Drug transporters

2018

Transporters

- membrane proteins able to facilitate flux of molecules into and out of cells
- primary function is to transport nutrients (sugars, aminoacids, nucleotides, vitamines) inside or to efflux endogenous and exogenous toxines outside the cell
- drugs bearing similar parts to natural substrates can be carried too – problems with bioavailability, efficiacy and toxicity (substrate competition)

Transporters

Passive transporters (facilitated transporters): move molecules down their electrochemical gradient

Active transporters works against electrochemical gradients

Primary transporters – move molecules consumpting ATP

Secondary transporters – use energy of facilitated transport (e.g. of ions)

-co-transporters (in same way)

-exchangers (in opposite way)

Transporters

Most transporters are expressed om barrier cells:
- liver
- kidney
- intestine
- placenta
- brain

Different transporters on inner and outer part of cells

Transporters classification

cellular level:
influx tr.
efflux tr.
pharmacological level:
absorptive tr. (absorption into bloodstream)
secretory tr. (transport from bloodstream into urine, bile or gut lumen)

conventionally, transporters enhancing absorption into brain and fetus are *absorptive*

Substrate classification

Organic cation transporter (OCT)
Organic cation/carnitine transporter (OCTN)
Organic anion transporter (OAT)
Organic anion transporter polypeptides (OATP)
Peptide transporter (PEPT)
Monocarboxylate transporter (MCT, SMCT)
Nucleoside transporter (CNT, ENT)
Bile acid transporter (NTCP, ASBT, BSEP, OST)
Multidrug resistance protein (MDR)
Multidrug resistance associated protein (MRP)
Breast cancer resistance protein (BCRP)

Mechanistical classification

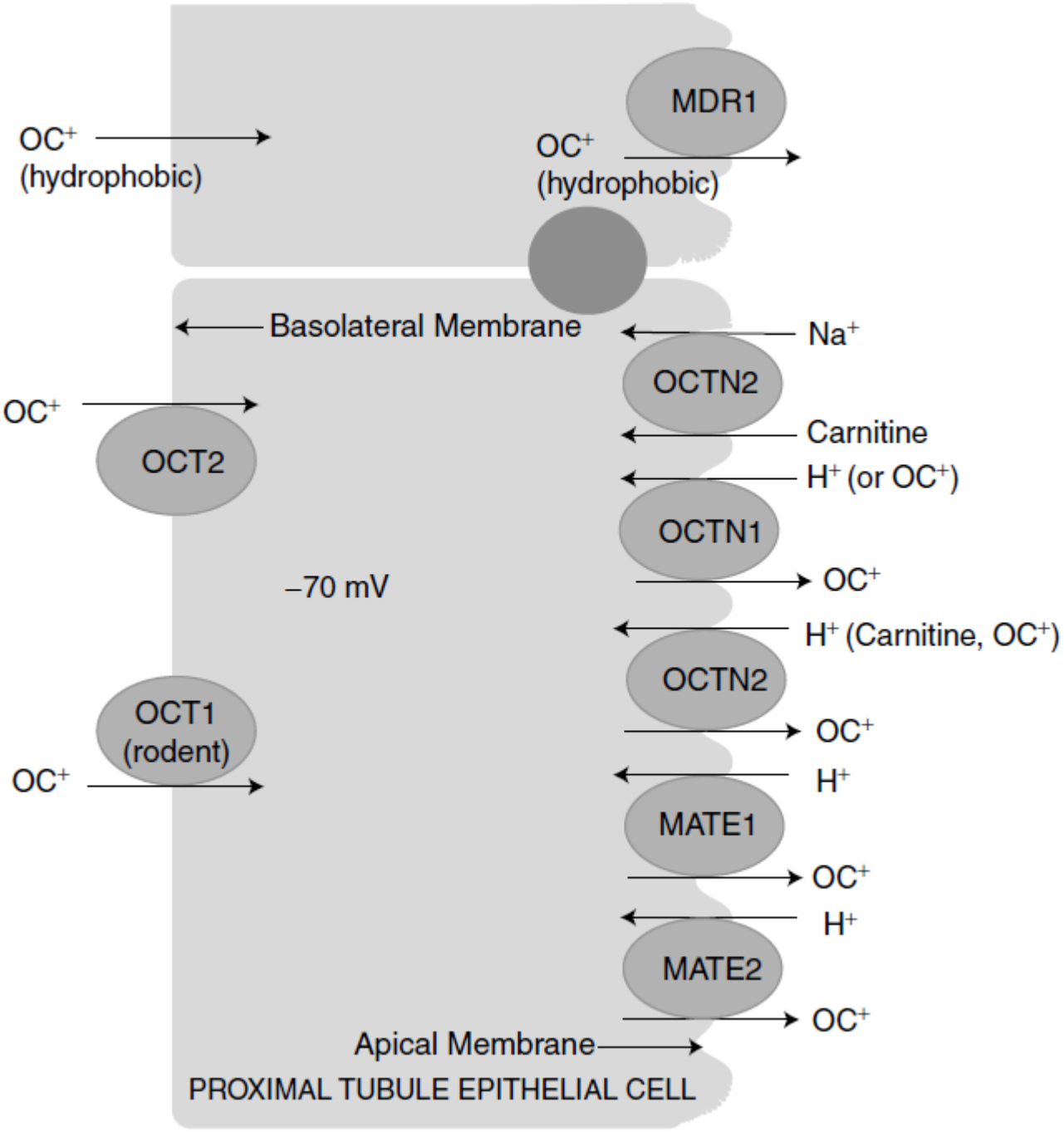
presence of ATP consumption

ABC (ATP-binding casette) – e.g. MDR, MRP, BCRP)

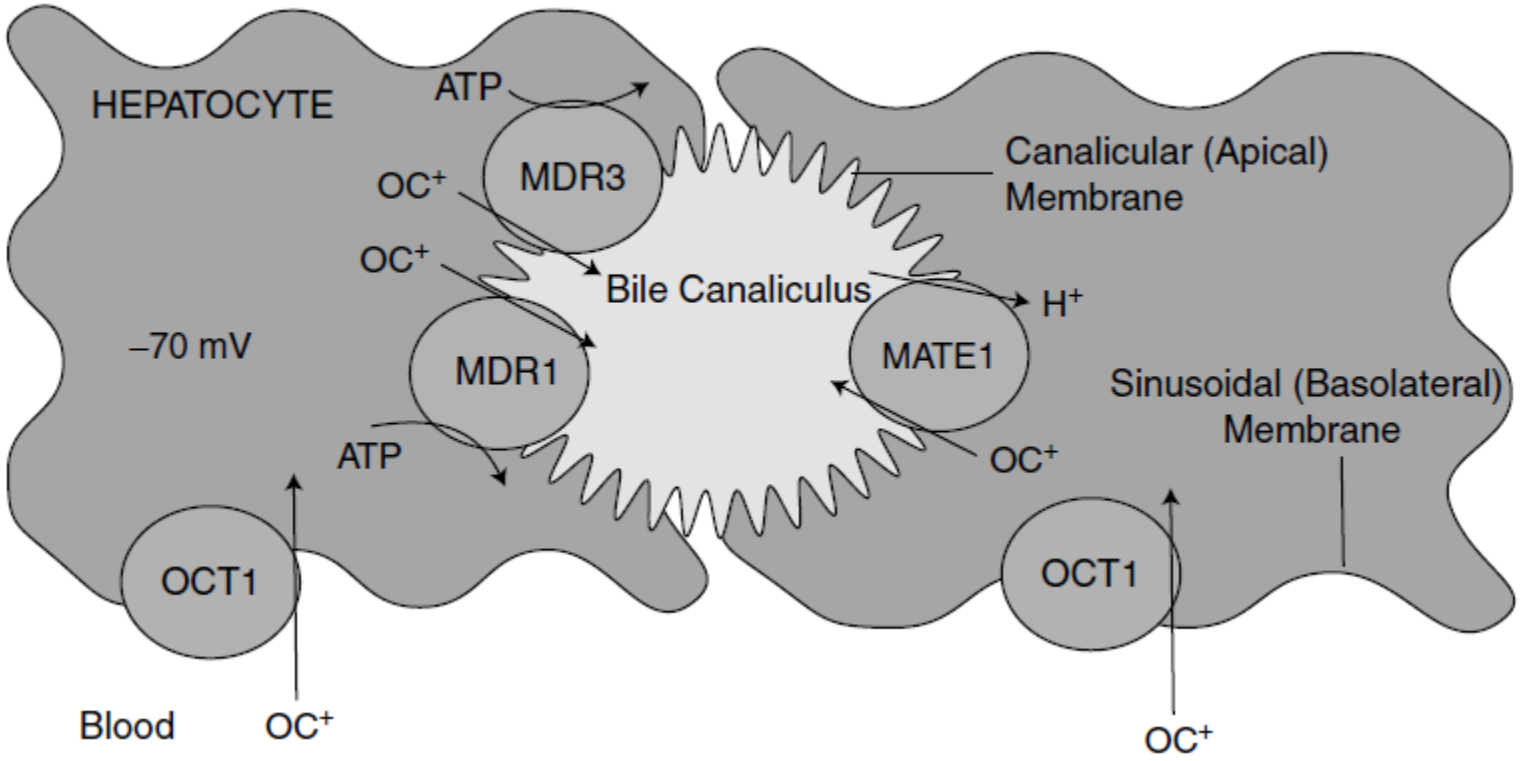
SLC (Solute carrier) – most of transporters

Organic cation transporters (OCT)

OCT 1, OCT 2, OCT 3
similar transmembrane topology
shared group of substrates
common transport mechanism


MDR1
OC+ (hydrophobic)
OC+ (hydrophobic)
Basolateral Membrane
Na+
OCTN2
OC+
OCT2
Carnitine
H+ (or OC+)
OCTN1
–70 mV
OC+
H+ (Carnitine, OC+)
OCTN2
OCT1 (rodent)
OC+
OC+
H+
MATE1
OC+
H+
MATE2
OC+
Apical Membrane
PROXIMAL TUBULE EPITHELIAL CELL

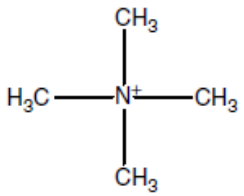
Organic cation transporter (OCT)



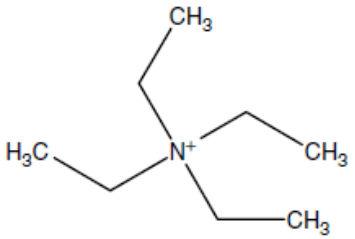
Organic cation transporter (OCT)

common substrates
generally low molecular weight
relativelly hydrophilic
organic cation
(positive charge not necessary:
anions – prostaglandines
neutral – beta estradiol)

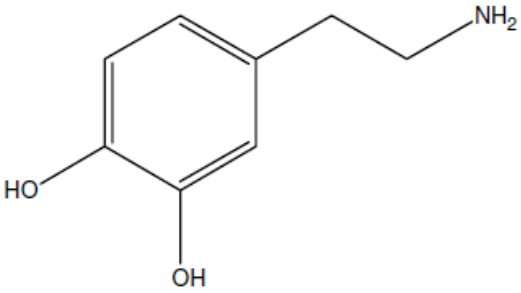
Organic cation transporter (OCT)



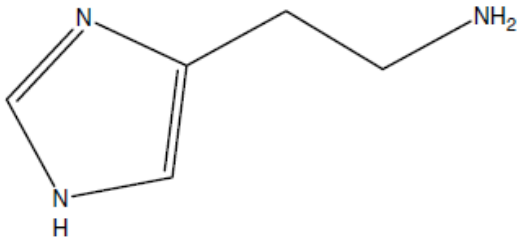
Tetramethylammonium (TMA)



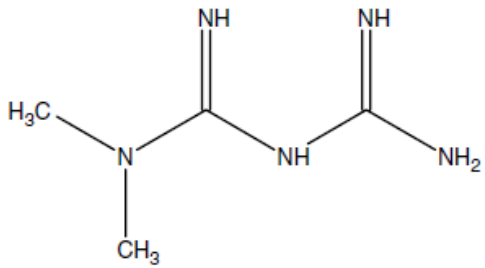
Tetraethylammonium (TEA)



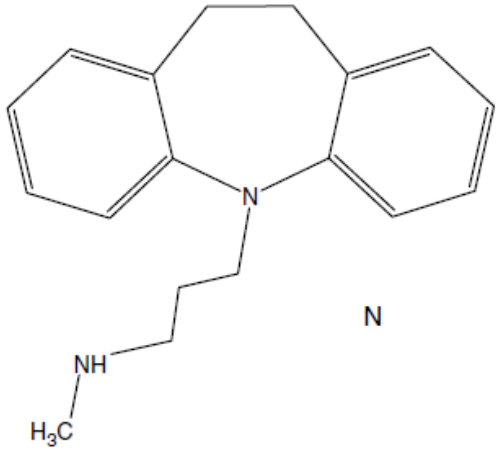
Dopamine



Histamine



Metformin



Desipramine

Organic cation transporter (OCT)

TABLE 2.2. Tissue Distribution of Human OCT Isoforms

	OCT1	OCT2	OCT3
Liver	+++	−	+
Kidney	−	+++	+
Lung	+	−	+
Trachea	−	−	−
Heart	+	−	++
Skeletal Muscle	++	−	++
Placenta	+	−	++
Pancreas	−	−	−
Brain	−	−	+
Spinal cord	−	−	+
Adrenal gland	+	−	−
Testis	−	−	−
Ovary	+	−	+
Fetal liver	+	−	−
Fetal lung	+	−	−
Fetal brain	+	−	−

Organic cation transporter (OCT)

Compound	OCT1		OCT2		OCT3	
	Inhibitor	Substrate	Inhibitor	Substrate	Inhibitor	Substrate
Acebutolol	+	N.D.	N.D.	N.D.	N.D.	N.D.
Acyclovir	+	+	N.D.	N.D.	N.D.	N.D.
Agmatine	+	+	+	+	+	+
Amantadine	+	N.D.	+	+	N.D.	N.D.
Aquinavir	+	N.D.	N.D.	N.D.	N.D.	N.D.
Choline	+	N.D.	+	+	N.D.	−
Cimetidine	+	N.D.	+	+	+	+
Clonidine	+	−	N.D.	N.D.	+	−
Cocaine	N.D.	N.D.	+	N.D.	N.D.	N.D.
Corticosterone	+	N.D.	+	N.D.	+	N.D.
Creatinine	+	N.D.	N.D.	N.D.	N.D.	−
Cyanine-863	N.D.	N.D.	+	N.D.	N.D.	N.D.
Debrisoquine	N.D.	N.D.	+	+	N.D.	N.D.
Decynium-22	+	N.D.	+	N.D.	+	N.D.
Desipramine	+	N.D.	+	N.D.	+	N.D.
Disopyramide	+	N.D.	N.D.	N.D.	N.D.	N.D.
Disprocynium-24	N.D.	N.D.	N.D.	N.D.	+	N.D.
Dopamine	+	N.D.	+	+	+	+
Epinephrine	N.D.	N.D.	N.D.	N.D.	+	+
β-Estradiol	+	N.D.	+	N.D.	+	N.D.
Famotidine	+	+	+	−	+	−
Ganciclovir	+	+	N.D.	N.D.	N.D.	N.D.
Guanidine	N.D.	N.D.	N.D.	N.D.	+	−
Histamine	+	−	+	+	+	+
Indinavir	+	N.D.	N.D.	N.D.	N.D.	N.D.
Memantine	N.D.	N.D.	+	+	N.D.	N.D.
Mepiperphenidol	N.D.	N.D.	+	N.D.	N.D.	N.D.

Organic cation transporter (OCT)

Compound	OCT1		OCT2		OCT3	
	Inhibitor	Substrate	Inhibitor	Substrate	Inhibitor	Substra
Metformin	+	+	+	+	N.D.	N.D.
O-Methylisoprenaline	+	N.D.	+	N.D.	+	N.D.
Midazolam	+	N.D.	N.D.	N.D.	N.D.	N.D.
MPP^+	+	+	+	+	+	+
Nelfinavir	+	N.D.	N.D.	N.D.	N.D.	N.D.
NMN	+	+	+	+	+	N.D.
Norepinephrine	N.D.	N.D.	+	+	+	+
Phenformin	+	N.D.	+	N.D.	N.D.	N.D.
Phenoxybenzamine	+	N.D.	+	N.D.	+	N.D.
Prazosin	+	N.D.	+	N.D.	+	N.D.
Procainamide	+	N.D.	+	N.D.	+	N.D.
Progesterone	+	N.D.	+	N.D.	+	N.D.
Quinidine	+	N.D.	+	N.D.	N.D.	N.D.
Quinine	+	N.D.	+	+	N.D.	N.D.
Ranitidine	+	+	+	+	+	−
Ritonavir	+	N.D.	N.D.	N.D.	N.D.	N.D.
Saquinavir	+	N.D.	N.D.	N.D.	N.D.	N.D.
Serotonin	N.D.	N.D.	+	+	+	+
Tetrabutylammonium	+	+	+	N.D.	N.D.	N.D.
Tetraethylammonium	+	+	+	+	+	+
Tetraheptylammonium	+	N.D.	N.D.	N.D.	N.D.	N.D.
Tetramethylammonium	+	+	+	N.D.	N.D.	N.D.
Tetrapropylammonium	+	+	+	N.D.	N.D.	N.D.
Tyramine	N.D.	N.D.	N.D.	N.D.	+	+
Vecuronium	+	N.D.	N.D.	N.D.	N.D.	N.D.
Verapamil	+	N.D.	+	N.D.	N.D.	N.D.

Organic cation/carnitine transporters (OCTN)

Carnitine

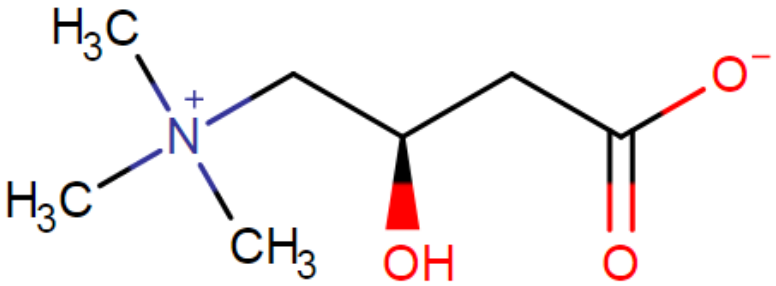
zwitterion

essencial cofactor in the lipid metabolism

involvement in beta-oxidation

absorbed from diet by OCTN

reabsorbed in distal tubulus by OCTN



L-Carnitine

Organic cation/carnitine transporters (OCTN)

OCTN 1
H^+ antiporter

OCTN 2
Na^+ cotransporter or cation uniporter

substrates:
quinidine, verapamil, small compounds with quarternary N
s. are competetive inhibitors and causes secondary carnitine deficiency

Organic anion transporters (OAT)

- organic acids secretory system – excretion of acidic metabolites into urine
- utilizes electrochemical gradient of substrate itself or another solute
- mechanism of action:

organic anion – dicarboxylate exchange

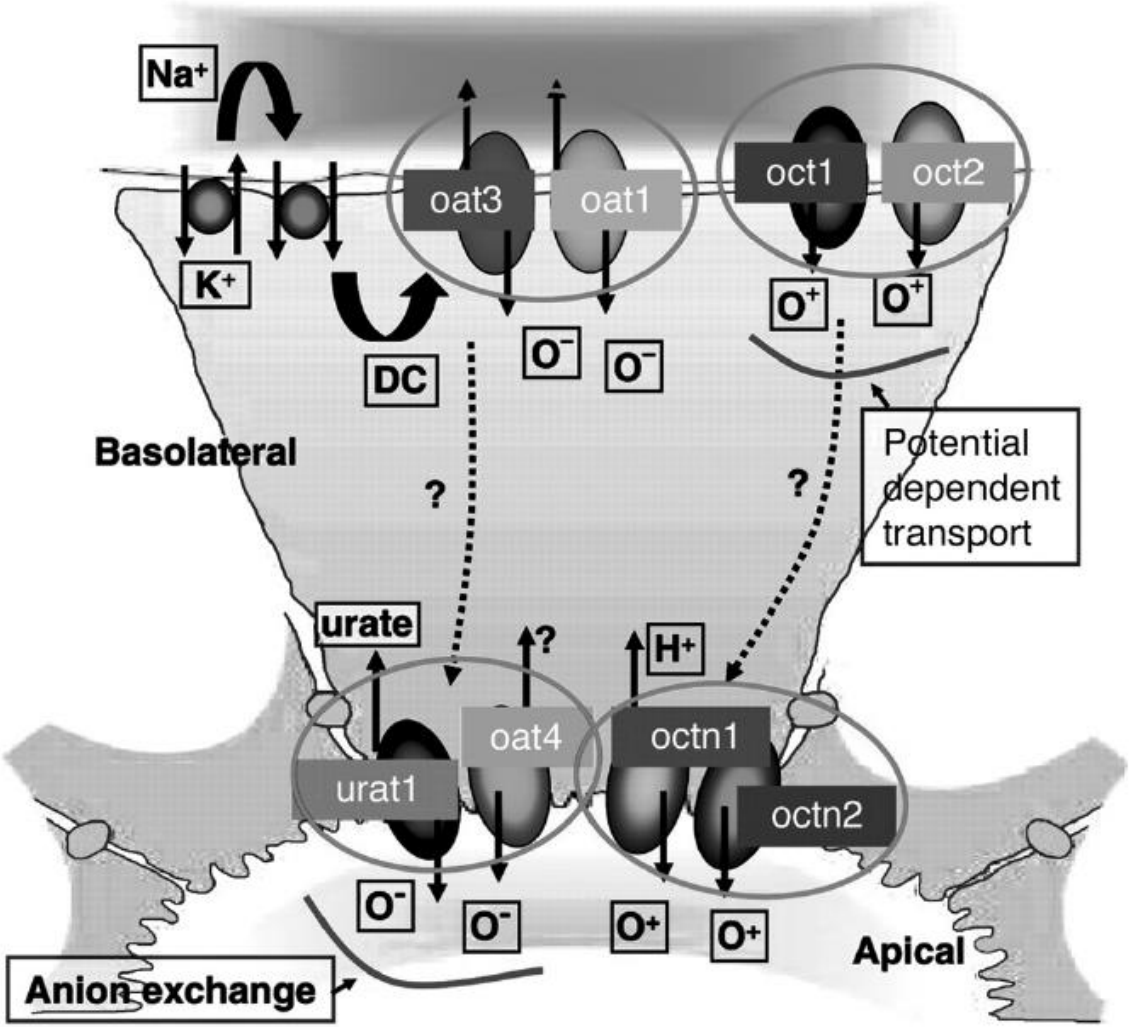
organic anion – urate exchange

Organic anion transporters (OAT)

OAT is mainly expressed in kidney
multispecific transporters binds very vast array of substrates
specifity based on general physicochemical properties:
charge
hydrophobicity
hydrogen bonding ability

Organic anion transporters (OAT)

Mechanism coupled with ion exchange:



Organic anion transporters (OAT)

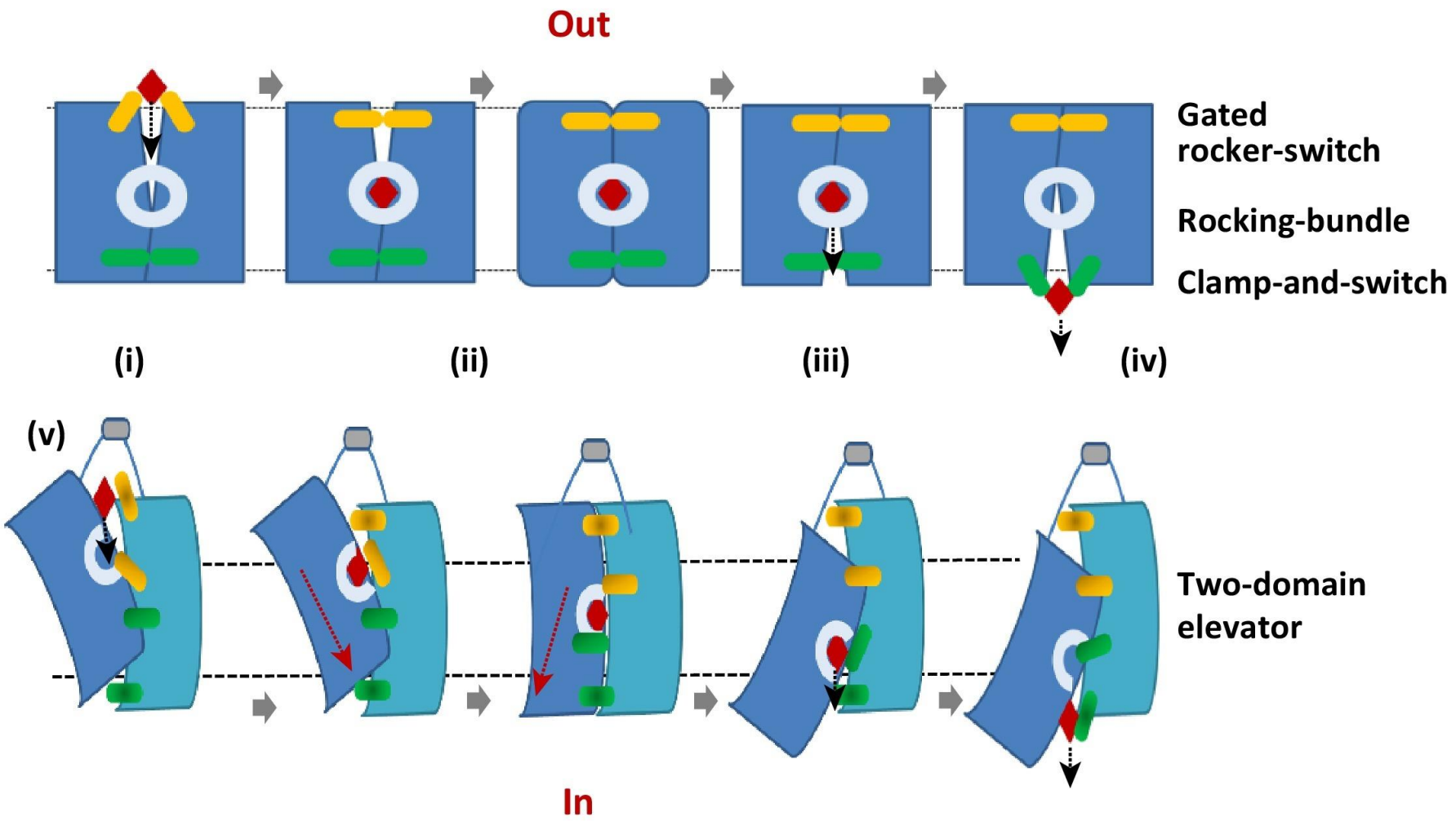
TABLE 4.2. Examples of Nephrotoxic and Neurotoxic Agents Demonstrated to Interact with OATs

- Nonsteroidal anti-inflammatory drugs
  - Acetaminophen
  - Diclofenac
  - Ibuprofen
  - Indomethacin
  - Ketoprofen
  - Naproxen
  - Phenacetin
  - Piroxicam
  - Salicylate
- Antibiotics
  - Cephalosporins
  - Penems
  - Penicillins
- Uremic toxins
  - Hippuric acid
  - Indoleacetic acid
  - Indoxyl sulfate
- Chemotherapeutics
  - Methotrexate
- Heavy Metals
  - Cadmium
  - Mercury
- Chlorinated phenoxyacetates
  - 2,4-Dichlorophenoxyacetic acid
- Chlorinated haloalkenes
  - 1,2-Dichlorovinyl-L-cysteines
- Antivirals
  - Acyclovir
  - Adefovir
  - Azidothymidine
  - Cidofovir
  - Ganciclovir
- Mycotoxins
  - Ochratoxin A
- Neurotransmitter metabolites
  - 3,4-Dihydroxymandelic acid
  - 3,4-Dihydroxyphenylacetic acid (DOPAC)
- Miscellaneous
  - Homovanillic acid (HVA)
  - Hydroxyindoleacetic acid (5-HIAA)

Organic anion transporting polypeptides (OATP)

Mechanisms are diverse
all posesses rocker-switch type of mechanism, exchanging different co-substrates

Substrates are relatively large (from benzylpenicilin 334 to cholecystokinin octapeptide 1143)
In general, substrates are steroid or cyclic peptide compounds, often negativelly charged



Trends in Genetics

Organic anion transporting polypeptides (OATP)

Endogenous substrates are:
thyroid hormones
bile acids
steroid hormones
bilirubin
prostaglandines
Whole drug families are substrates:
Statins
Sartans
ACE inhibitors (Prils)
Cardiac glycosides

Organic anion transporting polypeptides (OATP)

Transporter	Substrates	Nonsubstrates	Inhibitors
OATP1A2	Fexofenadine[124], BSP[15,27,125], T_3[27], T_4[27], E_2G[27], E_1S[27,125], GCA[15], TCA[15,27], DHEAS[27], deltophin[27], DPDPE[27], BQ-123[27], oubain[27,125], PGE_2[27], *N*-methylquinine[27], rosuvastatin[39], pitavastatin[126], MTX[127], microcystin-LR[128]	Digoxin[27], LTC_4[27]	Grapefruit juice[94], orange juice[94], apple juice[94]
OATP1B1	E_1S[27], benzylpenicillin, PGE_2[27], E_2G[27], BSP[27], T_3[27], T_4[27], E_2G[27], E_1S[27], GCA, TCA[27], DHEAS[27], DPDPE[27], BQ-123[27], cerivastatin[73,129], atorvastatin[73,130], rosuvastatin[39], pitavastatin[126], caspofungin[131], phalloidin[132,133], troglitazone-sulfate[134], rifampin[66], bilirubin[96,97], bilirubin-glucuronides[96], arsenic[135], atrasentan[81], valsartan[136], olmesartan[137], enalapril[138], MTX[38], temocaprilat[75], DADLE[64], microcystin-LR[128], SN-38[74]	Digoxin[27], oubain[27], *N*-methylquinine[27], deltorphin[27]	CyA[66,67], FK-506[67,132], rapamycin[132], glycirrizic acid[139], glibenclamide[67], ketoconazole[140], gemfibrozil[129], gemfibrozil-glucuronide[129], ciprofibrate[141], bezafibrate[67,141], clarithromycin[67], erythromycin[67], indinavir[66], nelfinavir[66], ritonavir[66], saquinavir[66], probenacid[67], rifamycin SV[142], digoxin[67], verapamil[67], warfarin[67], MK-571[141], biochanin A[143], Genistein[143], epigallocatechin-3-gallate[143], hyperforin[66]
OATP1B3	Fexofenadine[144], BSP[27], T3[27], T4[27], E_2G[27], E_1S[27], GCA[27], TCA[27], TUDC[145], GUDC[145], DHEAS[27], deltophin[27], DPDPE[27], BQ-123[27], oubain[27], PGE_2, digoxin[27], rosuvastatin[39], valsartan[136], pitavastatin[126], fluo-3[146], docetaxel[140], paclitaxel[140], CCK-8[147], phalloidin[132,133], rifampin[66,146], MTX, bilirubin[97], repaglinide, telmisartan[65], olmesartan[137], enalapril[138], temocaprilat[75], microcystin-LR[128]	*N*-Methylquinine[27], PGE_2[27], caspofungin[131], folate	Ketoconazole[140], glycirrizic acid[139], rifamycin SV[142]
OATP1C1	BSP[9], T_3[9], T_4[9], E_2G[9], E_1S[9]	GCA[9], TCA[9], DHEAS[9], deltophin[9], DPDPE[9], BQ-123[9], digoxin[9], oubain[9], LTC_4[9], PGE_2[9], *N*-Methylquinine[9], MTX[9], folate[9]	

Organic anion transporting polypeptides (OATP)

Transporter	Substrates	Nonsubstrates	Inhibitors
OATP2A1	PGE_2[118], PGE_1[118], $PGF_{2\alpha}$[118], PGD_2[118], TXB_2[118]	Iloprost[118]	Furosemide[118], TGBz T34[148]
OATP2B1	E_1S[116], benzylpenicillin[116], PGE_2[116], BSP[27], DHEAS[27], pravastatin[22], fluvastatin, rosuvastatin[39], glybenclamide[149], fexofenadine[17]	E_2G[116], GCA[27], TCA[27], oubain[27], digoxin[27], LTC_4[27], PGE_2[27], T_3[27], T_4[27], deltophin[27], DPDPE[27], BQ-123[27]	Benzoate[22], nicotinate[22], phthalate[22], PAH[150], indomethacin[150], TCA[150], cimetidine[150], salicylate[150], valproate[150], rifamycin SV[142], grapefruit juice[149], orange juice[149], naringin[149], naringenin[149], quercetin[149], bergamottin[149], dihydroxybergamottin[149], tangeritin[149], nobelitin[149], bilberry[151], echinacea[151], green tea[151], banaba[151], grape seed[151], ginkgo[151], soybean[151], mulberry[151], black cohosh[151], and Siberian ginseng[151]
OATP3A1	PGE_1[121], PGE_2[116,121], $PGF_{2\alpha}$[121], benzylpenicillin[116], E_1S[116]	PGD_2[121], TBX[121], iloprost[121], MTX[121], TCA[116], E_2G[116]	PGD_2[121], PAH[121]
OATP4A1	T_3[152], T_4[152], TCA[152], E_2G[116], benzylpenicillin[116], PGE_2[116], E_1S[116]	PAH[152], PGE_1[152], PGD_2[152], $PGF2\alpha$[152]	BSP[152]
OATP4C1	Digoxin[147], oubain[147], T_3[147], T_4[147], MTX[147], cAMP[147]	TCA[147], E_2G[147], PGE_2[147], PAH[147], pravastatin[147], temocaprilat[147], ASA[147], salicylate[147], urate[147], acyclovir[147], ochratoxin[147], benzylpenicillin[147], cGMP[147], TEA[147]	Digitoxin[147], Digitoxigenin[147]
OATP5A1	?	?	?
OATP6A1	rGST1 (T_3, T_4, DHEAS, TCA)[106]		rGST1 (β-estradiol, testosterone)[106]

Organic anion transporting polypeptides (OATP)

pharmacogenetics is very important

TABLE 5.5. SLCO1B1 Genotype and Pharmacokinetics

Drug	*SLCO1B1* Genotype	Ethnicity	PK Effect in Comparison with Reference Genotype[a]	Ref.
Pravastatin	*15/*15	Asian	AUC↑ 187%	69
	*1a/*5	Caucasian	AUC↑ 143%	70
	*1b/*1b	Caucasian	AUC↓ 40%	70
	*17/*17	Caucasian	AUC↑ 130%	71
	*1b/*1b	Asian	AUC↓ 35%	75
	*5, *15, *17 variant haplotype	Caucasian	AUC↑ 110%	89
	*15/*15	Caucasian, African American	AUC ↑ 92 %	unpublished
Rosuvastatin	521CC	Caucasian	AUC↑ 217%	77
Pitavastatin		Asian	AUC↑ %	76
Repaglinide	521CC	Caucasian	AUC↑ 188%	78
Nateglinide	521CC	Asian	AUC↑ 108%	79
Atrasentan	Low-activity genotype	Caucasian, non-caucasian	AUC↑ 73%	81
Valsartan	*1b/*1b	Asian	AUC↓ 27%	75
Fexofenadine	521CC	Caucasian	AUC↑ 127%	80
Irinotecan	*15 carriers	Asian	AUC↑ 182%	82
Ezetimibe-glucuronide	*15 carriers	Caucasian	AUC↑ 305%	83

Organic anion transporting polypeptides (OATP)

drug interactions very common

facilitating of fexofenidate excretion

suppresion of statins first-pass effect

TABLE 5.6. Drug Interactions Implicating a Role for OATPs in the Mechanism

OATP Implicated	Drug Affected	Interacting Substance	PK Impact on Affected Drug	Ref.
OATP1A2	Fexofenadine	Grapefruit juice	AUC↓ 63%	94
	Fexofenadine	Orange juice	AUC↓ 70%	94
	Talinolol	Grapefruit juice	AUC↓ 44%	156
OATP1B1	Pravastatin	Orange juice	AUC↑ 152%	157
	Pravastatin	Cyclosporine A	AUC↑	Pravachol product monograph
	Pravastatin	Gemfibrozil	AUC↑ 202%	158
	Rosuvastatin	Cyclosporine A	AUC↑ 710%	95
	Rosuvastatin	Gemfibrozil	AUC↑ 188%	159
	Cerivastatin	Cyclosporine A	AUC↑ 3 to 5-fold	160
	Cerivastatin	Gemfibrozil	AUC↑ 559%	161

Mammalian oligopeptide transporters (PEPT)

Aminoacids are mainly absorbed from the intestine in the form of di- and tri-peptides.

These are cleavaged by cytosolic peptidases and free aminoacids are transported into bloodstream (by other transporters).

4 isoforms:

PEPT1, PEPT2

PHT1, PHT2 (peptide-histidine transporters)

Mammalian oligopeptide transporters (PEPT)

Mechanism of action:

utilizating H^+ membrane gradient

- neutral and anionic peptides requires H^+ cotransport
- cationic peptides do not need H^+

Mammalian oligopeptide transporters (PEPT)

Molecular requirements for substrate molecules:

PEPT1: L-aminoacid

acid or hydrophobic moiety at C terminus

weakly basic group in α position of N terminus

ketomethylene / peptidic bond

PEPT2: as PEPT1

aminocarbonyl group in α or β position

PHT: not elucidaded yet

Endogenous substrates:

all aminoacid di- and tri-peptides

Mammalian oligopeptide transporters (PEPT)

Exogenous substrates:

β-lactam antibiotics, ACE inhibitors,

L-DOPA prodrugs, valacyclovir, valgancyclovir,

aminoacid prodrugs of bisphosphonates,

peptide analogs (e.g. linezolid)

Activity and expression of PEPTs are dependent on diet volume and composition

insulin / leptin regulation involved

Monocarboxylate transporters (MCT, SMCT)

MCT1-14 isoforms

MCT1-4 transports metabolic monocarboxylates (e.g. lactate, pyruvate, butyrate, acetoacetate)

other MCTs involved in aminoacids transport

MCT8 transports T3 and T4 thyroid hormones

Mechanism of action: H^+ cotransporters

Sodium-dependent monocarboxylate transporters (SMCT)

Mechanism of action: Na^+ cotransporters

Exogenous substrates: acidic β-lactams, statins, valproic acid crossing blood-brain barrier

Nucleoside transporters (CNT, ENT)

Nucleosides are hydrophilic and has low membrane permeability

two classes of transporters:

Concentrative nucleoside transporters (CNT)

Equilibrative nucleoside transporters (ENT)

Many therapeutic nucleoside analogues rely on these transporters to enter or exit cells

Concentrative nucleoside transporters (CNT)
mechanism of action: Na^+ cotransporter
3 isoforms:
CNT1, CNT2, CNT3
CNT1
typically found in epitelium of intestine, kidney and liver
mainly pyrimidine nucleosides, limited transport of adenosine
anticancer gemcitabine, cytarabine, capecitabine
antivirotic zidovudine, lamivudine, zalcitabine
cotransport nucleoside : Na^+ (1 : 1)

Concentrative nucleoside transporters (CNT)

CNT2

widely distributed in organism

purine nucleosides, limited transport of uridine

ribavirin, 5-fluorouridine

cotransport nucleoside : Na^+ (1 : 1)

CNT3

widely distributed in organism

purine and pyrimidine nucleosides

many nucleoside analogs are substrates too

cotransport nucleoside : Na^+ (1 : 2)

Equilibrative nucleoside transporters (ENT)
mechanism of action:
concentration-dependent facilitated transport
ENT1
ubiquitous distribution in organism
both purine and pyrimidine nucleosides
gemcitabine, fludarabine, cytarabine, ribavirin
dipyridamol is potent ENT1 inhibitor
ENT2
most abundant in muscle, but present in other tissues
lower afinity for guanosine and cytidine
transports also free nucleotide bases

Equilibrative nucleoside transporters (ENT)

ENT3

broadly selective for all nucleosides
and their analogues
located on lysozomal membrane

ENT4

in fact OCT, transports selectively adenosin

Bile acid transporters

primary bile acids: cholic acid
chenodeoxycholic acid

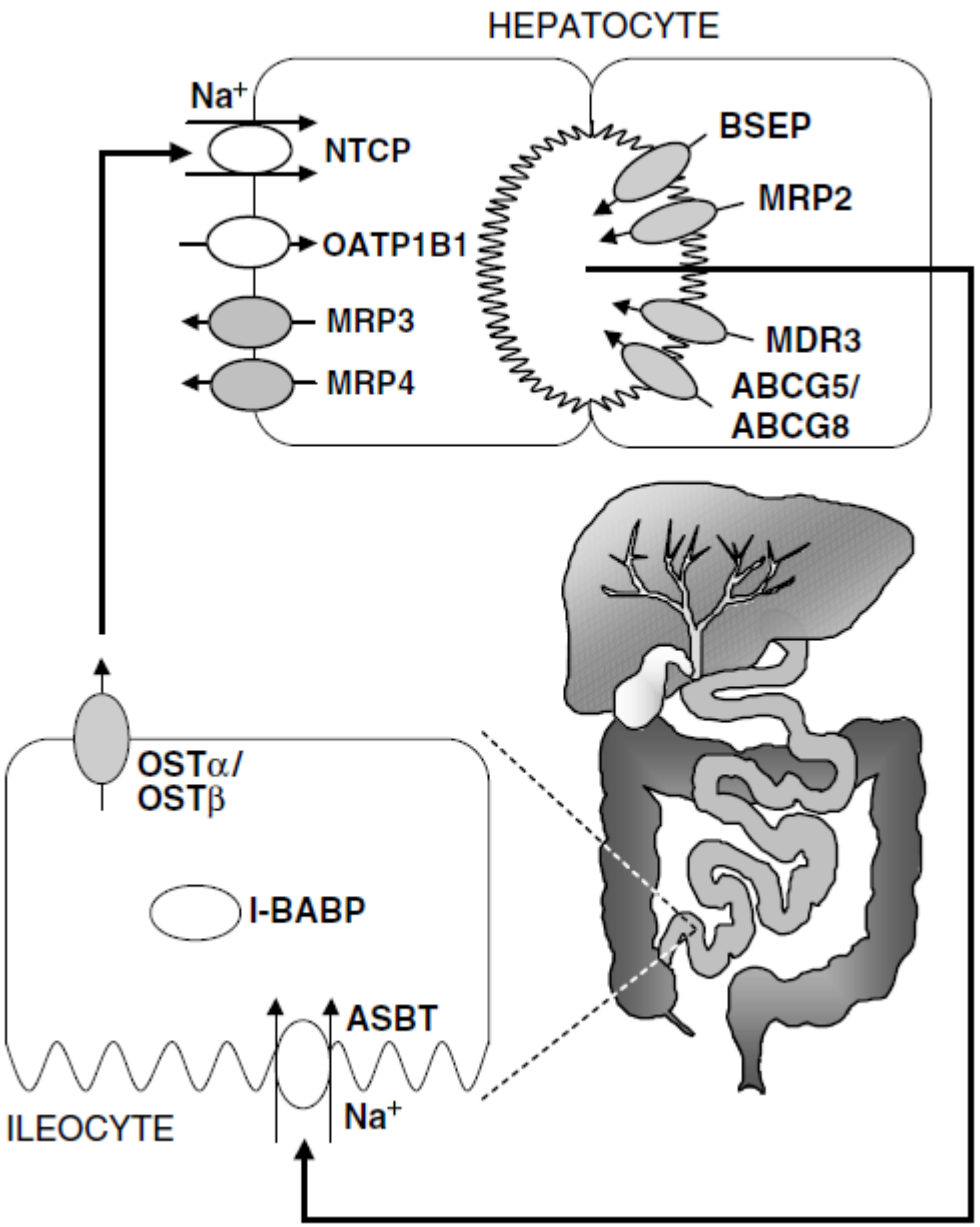
secondary bile acids: deoxycholic acid
lithocholic acid

produced from primary acids by intestinal microflora

amphipatic detergents crucial for lipid absorption

hepatobiliary circulation – one molecule of bile acid is secreted and reabsorbed approximately 12X a day

Bile acid transporters



Bile acid transporters

Bile salt export pump (BSEP)

secretes monovalent bile acid salts into bile

ATP binding casette transporter

Multidrug resistance protein 2 (MDR2)

secretes divalent and glucuronated bile acids, glucuronated and sulfatated drug metabolites, chemotherapeutics and antibiotics

ATP binding casette transporter

Multidrug resistance protein 3 (MDR3)

secretes phospholipids

Bile acid transporters

Apical sodium-dependent bile acid transporter (ASBT)

absorbs bile acid from ileum to enterocyte

Na^+ cotransporter

Organic solute transporter (OSTα/OSTβ)

transports bile acids from enterocyte to blood stream

Sodium-taurocholate cotransporting polypeptide (NTCP)

transports bile acids into hepatocytes

Na^+ cotransporter

Organic anion transporters (OATPs)

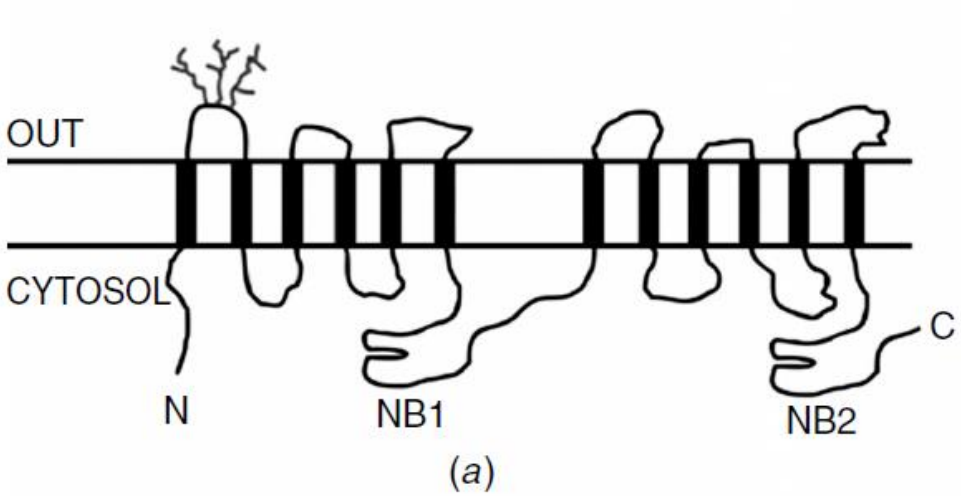
transports bile acids as well

Multidrug resistance protein (P-glycoprotein)
two main human isoforms: MDR1, MDR2
present in all tissues, predominantly in secretory organs
ATP binding casette transporters
systems are saturable
MDR1
transports broad spectrum of xenobiotics
substrates generally nonpolar, weakly amphipathic
MDR2
transports acetylcholin and other fosfolipids into bile

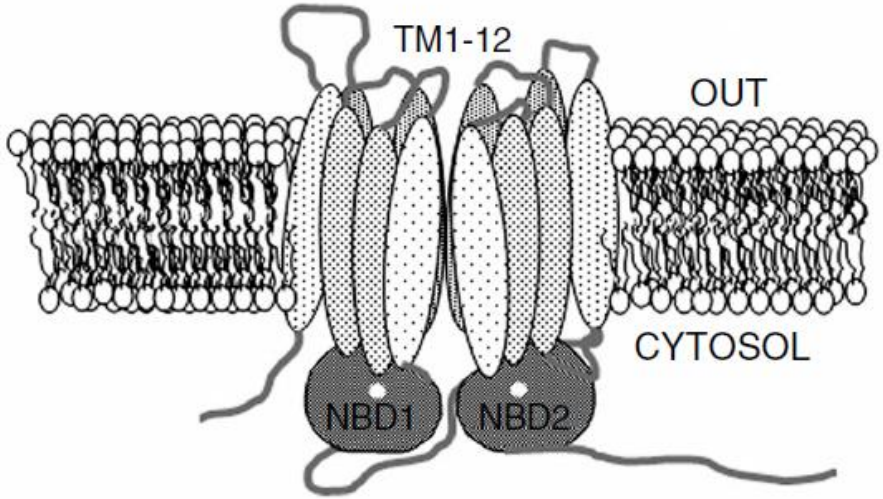
Multidrug resistance protein (P-glycoprotein)

Substrates		Modulators
Vinca alkaloids	*Detergents*	*Ca^{2+} channel blockers*
vinblastine	Triton X-100	verapamil
vincristine	nonylphenol ethoxylate	nifedipine
Anthracyclines	*Fluorescent dyes*	azidopine
doxorubicin	rhodamine 123	dexniguldipine
daunorubicin	tetramethylrosamine	*Calmodulin antagonists*
Taxanes	Hoechst 33342	trifluoperazine
paclitaxel	LDS-751	chloropromazine
docetaxel	calcein acetoxymethyl ester	*trans*-flupenthixol
Epipodophyllotoxins	*Linear/cyclic peptides*	*Cyclic peptides*
etoposide	ALLN	cyclosporin A
teniposide	NAc-LLY-amide	PSC833
Steroids	leupeptin	*Steroids*
aldosterone	pepstatin A	progesterone
dexamethasone	*Ionophores*	tamoxifen
HIV protease inhibitors	gramicidin D	cortisol
indinavir	nonactin	*Miscellaneous*
saquinavir	beauvericin	GF120918
nelfinavir	*Cytotoxic agents*	LY335979
ritonavir	colchicine	XR9576
Analgesics	actinomycin D	OC144-093
morphine	mitoxantrone	disulfiram
Cardiac glycosides	*Miscellaneous*	quinidine
digoxin	loperamide	chloroquine
Antihelminthics	cimetidine	reserpine
ivermectin		amiodarone
		terfenadine

Multidrug resistance protein (P-glycoprotein)



(a)



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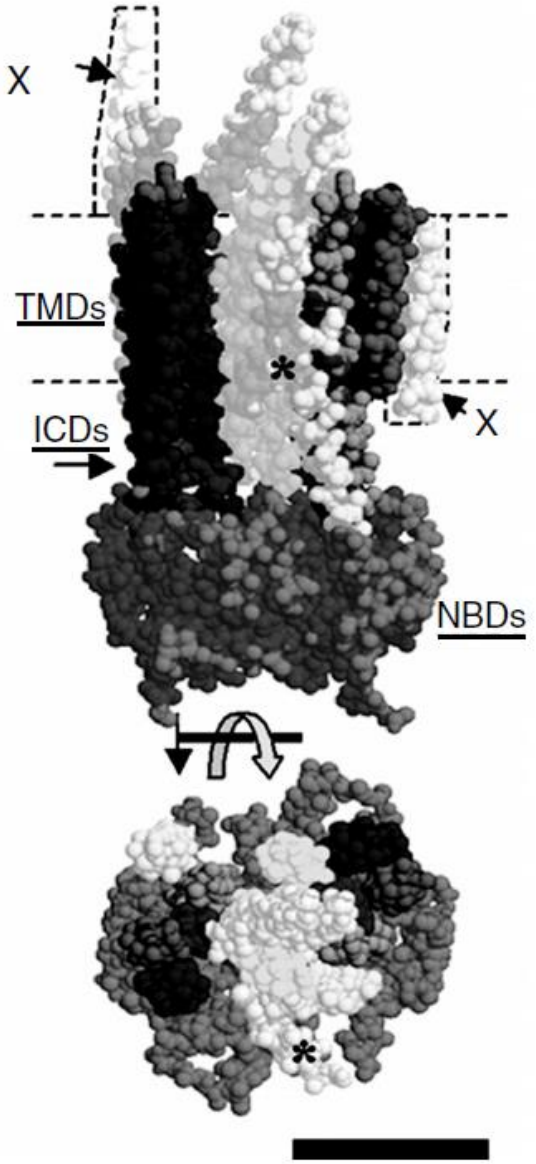

(c)

Multidrug resistance proteins (MRP)
12 isoforms
MRP1-9
cystic fibrosis transmembrane conductance regulator (**CFTR**)
sulfonylurea receptors (**SUR1, SUR2**)

- all ATP binding casette proteins
- effluxes many endogenous and xenobiotic lipophilic organic anions
- predominant localization in renal epithelia, hepatocytes and blood-tissue barriers

Multidrug resistance proteins (MRP)

MRP1

ubiquitous transporter

substrates:

glucuronates of leucotriens, estradiol, bilirubin, cholic acid, methotrexate

MRP2

main hepatocytar transporter

similar substrates as MRP1

MRP3

hepatocytar transporter

similar substrates as MRP1 and MRP2

Multidrug resistance proteins (MRP)

MRP4

ubiquitous transporter

substrates as MRP1, additionally prostanoids, urate, topotecan

MRP5

urogenital tract and vascular system epitelium

substrates: cAMP, cGMP, fluorouracil, methotrexate

MRP6

kidney, liver

low affinity, same substrates as MRP1

Multidrug resistance proteins (MRP)

MRP7, MRP9

little known

MRP8

predominant in periferal neurons

substrates similar to MRP1,

additionally cAMP and cGMP

Breast cancer resistance protein (BCRP)

ATP binding casette protein

located in GIT, genitals, placenta, liver

and blood-brain barrier

overexpressed in some carcinoma cells

substrates:

anticancers: mitoxantron, etoposide, topotecan, irinotecan, methotrexate

tyrosin kinase inhibitors: gefitinib, imatinib

photodynamic therapeutics: porfyrins, chlorins

steroids, antivirals, HMG-CoA reductase inhibitors, antibacterial quinolones, macrolides, nitrofurantoin