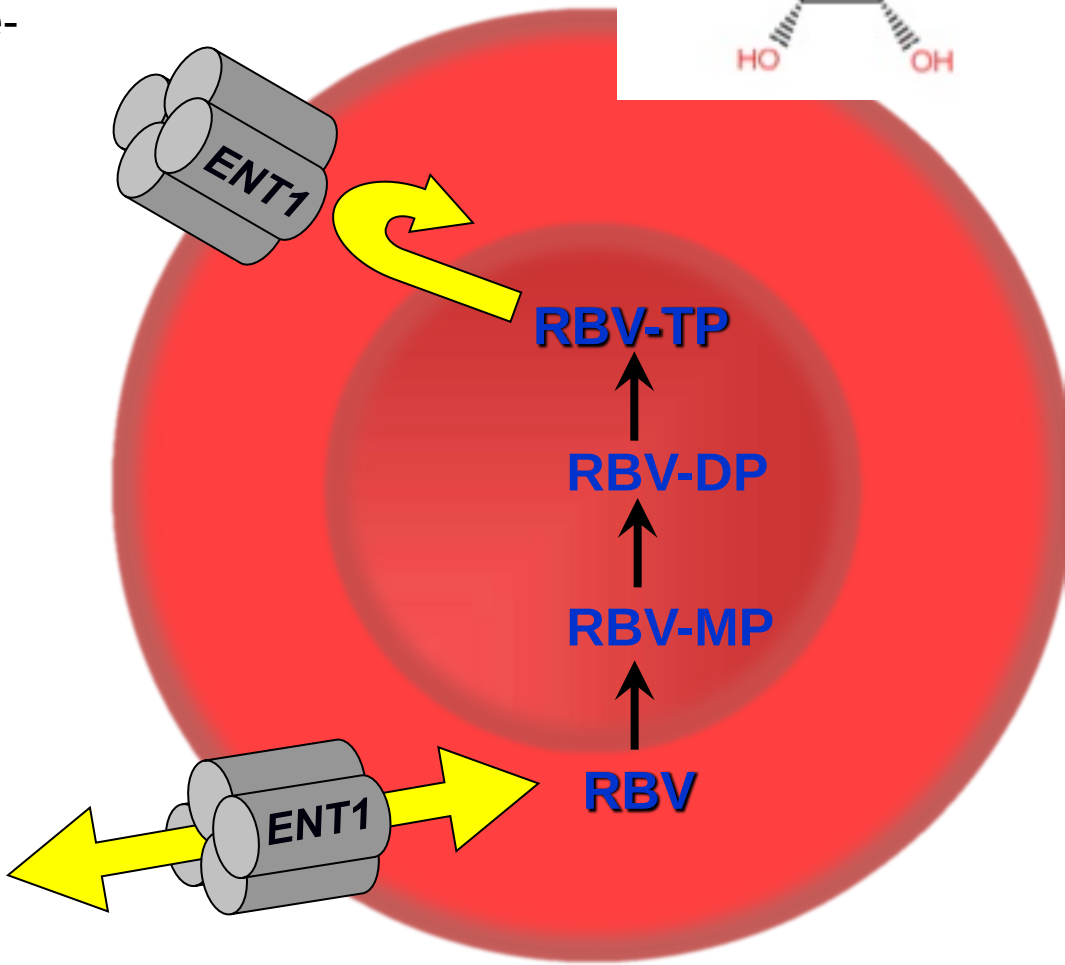
- High ENT1 mRNA expression in pancreatic tumors correlated with longer overall and disease free survival in patients treated with gemcitabine.

Giovanetti et al, Clin Cancer Res 2006; 66(7) 3928-5

Ribavirin

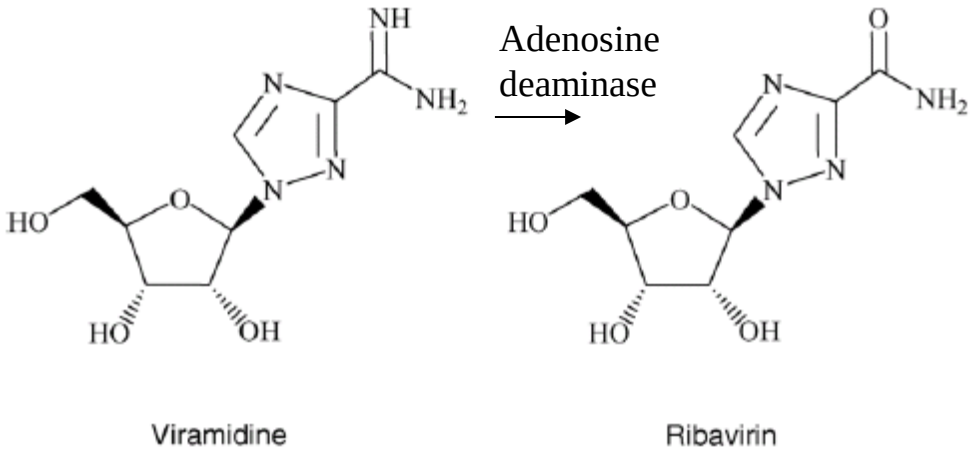
- ✓ Ribavirin is frontline Rx for hepatitis C
- ✓ Ribavirin Rx is limited by its dose-limiting hematological toxicity
- ✓ Ribavirin transported into erythrocyte by ENT1.
- ✓ Phosphorylated to RTP.
- ✓ RTP cannot diffuse or be transported out.
- ✓ Erythrocytes not capable of purine dephosphorylation and results in derangement of ATP homeostasis





Fundamentals of Drug Transporters

- **Ribavirin is front-line Rx for hepatitic C. Its effectiveness is limited by its hematological toxicity. Viramide (Taribavrin), a prodrug, has lower hematological toxicity and greater distribution into the liver (perhaps due to greater lipophilicity or transport?).**



Viramidine Ribavirin

Fundamentals of Drug Transporters

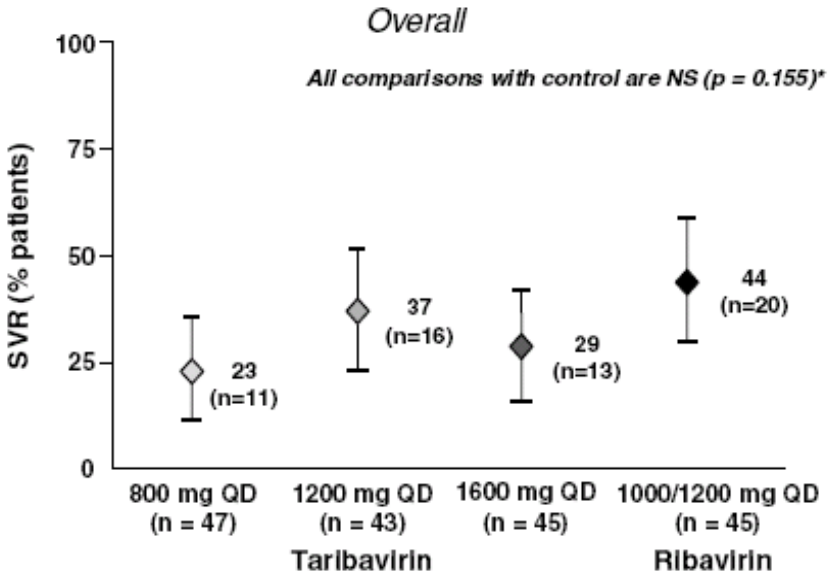
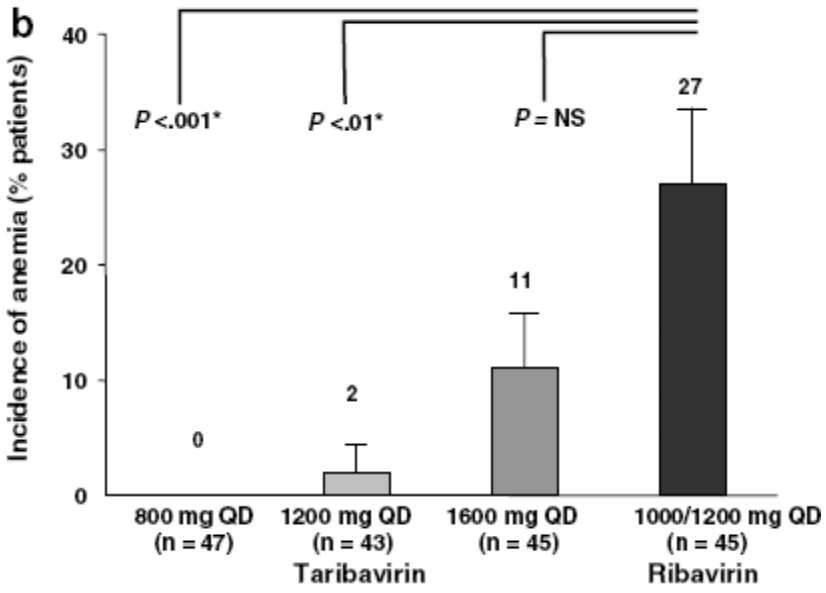


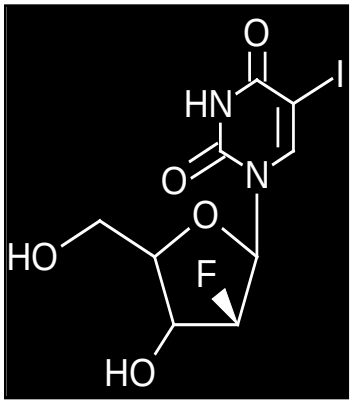
Fig. 4. Proportion of all patients with sustained virological response 24 weeks after end of treatment – intent-to-treat analysis (Bayer TMA Assay; sensitivity to 5 IU/mL, 25 copies/mL). Bars represent confidence intervals. SVR, sustained virological response.



Fundamentals of Drug Transporters

Other transporters - hepatotoxicity

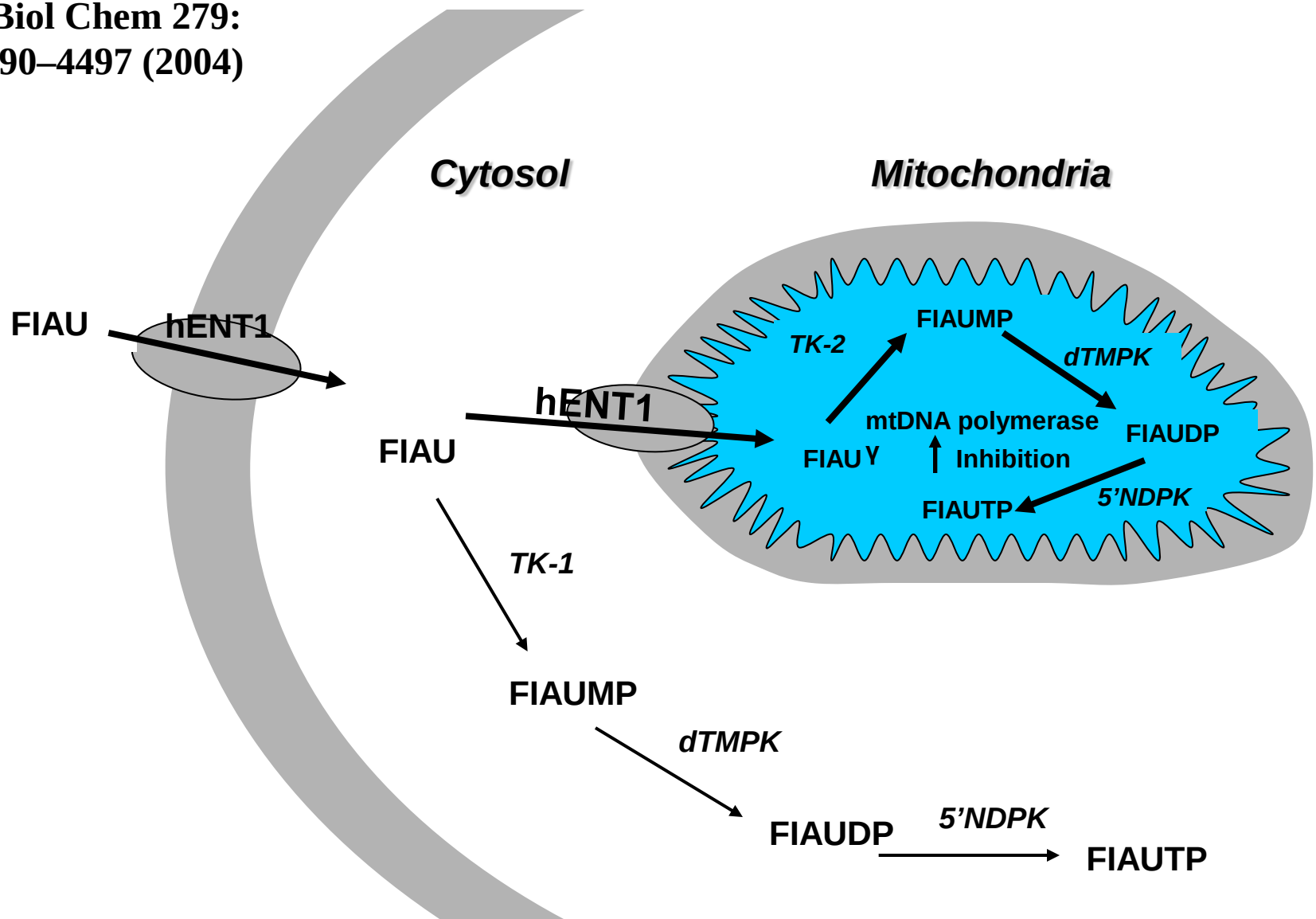
- **A phase 2 trial of fialuridine (FIAU), for hepatitis B, resulted in massive mitochondrial toxicity and hepatic failure in 7 of 15 individuals.**
- **5 patients died and 2 survived only after liver transplant**
- **Major toxicities were hepatic failure, pancreatitis and myopathy**
- **Mechanism of toxicity is associated with inhibition of mitochondrial DNA polymerase gamma and depletion of mitochondrial DNA**



FIAU
Fialuridine

Transport and Intracellular Metabolism of FIAU

Lai, Tse and Unadkat.
J Biol Chem 279:
4490–4497 (2004)



Fundamentals of Drug Transporters

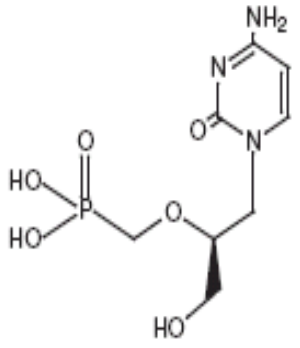
Mitochondrial toxicity of nucleoside drugs

- hENT1 and hENT2 are localized to the mitochondrial membrane
- This localization facilitates the transport of nucleosides **INTO** the mitochondrial compartment
- Mitochondrial-specific kinases convert the nucleoside drugs to the nucleotides
- Antiviral nucleotides inhibit DNA-polymerase gamma and deplete mtDNA resulting in mitochondrial toxicity
- Hydrophilic nucleoside drugs that are **NOT** substrates of nucleoside transporters are NOT mitochondrial toxins

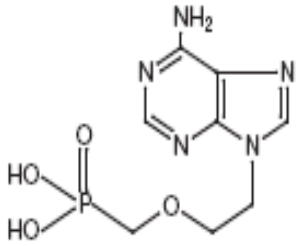
Fundamentals of Drug Transporters

Other transporters - nephrotoxicity

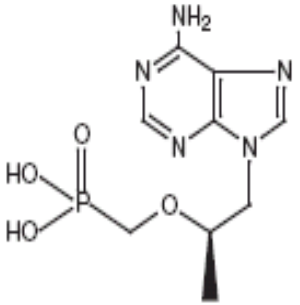
- **Cidofovir, adefovir dipivoxil and tenofovir disoproxil are potent CMV, hepatitis and HIV drugs respectively. All these drug are cleared predominately by the kidney with >70% excreted unchanged in the urine.**



Cidofovir



Adefovir



Tenofovir

Fundamentals of Drug Transporters
Other transporters - nephrotoxicity

- Cidofovir and adefovir are nephrotoxic. The in vitro and in vivo toxicity of these drugs is facilitated by hOAT1. An inhibitor of hOAT1, probenecid, considerable reduces the cytotoxicity of these drugs.

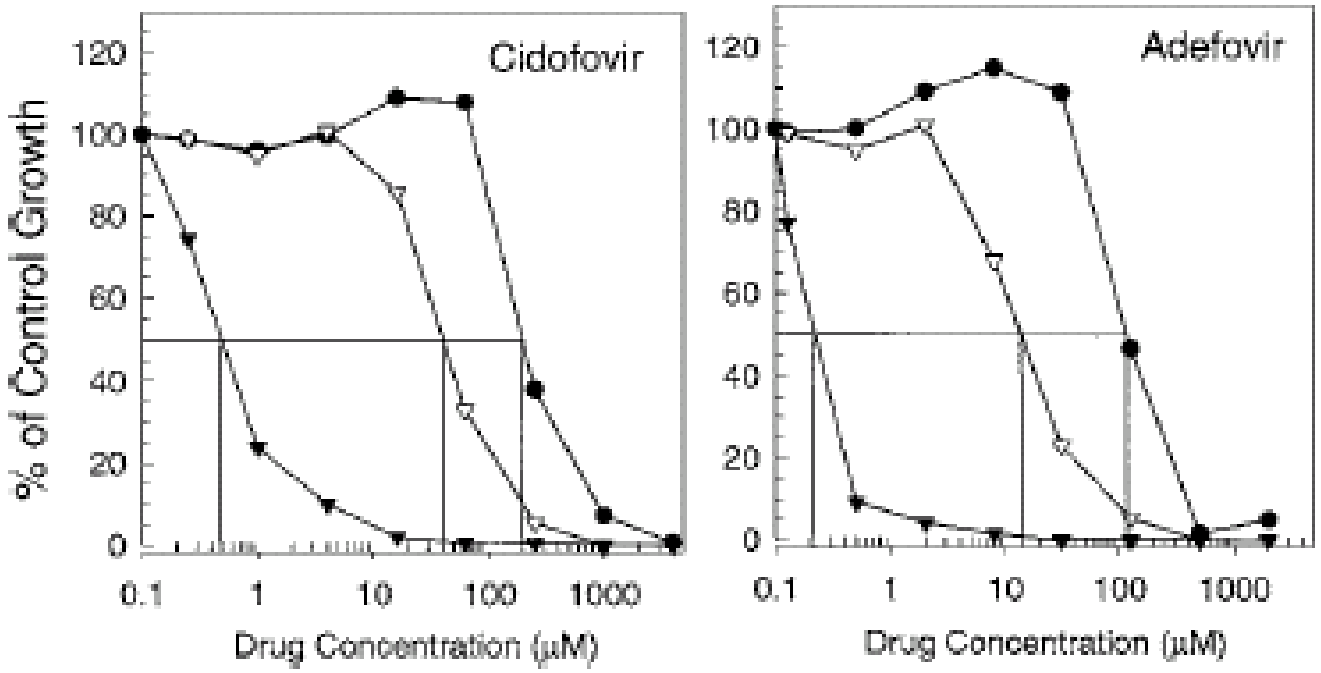


Figure 2. Cytotoxicity of cidofovir, adefovir, in CHOpIRES cells (solid circles) and in CHOhOAT cells in the absence of probenecid (solid triangles) and in the presence of 1 mM probenecid (open triangles).

Chilar et al., NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS, 20(4–7), 641–648 (2001)

Fundamentals of Drug Transporters

CTYOMEGALOVIRUS RETINITIS – from micromedex

- Cidofovir used IV 5 milligrams/kilogram (1hr infusion) once weekly for two weeks followed by 5 milligrams/kilogram once every other week until retinitis progression or therapy-limiting toxicity

- Prehydration therapy and probenecid are recommended to prevent nephrotoxicity

- Side effects of probenecid are serious, causing rash, dyspepsia and allergic phenomena. Adverse effects occurr in 48% of patients, and are severe in 3%.

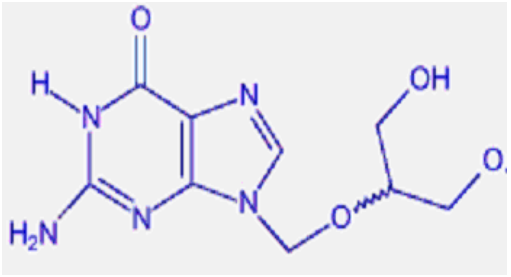
- Antihistamines useful in treating probenecid side effects, and/or a 3-week probenecid desensitization program has enabled continuation of cidofovir-probenecid therapy in a patient with previous probenecid intolerance (hypersensitivity) (Lalezari et al, 1995; Lalezari et al, 1994; Higgins, 1994).

Fundamentals of Drug Transporters

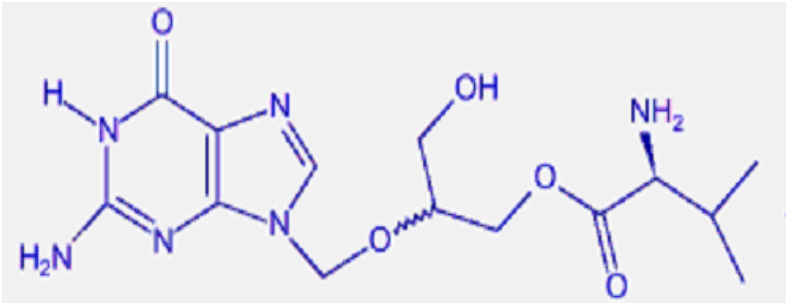
Role of Transporters in Drug Delivery

<u>Utilization to improve bioavailability</u>

- Ganciclovir: Drug for cytomegalovirus (CMV) infection



Ganciclovir (F = 5%, variable)

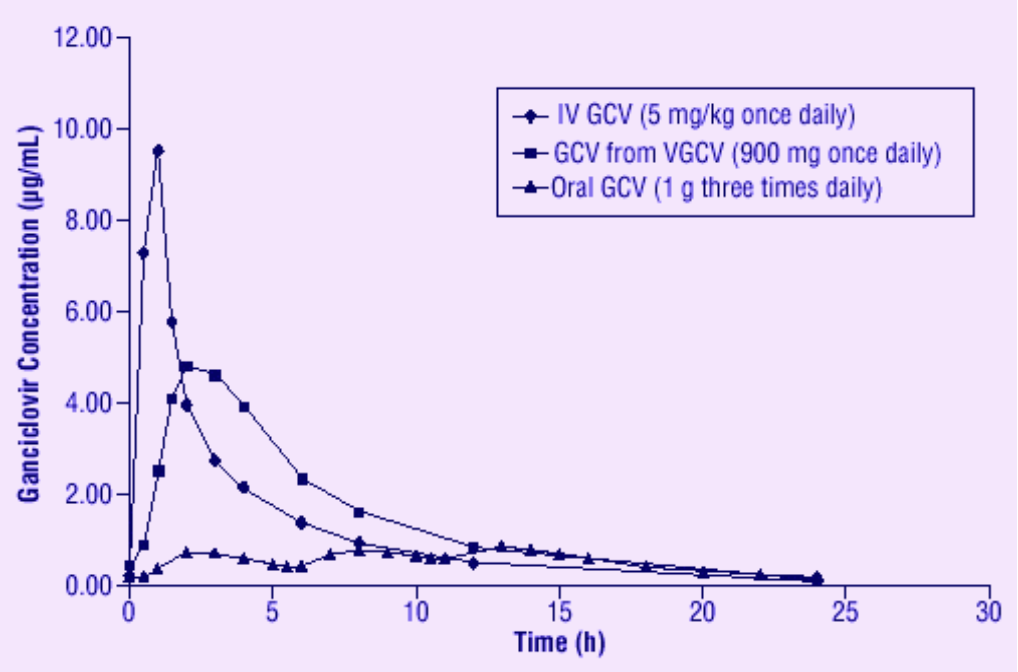


Valganciclovir (Valcyte, F = 60%)

Fundamentals of Drug Transporters

Utilization of transporters to improve bioavailability

- Ganciclovir (GCV): Drug for cytomegalovirus (CMV) infection (F = 5%, variable)



Increased bioavailability of valganciclovir is thought to be due to its transport by the PEPT1 transporter expressed in the intestine.

Fundamentals of Drug Transporters

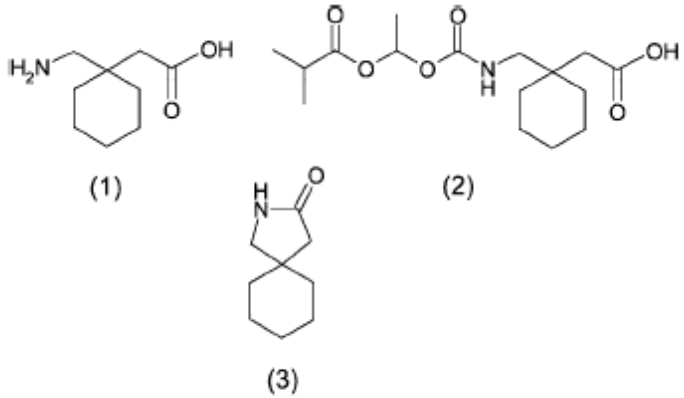
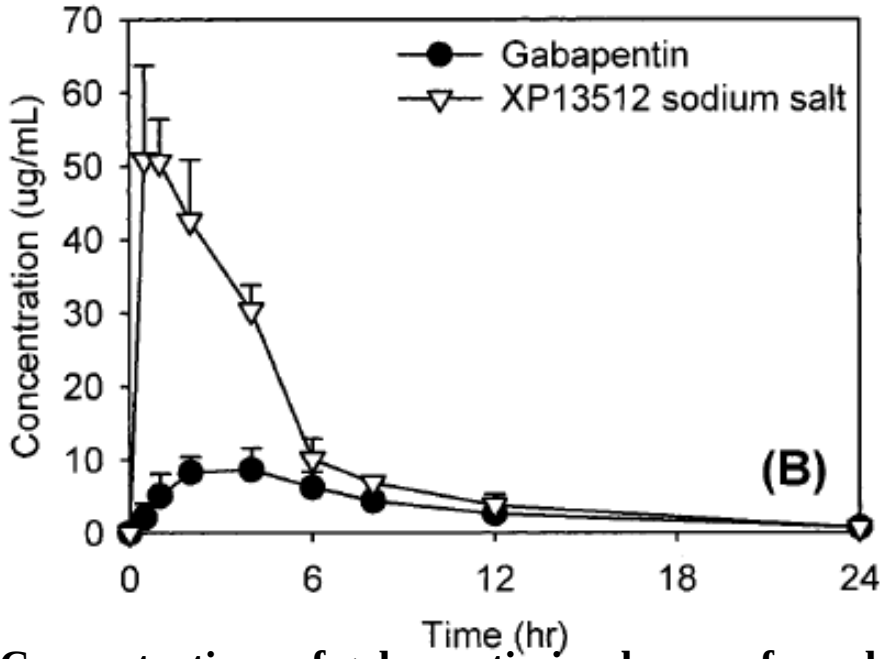
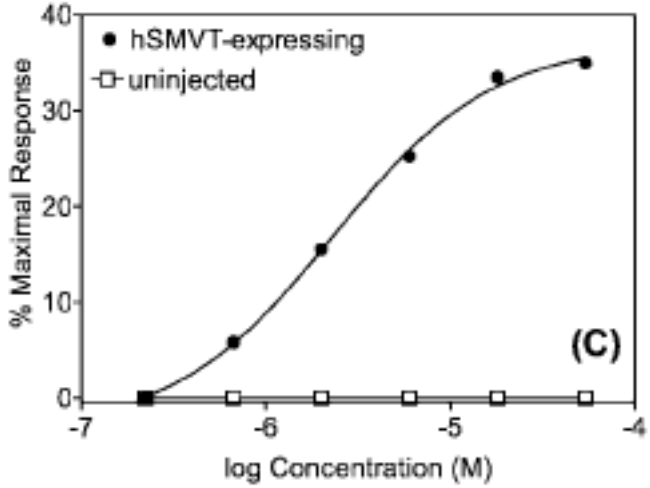


Fig. 1. The structures of gabapentin (1), XP13512 (2), and gabapentin lactam (3).



Concentrations of gabapentin in plasma of monkeys following oral administration of gabapentin (closed circles) or XP13512 sodium salt (open triangles).



Effect of XP13512 on electrophysiological responses of SMVT expressing oocytes. The maximal current induced by XP13512 (Vmax) was approximately 40% of that produced by biotin (C).

Cundy et al. J Pharmacol Exp Ther. 2004;311:315-33.

Fundamentals of Drug Transporters

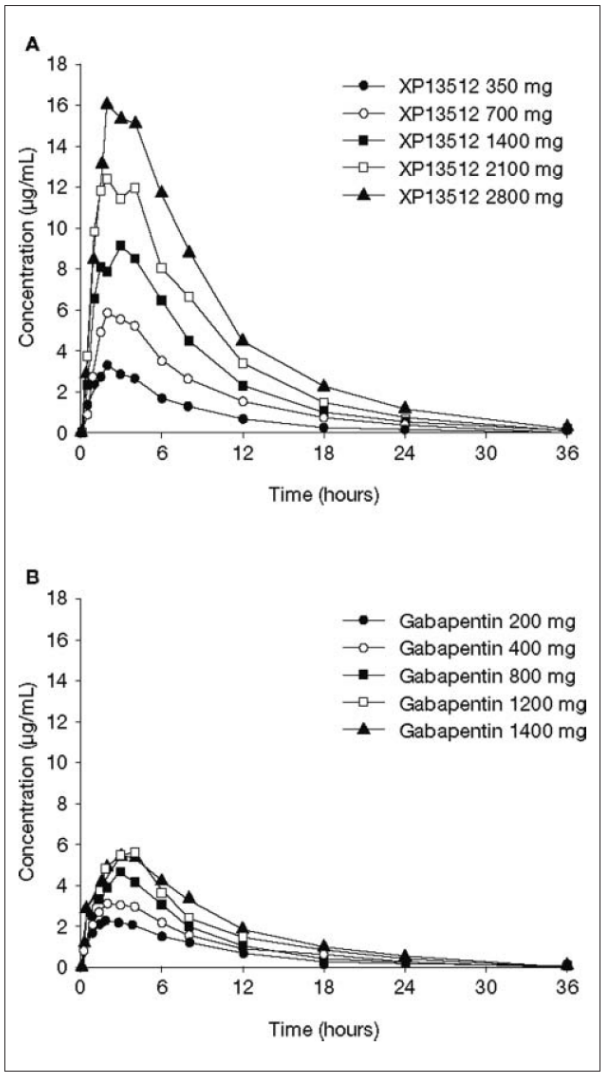


Figure 2. Study IR-1: Mean concentrations of gabapentin in blood after oral dosing of approximately equimolar doses of (A) XP13512 IR capsules (n = 8 per dose level) or (B) oral gabapentin (n = 10 per dose level).

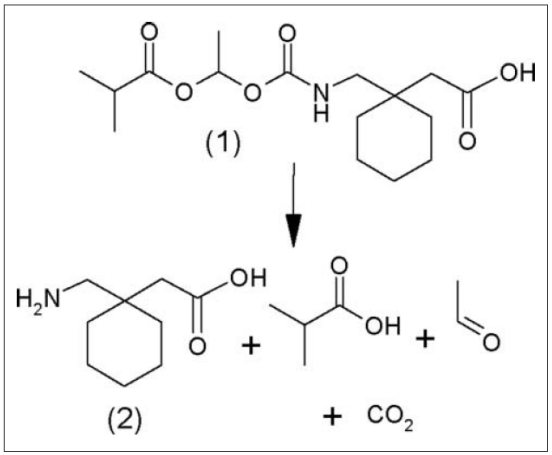
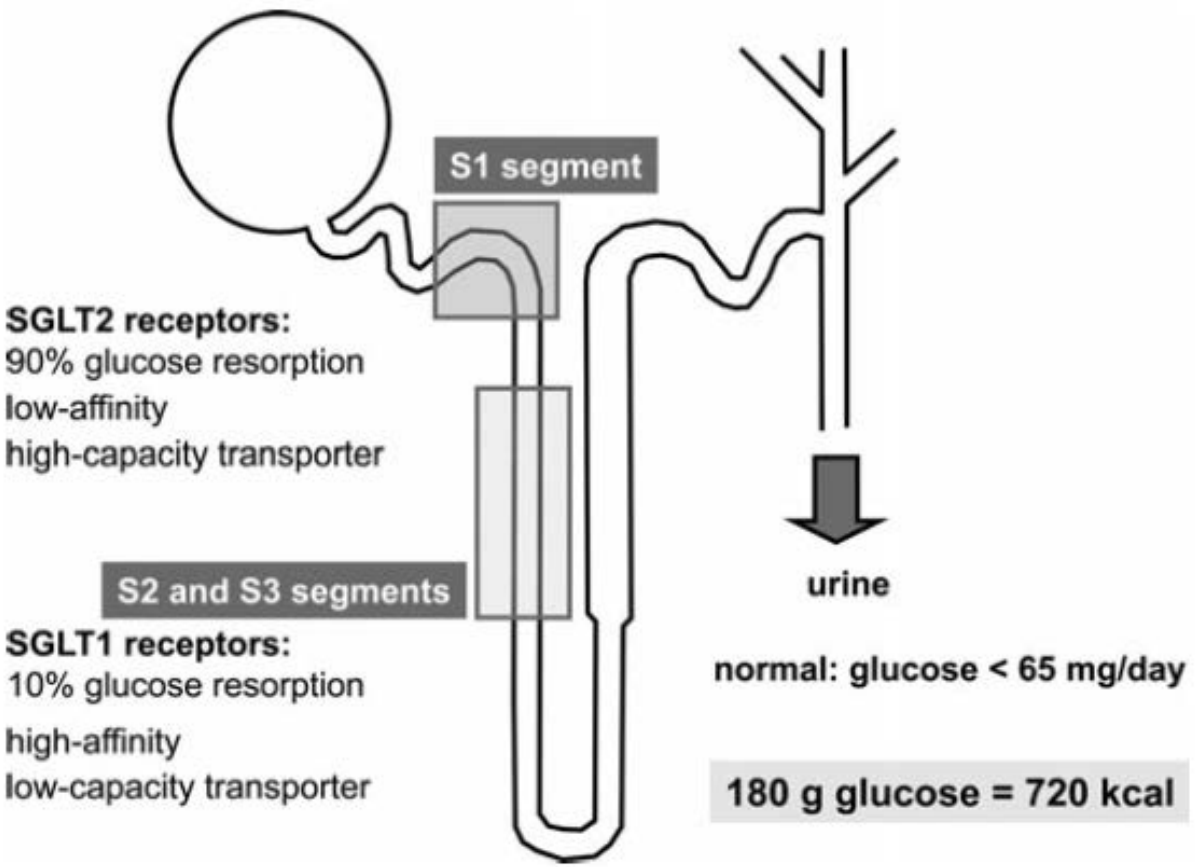


Figure 1. Chemical structure of XP13512 (1) and its enzymatic conversion to gabapentin (2), isobutyric acid, carbon dioxide, and acetaldehyde.

From Cundy KC J Clin Pharmacol. 2008 Dec;48(12):1378-88

Fundamentals of Drug Transporters



canagliflozin,
dapagliflozin,
empagliflozin

FIGURE 1: Schematic overview on the predominant distribution of SGLT1 and SGLT2 receptors along the nephron.

Vlotides G and Mertens P Nephrol Dial Transplant (2014) 0: 1–5

When are Transporters Relevant to ADME?

- When a significant fraction of the drug is absorbed, distributed into an eliminating or non-eliminating tissue, or cleared from the body via transporters (i.e. f_t is large)
  - e.g. when $CL_{hepatic\ uptake\ transport}$ vs. $CL_{hepatic\ diffusion}$ is large

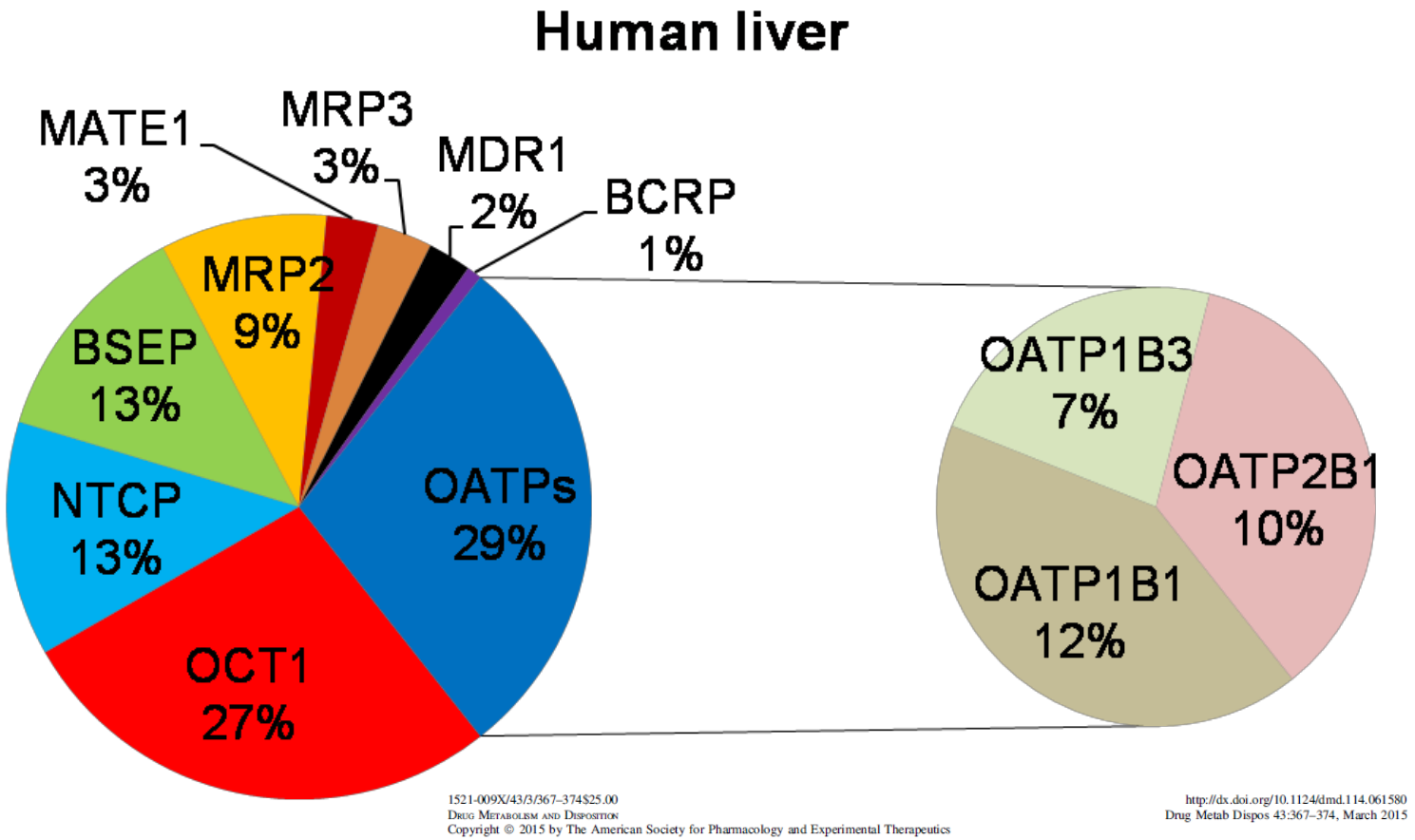
- If the fraction of the dose distributing into a tissue via a transporter is NOT significant, modulation (e.g. DDI) of this transporter
  - will NOT significantly affect the systemic CL of the drug
  - But, will have a **profound** impact on the local tissue concentration and therefore potentially the toxicity and efficacy of the drug – disconnect between the plasma and tissue conc.

.

Some Principles

- When a new molecular entity is found to be a substrate of a transporter, consider the following :
  - Is the transporter(s) present in the tissue of interest?
  - If so, what is its contribution relative to $CL_{diffusion}$ and $CL_{other\ transporters}$?
  - In vitro transport ≠ in vivo relevance because transfected cell lines (or *X. oocytes*) often exaggerate **ft** by the transporter due to high expression of the transporter
  - A substrate can be a potent inhibitor of a transporter without being a substrate
  - Even if the **affinity** of the substrate for the transporter is **low** and the expression of the transporter in the tissue of interest is low, that transporter could still be important in determinig the tissue conc. and/or clearance of the drug if **ft** via that transporter is large.
  - **ft is king**!

Relative Transporter Abundance Pie Chart



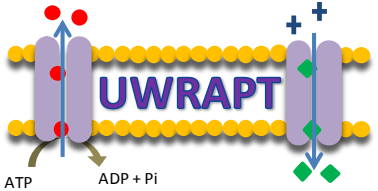
1521-009X/43/3/367–374$25.00
Drug Metabolism and Disposition
http://dx.doi.org/10.1124/dmd.114.061580
Drug Metab Dispos 43:367–374, March 2015

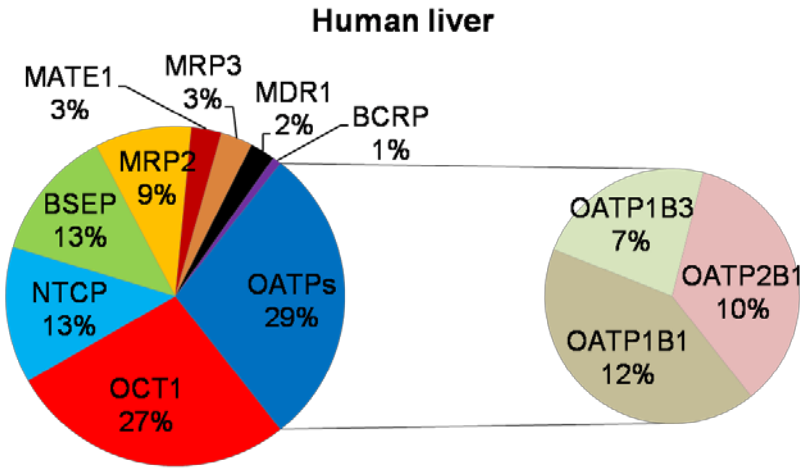
Interspecies Variability in Expression of Hepatobiliary Transporters across Human, Dog, Monkey, and Rat as Determined by Quantitative Proteomics

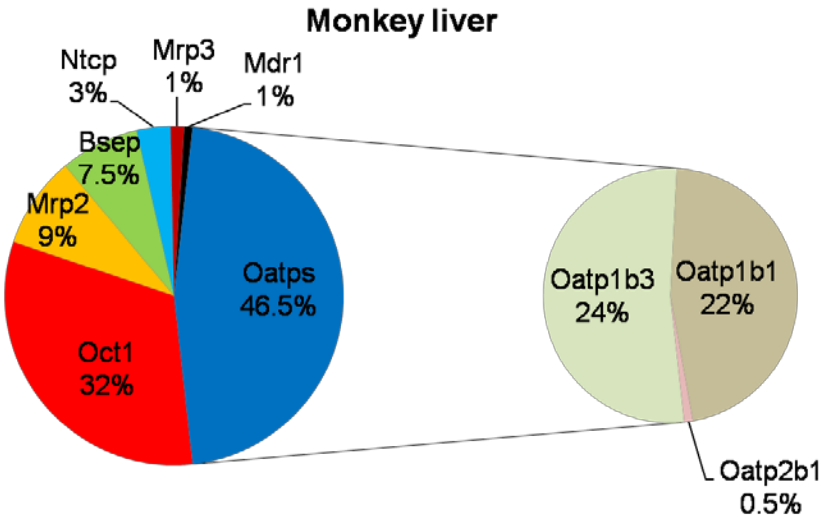
Li Wang, Bhagwat Prasad, Laurent Salphati, Xiaoyan Chu, Anshul Gupta, Cornelis E.C.A. Hop, Raymond Evers, and Jashvant D. Unadkat

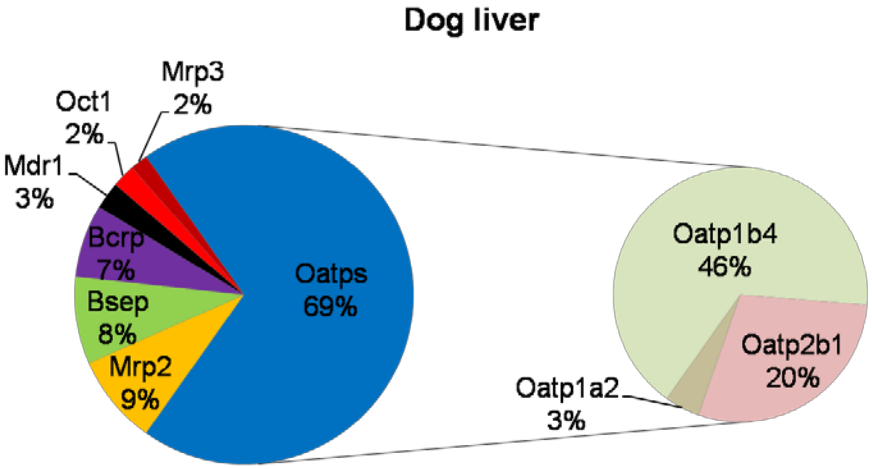
Li et al. DMD 2015

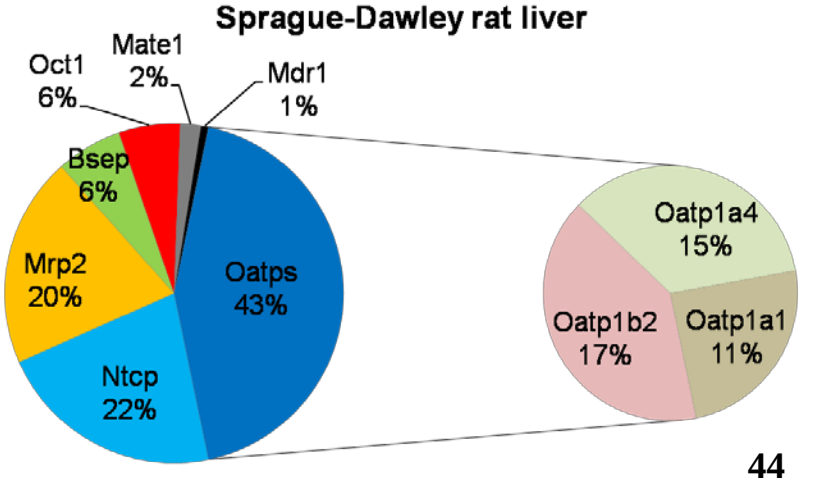
Relative Transporter Abundance Pie Charts



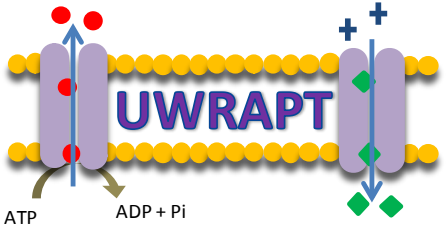








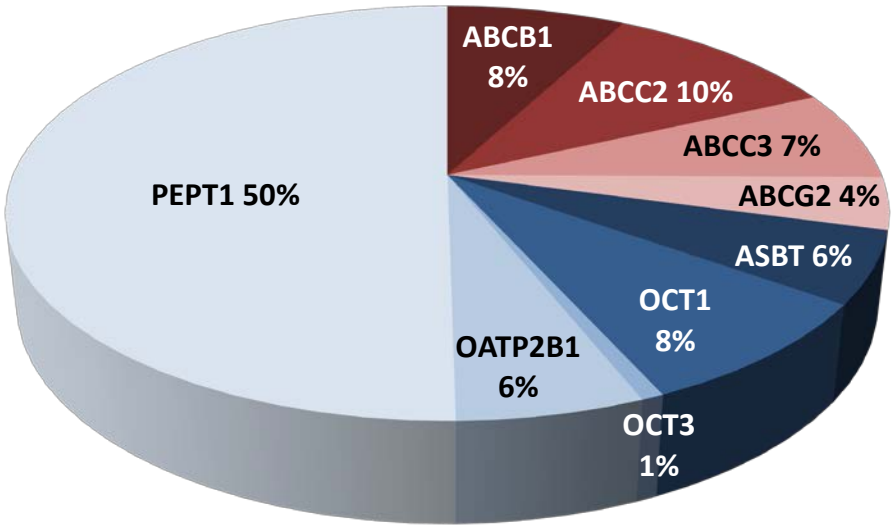
Transporter Expression in Human Intestines



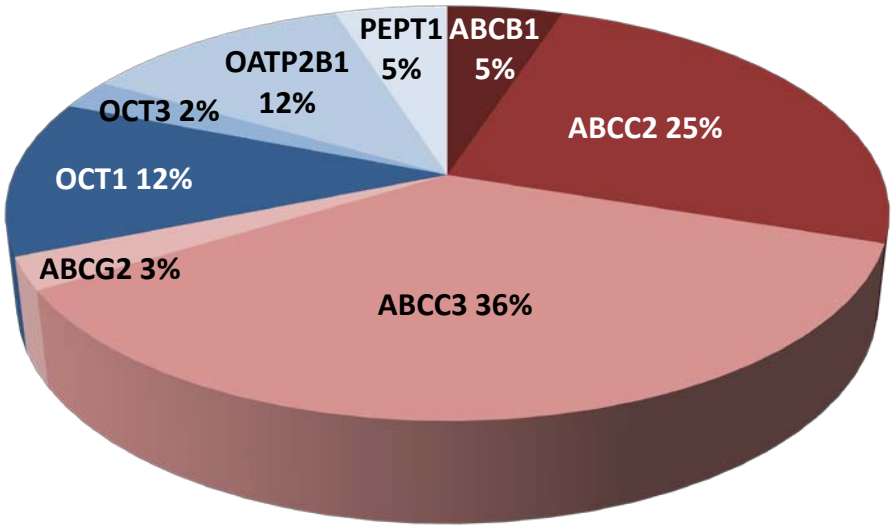
N=6, 5 males, 1 female;

Relative contribution

small intestine



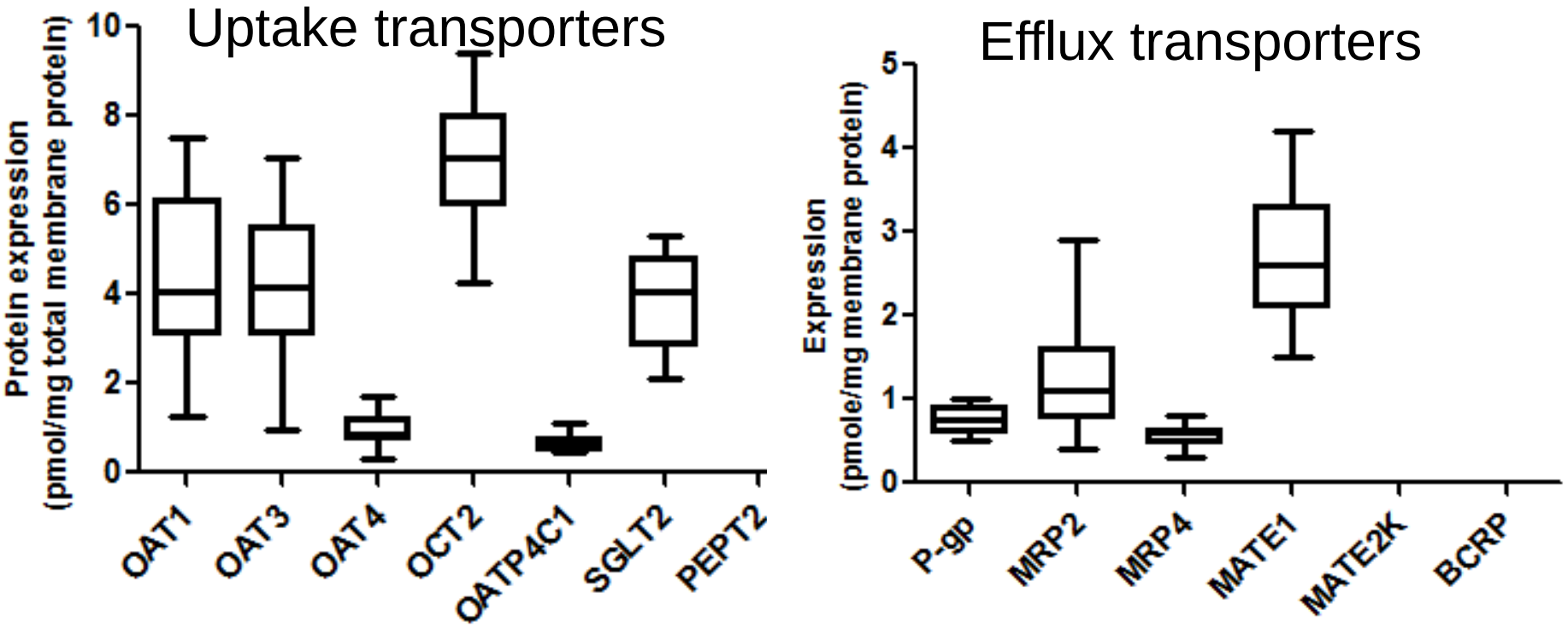
colon



OATP1A2 could not be detected in the small intestine

Drozdzik M Mol Pharm. 2014 Oct 6;11(10):3547-55.

Interindividual Variability in Human Kidney (Cortex) Transporter Expression (N=14)



- Expression of MATE2K and PEPT2 was below the lower level of quantification. BCRP could not be detected.

- Protein expression was not correlated with age or sex

Modified Clearance Concepts

$$\mathbf{CL=}\ \frac{f_u CL^s_{in} CL_{Other}\left(CL^c_{ef}+CL_{\text{int}}\right)+Q_L\left(CL_{Other}\left(CL^c_{ef}+CL_{\text{int}}+CL^s_{ef}\right)+f_u CL^s_{in}\left(CL^c_{ef}+CL_{\text{int}}\right)\right)}{\left(f_u CL^s_{in}\left(CL^c_{ef}+CL_{\text{int}}\right)+Q_L\left(CL^c_{ef}+CL_{\text{int}}+CL^s_{ef}\right)\right)}$$

When $CL_{other} = 0$

$$\frac{f_u Q_L CL^s_{in}\left(CL^c_{ef}+CL_{\text{int}}\right)}{\left(f_u CL^s_{in}\left(CL^c_{ef}+CL_{\text{int}}\right)+Q_L\left(CL^c_{ef}+CL_{\text{int}}+CL^s_{ef}\right)\right)}$$

and when $CL^s_{ef} \approx 0$ or $<<$ $\left(CL^c_{ef}+CL_{\text{int}}\right)$

$$\frac{f_u Q_L CL^s_{in}}{\left(f_u CL^s_{in}+Q_L\right)}$$

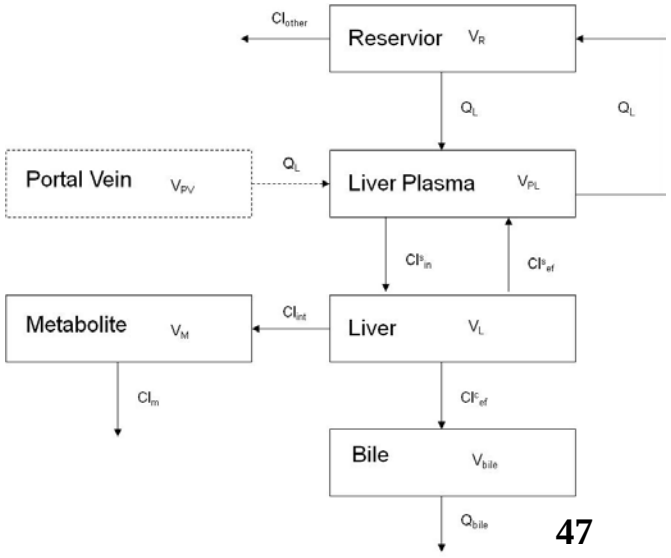
and when $CL^s_{in}/CL^s_{ef} = \infty$ (no permeability limitation)

$$\frac{f_u Q_L\left(CL^c_{ef}+CL_{\text{int}}\right)}{Q_L+f_u\left(CL^c_{ef}+CL_{\text{int}}\right)}$$

and when $CL^c_{ef} = 0$ (only metabolic elimination)

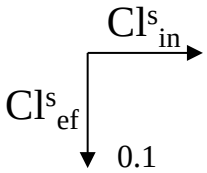
$$\frac{f_u Q_L CL_{\text{int}}}{Q_L+f_u CL_{\text{int}}}$$

the equation reduces to the well-stirred model

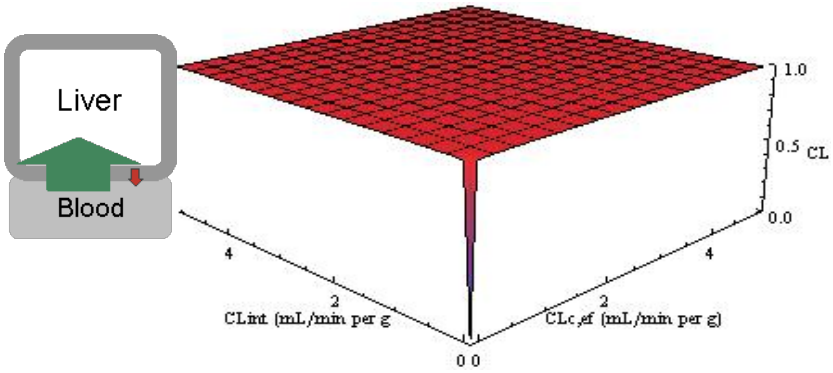


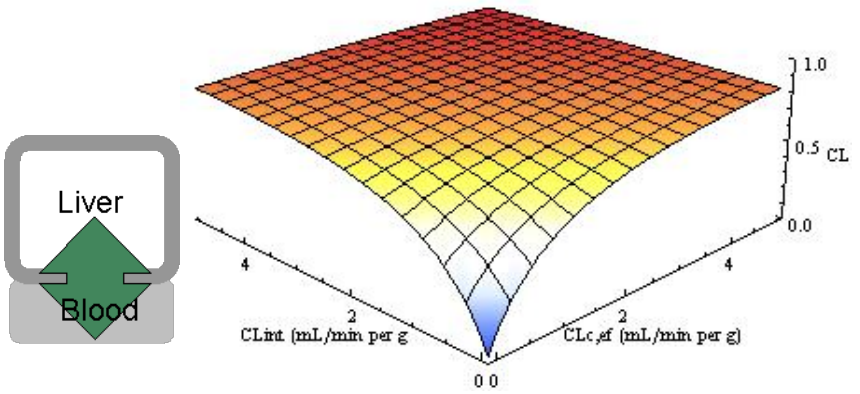
Endres et al., Mol Pharm. 2009 6:1756-65

Dependence of Systemic Clearance (CL) on CL_{int} and CL^{c}_{ef} Clearances



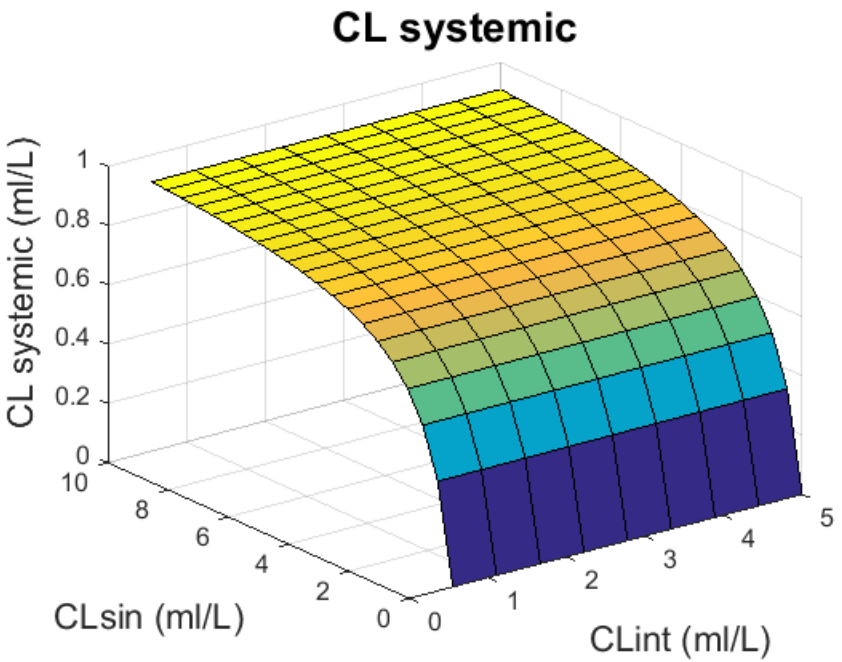
When sinusoidal distributional CL is 100-fold Q_L (=1), then Cl_{sys} is limited by **Q_L**. **When the NET sinusoidal CL is low (e.g. when the drug is highly permeable) CL^{c}_{ef} / CL_{int} determines CL**. Note when **CL^{s}_{in} is high,** inhibition (DDI) of CL^{c}_{ef} / CL_{int} will have minimal effect on Cl_{sys} but a dramatic effect on hepatic conc.





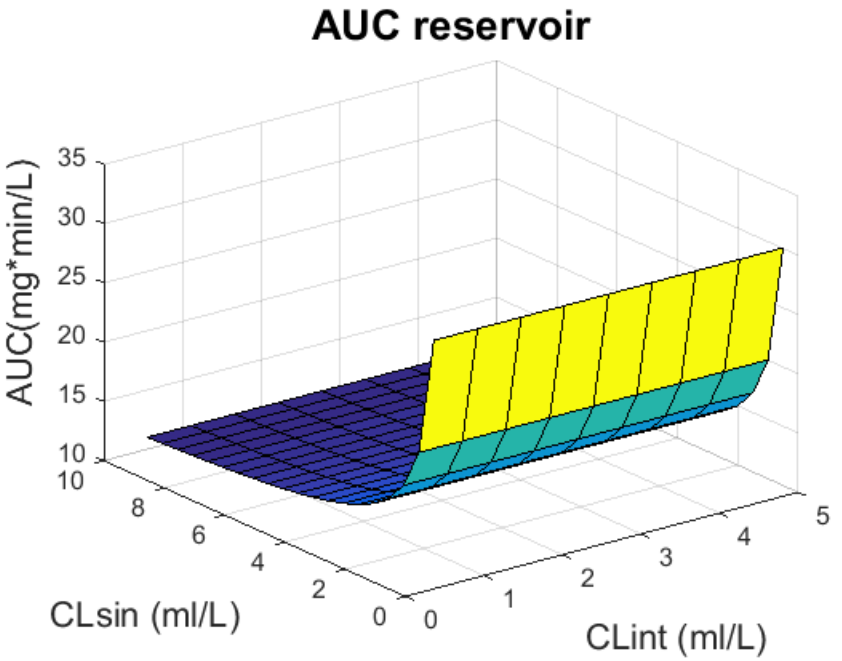
Assumptions: $CL_{other} = 0$
Q_L=1 (arbitrary vol/time units); $F_p/F_L = 1$

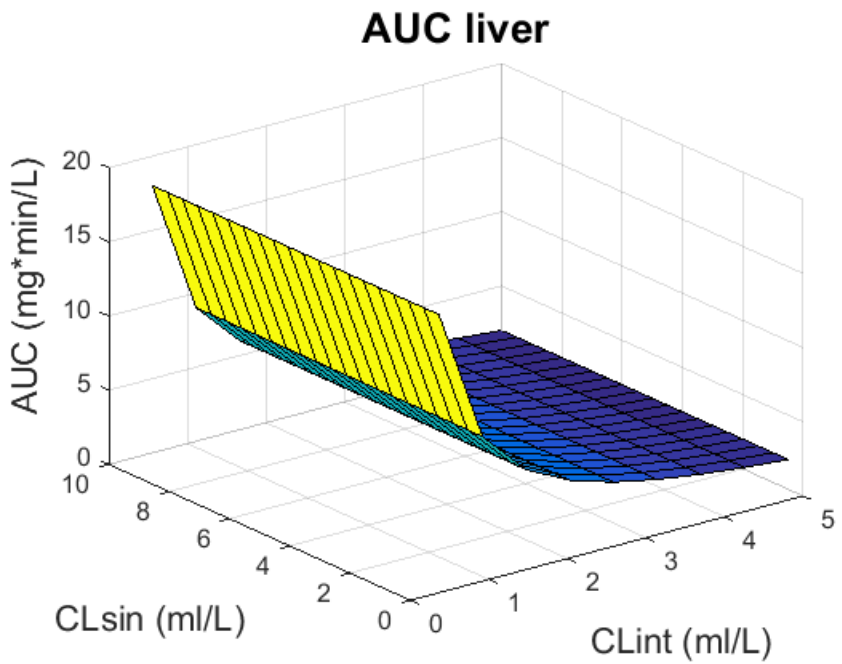
Endres et al., Mol Pharm. 2009 6:1756-65



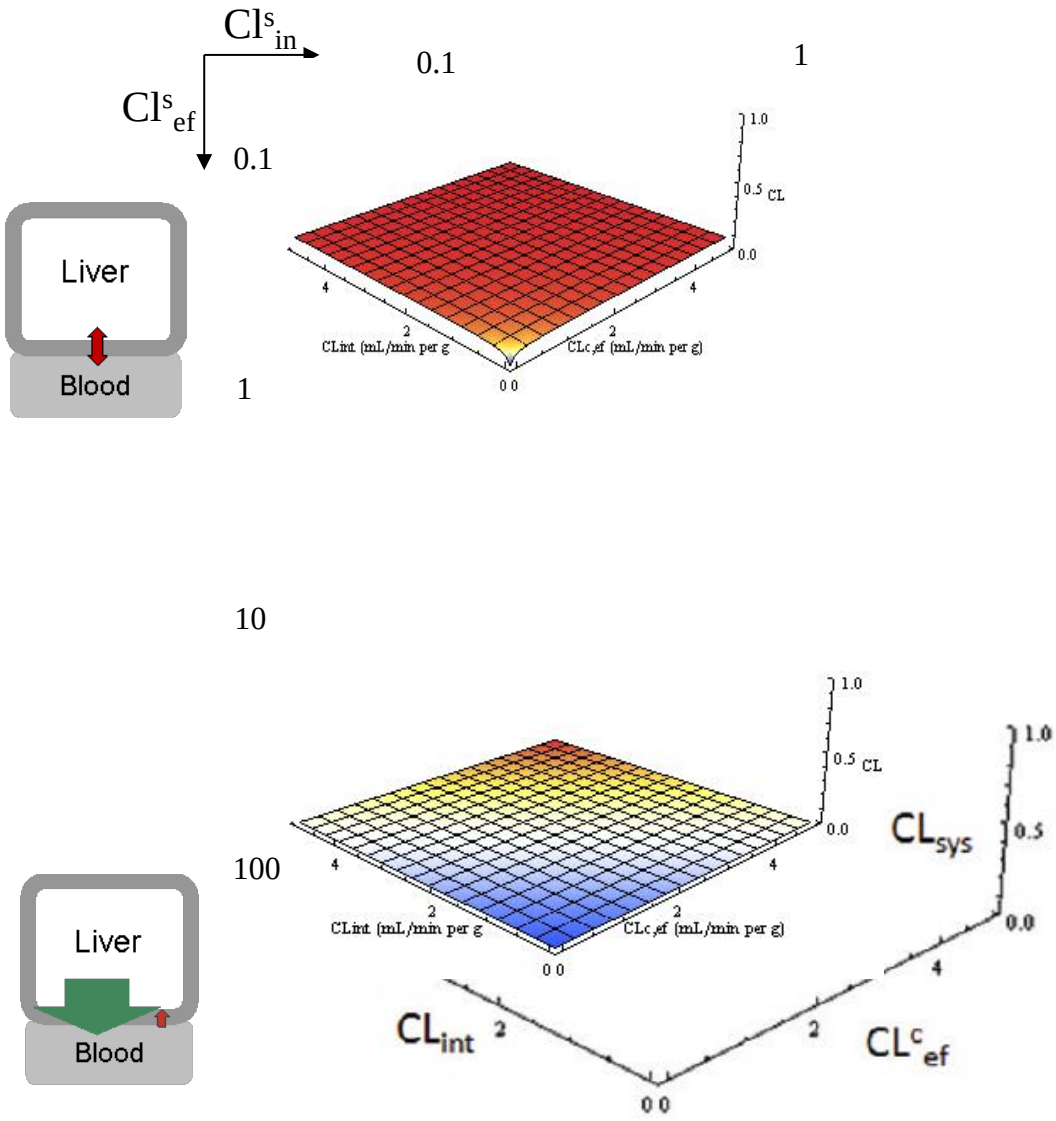
When sinusoidal efflux is very small and there is no CLother:
~As sinusoidal influx ↑, CL ↑, AUC reservoir ↓
As CLint ↑, CL↔, AUC reservoir ↔

However, in the LIVER:
~As sinusoidal influx ↑, AUC liver ↔
As CLint ↑, AUC liver ↓





Dependence of Systemic Clearance on Sinusoidal Distributional Clearance



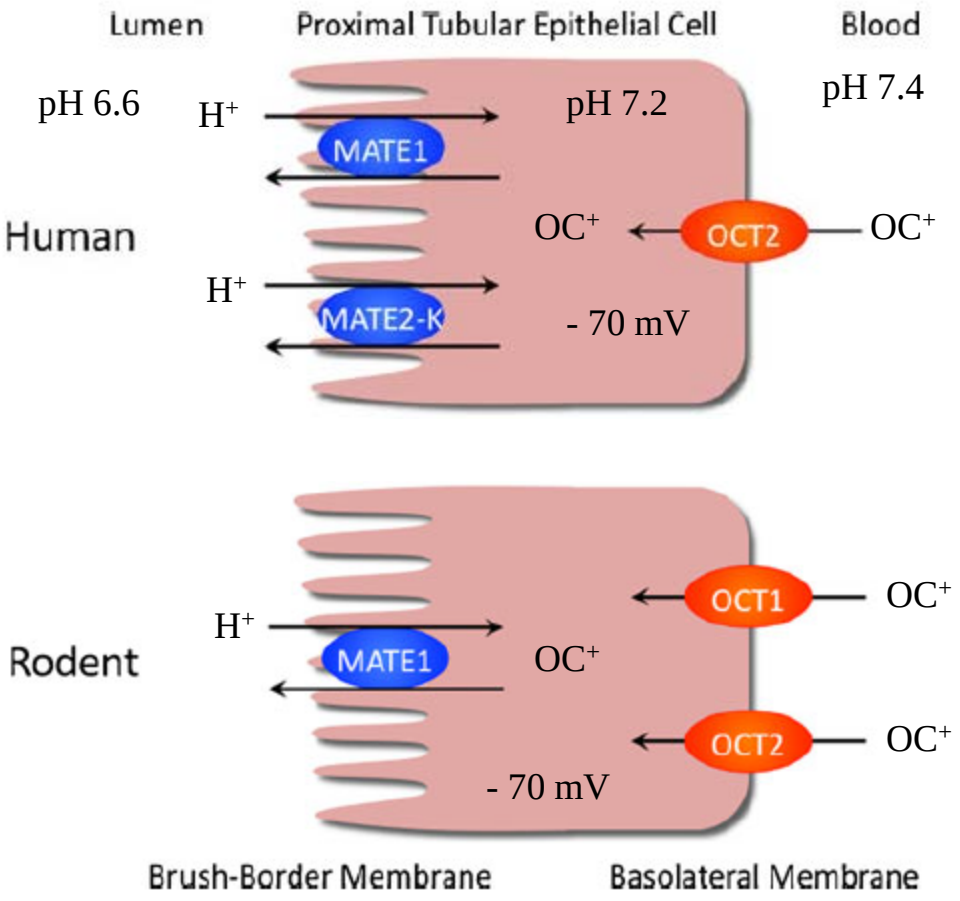
When **CL^s_{in} is low or << CL^s_{ef},** hepatic distribution becomes **permeability rate limited -** changes in either CL_{int} or CL^c_{ef} have **decreasing** impact on Cl_{sys}. A metabolic drug interaction may be predicted from microsomal data but **NONE** is observed in vivo

Assumptions: $CL_{other} = 0$
Q_L=1 (arbitrary vol/time units);
$F_p/F_L = 1$

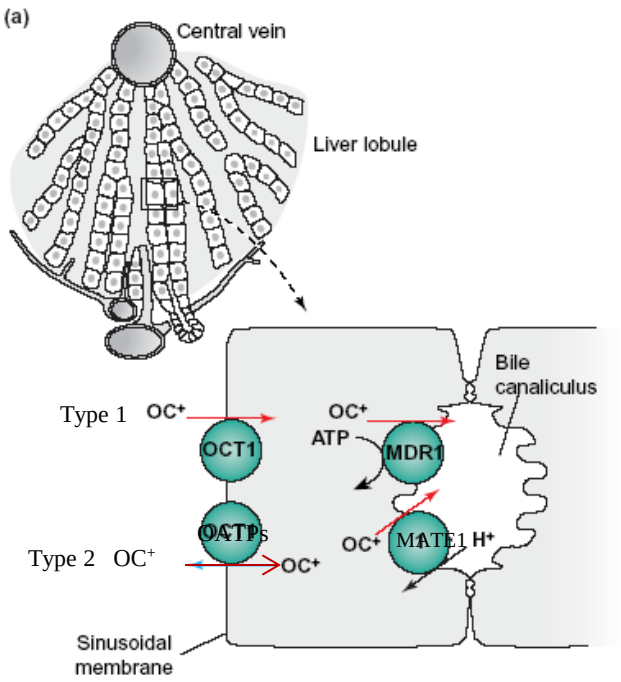
Endres et al., Mol Pharm. 2009 6:1756-65

Models of Renal and Hepatic OC Elimination

Kidney

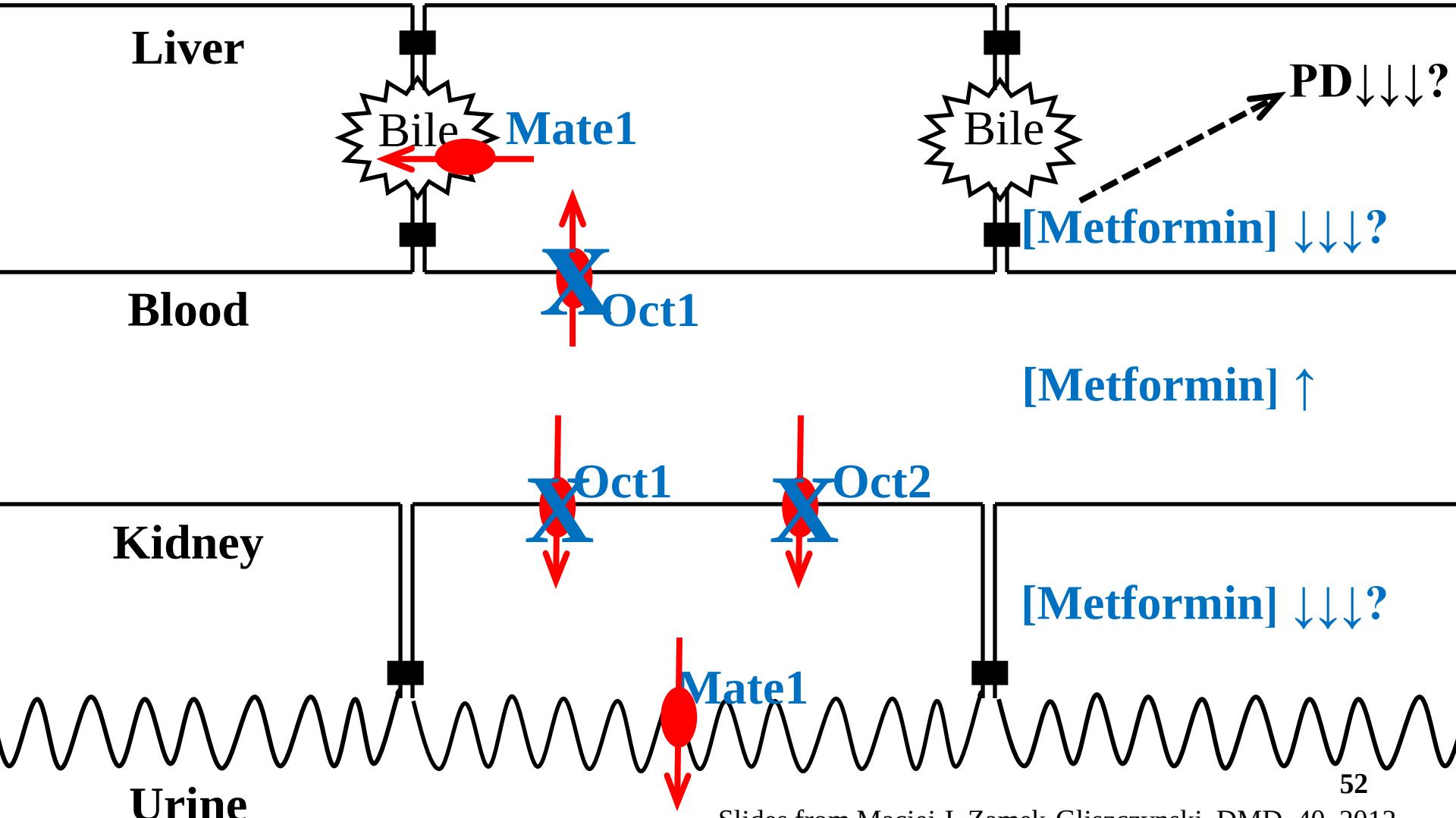


Liver



Courtesy Dr. J Wang

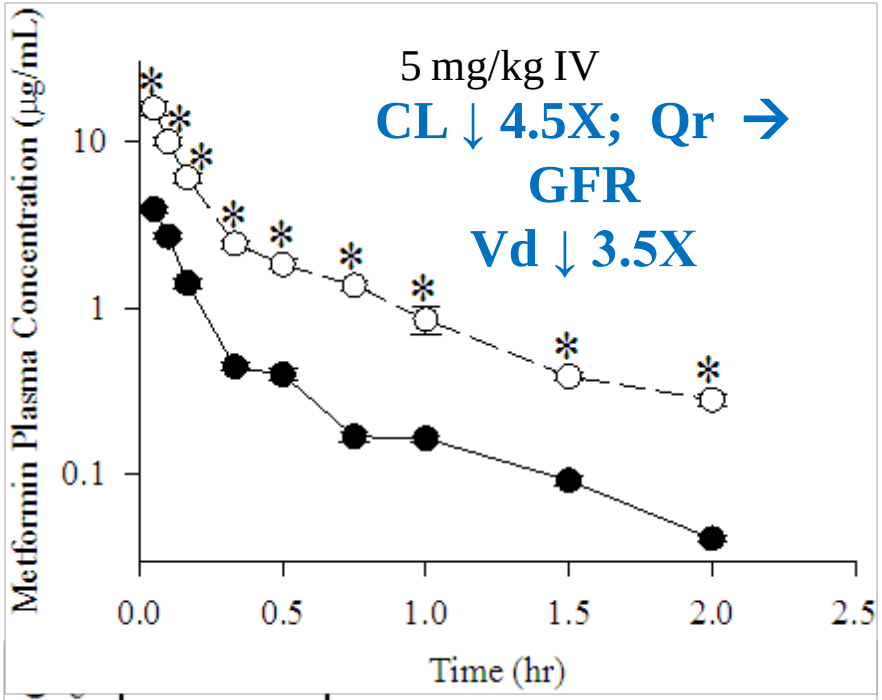
What Happens to Metformin PK, Distribution and PD Following Ablation of Oct1/2?

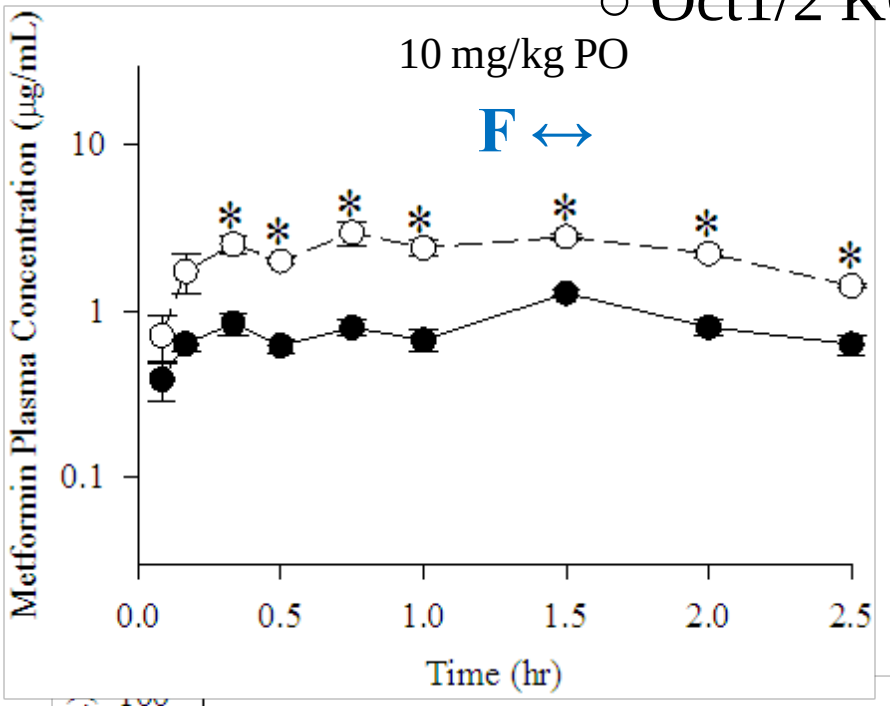


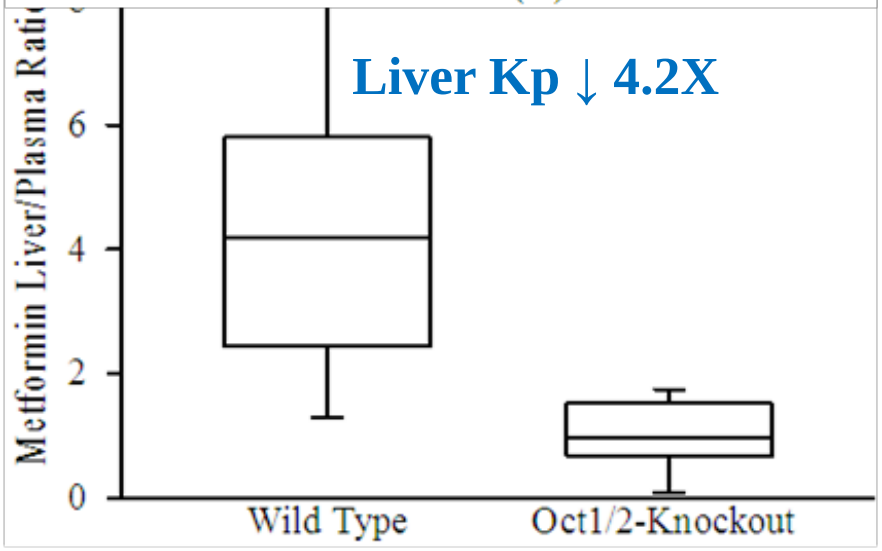
Slides from Maciej J. Zamek-Gliszczynski DMD 40, 2012

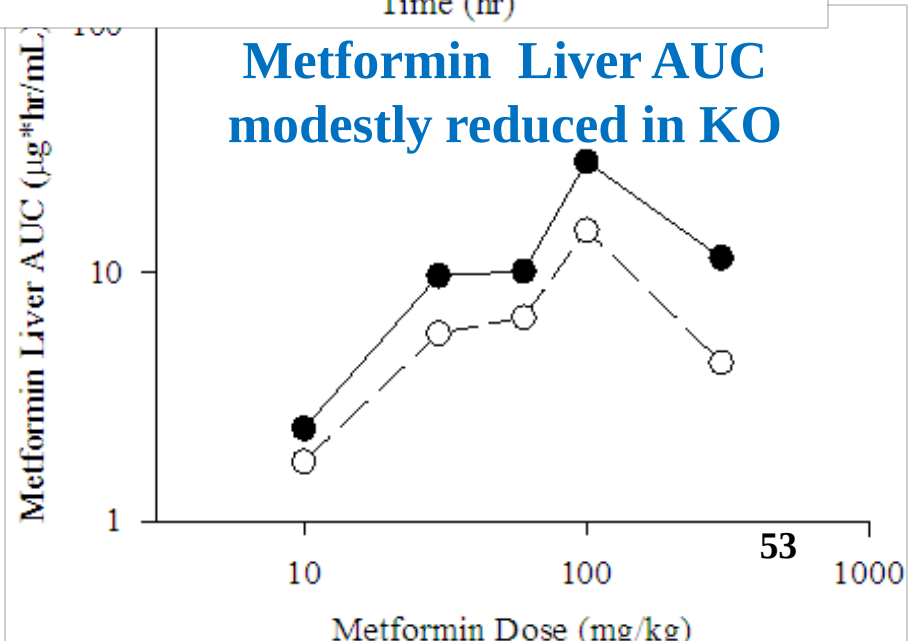
Metformin PK

● wild type
○ Oct1/2 KO

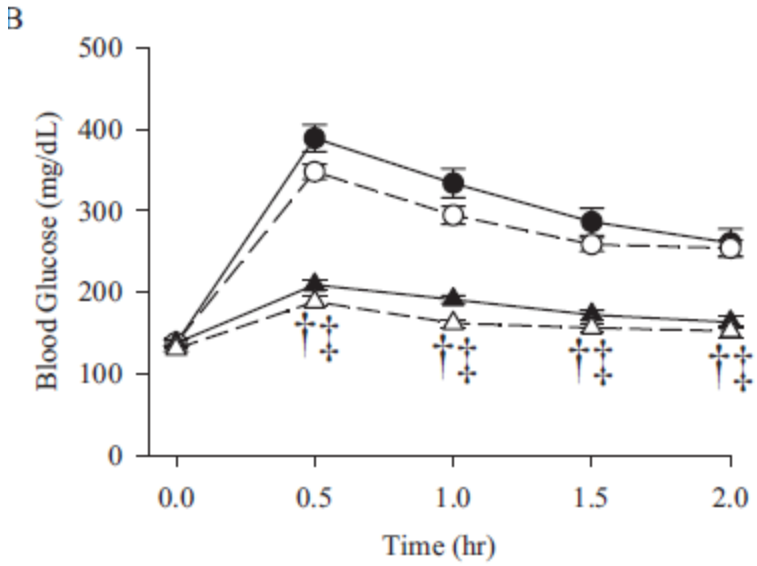








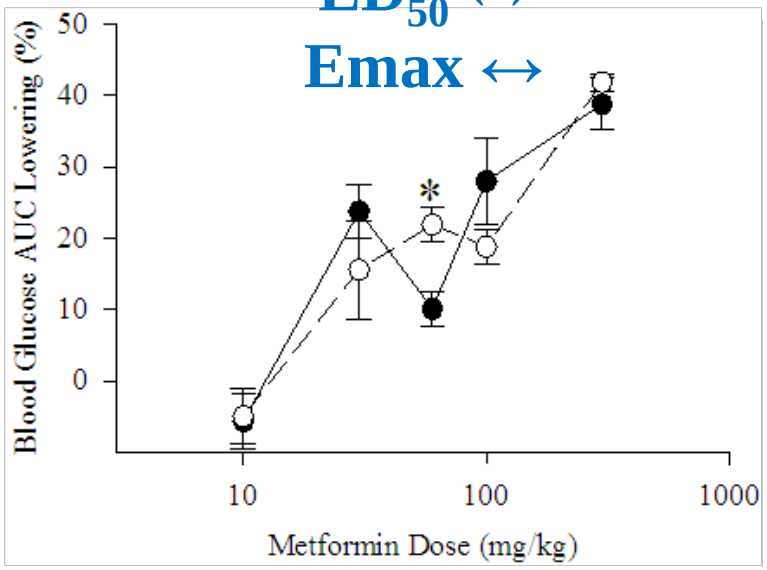
Metformin Pharmacodynamics



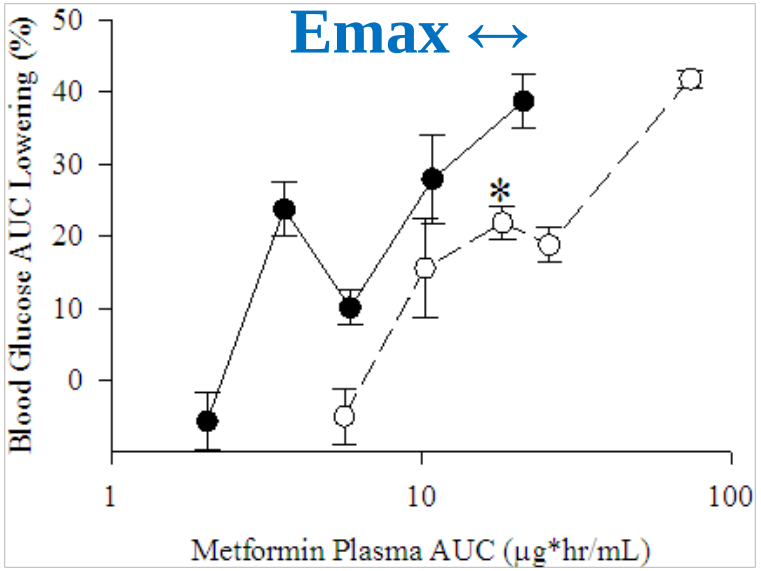
● wild type ▲ wild type + metformin
○ Oct1/2 KO Δ Oct1/2 KO + metformin

Complete hyperglycemic control

ED_{50} ↔
Emax ↔

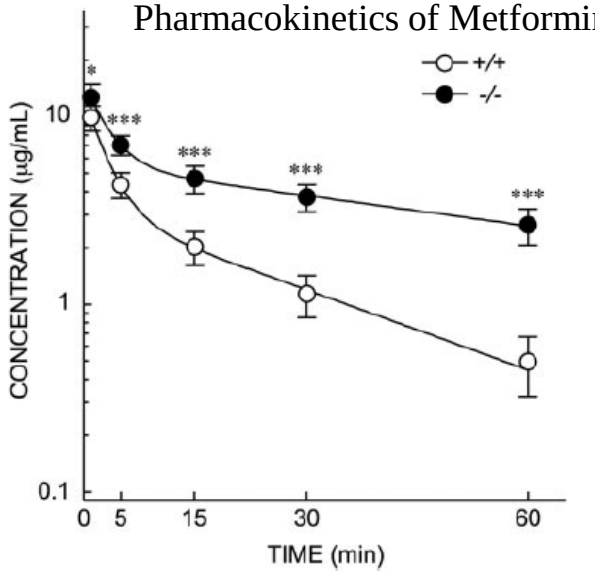


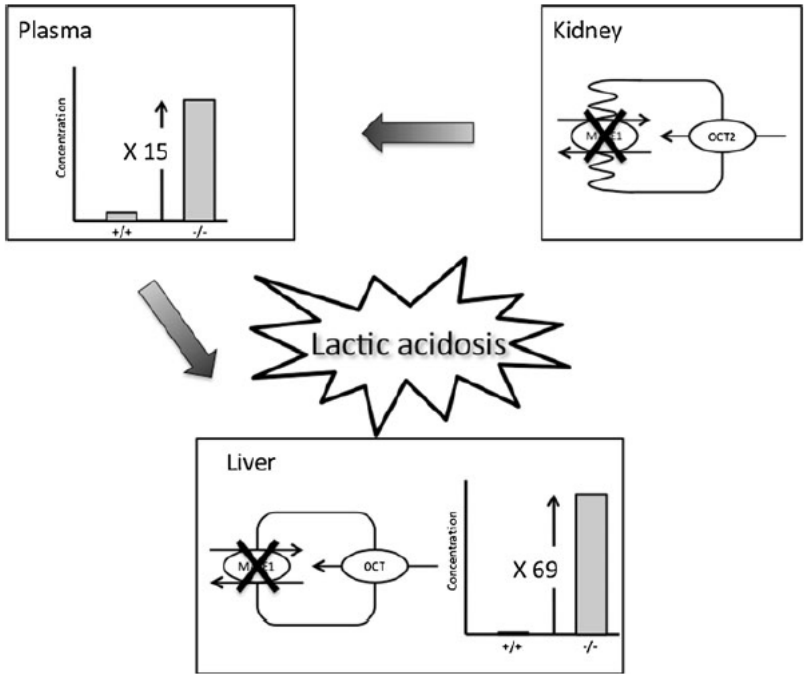
$EAUC_{50}$ ↑ 3X
Emax ↔

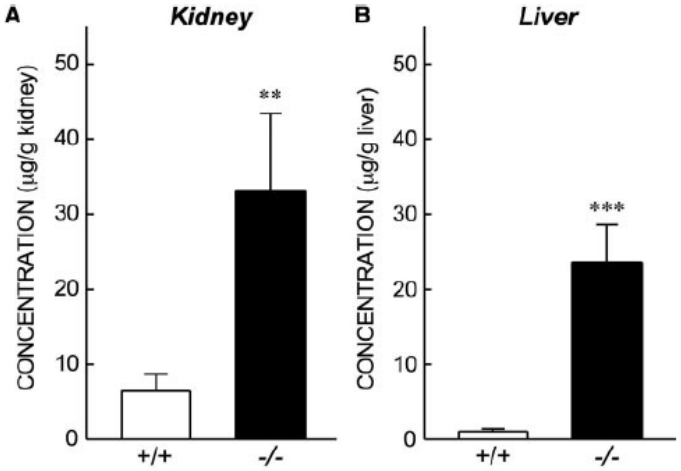


Reduced Renal Secretion and increased Hepatic and Renal conc. of Metformin in Mate1 Knockout Mice

Pharmacokinetics of Metformin after IV injection in WT and KO Mate1 Mice







Merck

Courtesy Dr. J Wang

Tsuda *et al., Mol Pharmacol* **75**:1280–1286, 2009.

Summary

- **Renal (and hepatic) transporter(s):**
  - ➢If the uptake transport is a concentrative transporter, it may be the rate-limiting step. Modulation of this transport (e.g. DDI, SNPs) may profoundly affect the systemic conc. of the drug. **But,** the impact on tissue conc. is likely to be much smaller because:
    - $dX/dt_{renal\ uptake} = CL_{uptake\ remainder}$ x Cp,u and Cp,u is ↑
    - If the drug is mostly cleared by renal/hepatic CL, it will eventually be eliminated by passage through the kidney/liver
  - ➢Inhibition of the efflux transporter (e.g. at apical membrane) can profoundly increase the renal conc. and therefore potential toxicity/efficacy of the drug

CAUTION: DDI

- Many transporters are allosteric and demonstrate multiple binding sites
- DDI may be substrate dependent
- Need to better characterize the in vivo relevance of allosterism/multiple binding sites