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Review Article

A REVIEW ON MECHANISM & TRANSPORT OF XENOBIOTICS

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Abstract:

Detoxication refers to the series of biochemical reactions occuring in the body. Transporter mediated absorption, secretion, and reabsorption of chemicals are increasingly recognized as important determinants in the biological activities of many xenobiotics. In recent years, the rapid progress in generating and characterizing mice with targeted deletion of transporters has greatly increased our knowledge of the functions of transporters in the pharmacokinetics of xenobiotics. We focus on functions of transporters learned from experiments on knock out mice as well as humans and rodents with natural mutations of these transporters. Efflux transporters in intestine, liver, kidney, brain, testes, and placenta can efflux xenobiotics out of cells and serve as barriers against the entrance of xenobiotics into cells, whereas many xenobiotics enter the biological system via uptake transporters. The functional importance of a given transporter in each tissue depends on its substrate specificity, expression level, and the presence/absence of other transporters with overlapping substrate preferences. Nevertheless, a transporter may affect a tissue independent of its local expression by altering systemic metabolism. Further studies on the gene regulation and function of transporters, as well as the interrelationship between transporters and phase I/II xenobiotic-metabolizing enzymes, will provide a complete framework for developing novel strategies to protect us from xenobiotic insults.

Key words: Mechanism, Phases, Transporter, Function & Xenobiotics,

Introduction

Man is continuosly exposed to several foreign compounds such as drugs, pollutants, foods additives, cosmetic, pesticides etc., certain un-wanted compounds are produced in the large intestine by the bacterial which enter the

circulation. These include indole from tryptophan, cadaverine from lysine, tyramine from tyrosine, phenol from phenylalanine etc. In the normal metabolism of thebody, certain waste compounds (eg., bilirubin) are formed. A vast majority of the foreign compounds or the unwanted substances produced in the body, are toxic and, therefore they should be quickly eliminated from the body.

The term detoxication or detoxification refers to the series of biochemical reactions occuring in the body to convert the foreign (often toxic) compounds to non-toxic, and more easily excretable forms[1].

Detoxification a misnomer?

Detoxification is rather misleading, since sometimes a detoxified product is more toxic than the original substances (eg. Procarcinogens to carcinogens). It appears that the body tries to get rid of a foreign substances by converting it into a more soluble (often polar), and easily excretable compounds and this may be sometimes associated with increased toxcity[2].

In recent years, the term detoxification is replaced by biotransformation or metabolism of xenobiotics (Greek: xenos- strange, foreign) or simply metabolism of foreign compounds.

Site of detoxification

The detoxification reactions are carried out mainly in the liver which is equipped with the enzyme machinery. Kidney and other organs may sometimes be involved. The products formed by detoxifications are mostly excreted by the kidneys, less frequently excreted via feces or expired air[3].

Mechanism of detoxification

The metabolism of xenobiotics may be divided into two phases which may occur together or separately

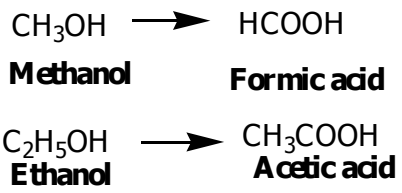
Phase I: The reactions of phase 1 are oxidation, reduction and hydrolysis

Phase 2: These are the conjugations reactions, involving compounds such as glucoronic acid, aminoacids (glycine), glutathion, sulfate, acetate and methyl group.

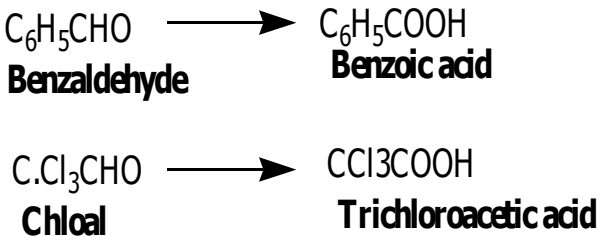
Generally detoxification of a compound involves phase 1 as wel as phase II reactions. For instance, oxidation follwed by conjuggation is the most frequent process in the metabolism of xenobiotics[4].

Oxidation: A large number if fireubgb substances are detixufued by oxidation. These unclude alcohols, aldehydes, amines,aromatic hydrocarbons and sulfur compounds. In general, aliphatic compound are mkire easily oxidized than aromatic ones.

Alcohols: Aliphatic and aromatic alcohols undergo to form the corresponding acids.

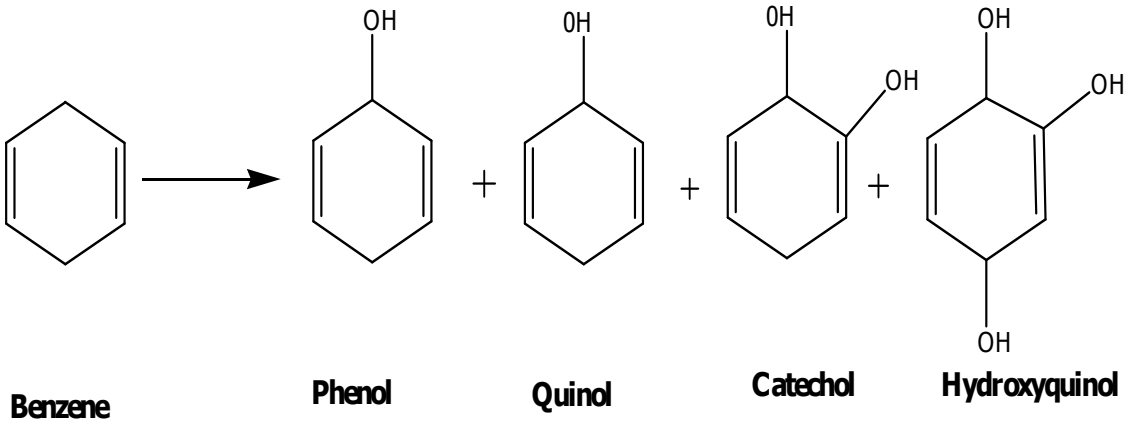


Aldehydes : Aldehydes are oxidized to produce the corresponding acids.



Amines amd thir devivatives : Alipahtic amines are converted tothe corresponding acids,liberating urea While aromatic amino acids are oxidized to phenols.

Aromatic hydrocarbons: Benzene may be oxidized to mono, di-and trihydroxy phenols as shown below



Sulfur compound : Organic sulfur is ixidized to sulfuric acid.

Drugs: Meprobamate is a tranquilizer. It is oxidized to hydroxymeprobamate and excreted in urine.

Role ofcytochrome p450: Most of the oxidation reaction of detoxification are catalysed by monooxygenase or cytochrome p450. This emzyme, also called **mixed function oxidase,**

Is associated with the microsomes. The usage p450 refers to the absorption peak (at 450 nm), exhibited by the enzyme when exposed to carbon monoxide.

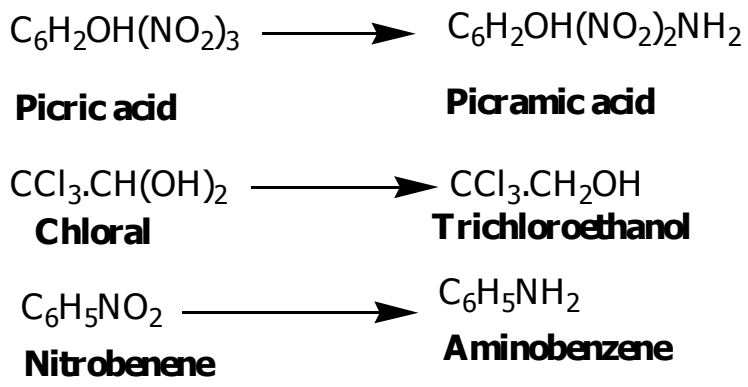
Most of the reactions of cytochrome p450 involve the addition of a hydroxyl group to aliphatic or aromatic compounds[5].

Salient features of cytochrome P450

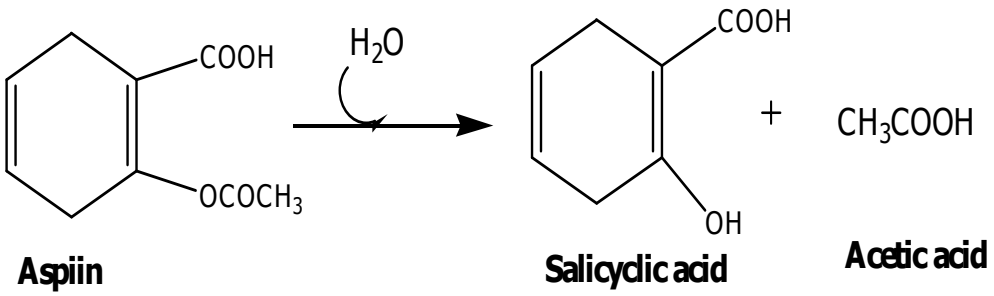
1. Multiple forms of cytochrome p450 are believed to exist, ranging from 20 to 200. At least 6 species havebeen isolated and worked in detail.
2. They are all hemoproteins, containing heme as the prosthetic group.
3. Cytochome p450 species are found in the highest concentration in the microsomes of liver. In the adrenal gland, they occur in mitochondria.
4. The mechanism of action of cytochrome P450 is complex and is dependent on NADPH.
5. The phospholipid-phosphatidylcholine is a constituent of cytochrome p450 system which is necessary for the action of this enzyme[6].
6. Cytochrome p450 is an **inducible enzyme.** Its synthesis is increased by the administration of drugs such as phenobarbitol.
7. A distinct species namely cytochrome p448(with absorption peakat 448 nm) has been studied. It is specific for the metabolism of polycylic aromatic hydrocarbons, hence it is also known as aromatic hydrocarbons hydroxylase.

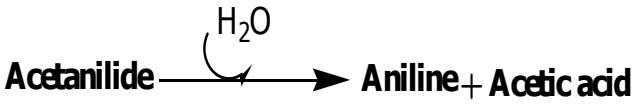
Reduction

A few examples of detoxification by reduction are given.



Hydrolysis: The hydrolysis of the bonds such as ester, glycoside and amide is important in the metabolismof xenobiotics. Several compounds undergo hydrolysis during the course of their detocification.These include aspirin,acetanilide, dilisopropylflurrophosphate, atropine and procaine[7].





Conjugation

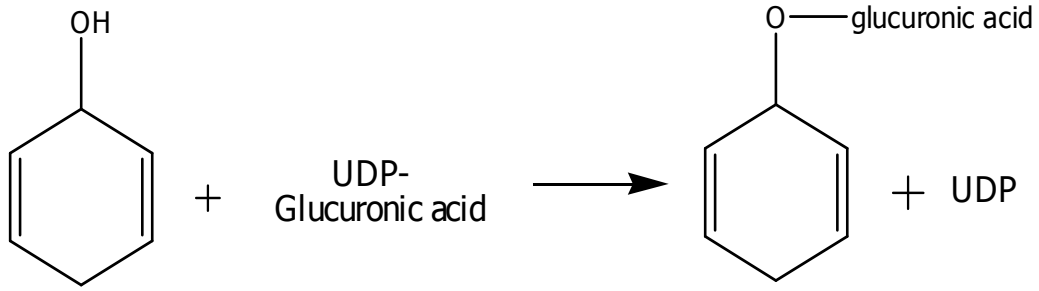
Several xenobiotiecs undergo detoxification by conjugation to produce less toxic and/or more easily excretable compound conjugation is the process in which a foreign compound combines with a substance produced in the body. The process of conjugation may occur either directly or after the phase I reactions. At least 8 different conjugating agents have been identified in the body. These are glucuronic acid, glycine cysteine(of glutathione), methylgroup, sulfate, acetix acid and thiosulfate[8].

Glucuronic acid

Conjugation with glucuronic acid is UDP-glucuronic acid produced in the uronic acid pathway. The microsomal enzymes UDP-glucuronyl transferases participate in glucuronide formation. A general reaction of glucuronide conjugation is shown below (X-OH represents xenobiotic).

Certain drugs (e.g. barbiturates) when administered induce glucuronyltransferase and this increases the glucuronide formation.

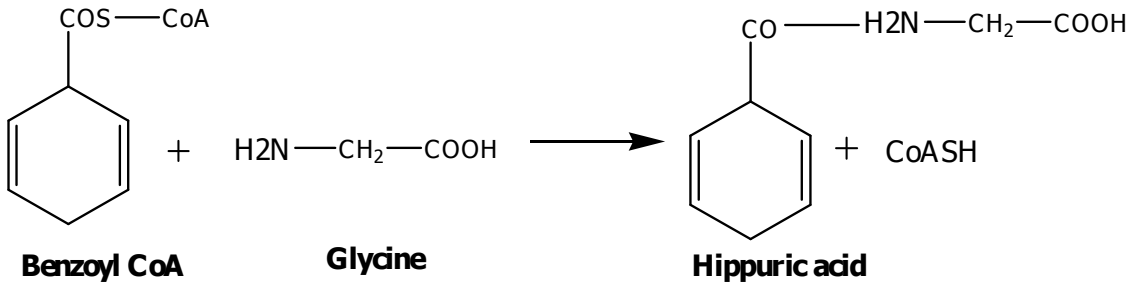
Glucuronic acid conjugation may occur with compound containing hydroxyl, carbonyl, sulfhydryl or amino groups. A few examples of glucuronide conjugation are given here.



Phenol **Phenyl glucuronide**

Benzoic acid + **UDP-Glucuronic acid** → **Benzoyl glucuronide** + **UDP**

Glycine: Many aromatic carboxylic acids (e.g. benzoic acid, penylacetic acid) are conjugated with glycine. Hippuric acid is formed. When glycine is conjugated with benzyl COA[9]. The excretion of hippuric acid (Greek : hipposhorse) was first reported in1829 in the urine of cows and horses.



Benzoyl CoA **Glycine** **Hippuric acid**

Cholic acid + **Glycine** → **Glycocholic acid**

Glutathione: The tripeptide glutathione (Glu-Cys-Gly), is the active conjugating agent. A wide range of organic compounds such as alkyl or aryl halides, alkenes, niro compounds and or aryl halides, alkenes, niro compounds and glycine of glutathione are removed and an acetyl group is added to the cysteine residue[9].

Glutamine: Phenylacetic acid is conjugated with glutamine to form phenylacetyl glutamine Conjugation with glutamine is, however, relatively less important.

Methyl group: The methyl group (-CH_3) of **S-adenosylmethionine** is frequently used to methylate certain xenoiotics. This is catalysed by the enzyme methyltransferase**.**

S-Adenosylmethionine + **X-OH** → **S-Adenosylhomocysteine** + **XO-CH_3**

Detoxification by drugs: It may be surprising to know that some drugs areadministered to detoxify foreign substances. The toxic effects of certain metals such as arsenic, mercury and cadminum could be overcome by administering BAL (British antilewisite). This compound was developed during the World War ll and was used as a detoxifying agent for certain war poisons. The mechanism of action of BAL is not clearly known. It is believed that BAL readily combines with metal and gets easily excreted into urine.

Transporters In Intestine[10,11,12]: As the site of oral absorption, the intestine has high expression of various uptake transporters (Fig. 1) facilitating the absorption of structurally diverse substrates. Uptake transporters. The common names of uptake (left side) and efflux (right side) xenobiotic transporters enriched in enterocytes are shown with arrowheads pointing to the direction of xenobiotic transport. Gene names in lower case represent mouse genes. Human orthologs (in all capital) of these mouse genes have been identified (with the same names unless otherwise indicated). Compared to mice, humans and rats have similar expression patterns for all genes shown except that humans have high levels of OCTN2 but minimal expression of ENT1 in intestine. In human intestine, OATP1A2 was detected using reverse transcriptase PCR andimmunohisto chemistry but undetectable using real-time PCR enriched on the apical membrane of enterocytes include peptide transporter 1 (Pept1, Slc15a1), concentrative nucleoside transporters (Cnt) Cnt1 (Slc28a1) and Cnt2 (Slc28a2), organic cation transporter n1 Octn1 (Slc22a4), organic anion transporting polypeptides (Oatp, Slco), cholesterol transporter Niemann-Pick C1-Like 1 (Npc1L1), apical sodium dependentbile acid transporter (Asbt, Slc10a2), as well as divalent metal transporter 1 (Dmt1, Slc11a2). As the first barrier against xenobiotics, the intestine has high expression of efflux transporters on the apical membrane of enterocytes, including multidrug resistance 1 (Mdr1, Abcb1), multidrug resistance associated protein 2 (Mrp2, Abcc2), breast cancer resistance protein (Bcrp, Abcg2), ATP-binding cassette (Abc) g5, and Abcg8. On the basolateral membrane of enterocytes, efflux transporters Mrp3 (Abcc3), organic solute transporter (Ost) alpha and beta, cholesterol transporter Abca1, and equilibrative nucleoside transporter 1 (Ent1, Slc29a1) are highly expressed Apical Uptake Transporters in Intestine Pept1 is predominantly expressed in small intestine, responsible for intestinal absorption of di- and tri-peptides as well as various peptide-like drugs, including b-lactam antibiotics (e.g., penicillin, ceftibuten, and cefadroxil), angiotensinconverting enzyme inhibitors (e.g., captopril, enalapril, or benazepril), renin inhibitors (S 86,2033 and S 86,3390), thrombin inhibitors (e.g., CRC 220), the aminopeptidase inhibitor bestatin, and certain

nonpeptidyl substrates (e.g., the monoamine oxidase inhibitor 4-aminophenylacetic acid, amino acid ester prodrugs of acyclovir, and zidovudine). Cnt1 and Cnt2 transport endogenous substrates such as adenosine, thymidine, cytidine, guanosine, uridine, inosine, and hypoxanthine. Cnts facilitate Na dependent uptake of nucleosides into cells against concentration gradients, with high affinity for their natural substrates. Cnt1 preferentially transports pyrimidine nucleosides; Cnt2 preferentially transports purine nucleosides. Many pharmaceutically important anticancer and antiviral drugs are nucleoside or nucleobase analogs; most of them are hydrophilic and cannot freely cross the plasma membrane. Octn1 is a pH-dependent and Na independent multispecific transporter-mediating transport of a variety of structurally diverse organic cations (e.g., desipramine, dimethylamiloride, cimetidine, procainamide, and verapamil). In humans, rare variants in NPC1L1 are associated with reduced sterol absorption and plasma low-density lipoprotein levels Consistently, Npc1L1-null mice have a marked decrease in intestinal absorption of cholesterol and phytosterols and are completely resistant to diet-induced hypercholesterolemia. Over 95% of bile acids secreted into bile are reabsorbed through highly regulated transport systems in liver and gastrointestinal tract. In humans, missense mutations of ASBT at conserved amino acid positions, L243P and T262M are associated with primary bile acid malabsorption. Studies in Asbt-null mice demonstrate that Asbt is essential for efficient intestinal absorption of bile acids.

Apical Efflux Transporters in Intestine[13]

Mdr1, also known as P-glycoprotein, was the first identified efflux transporter due to its prominent role in mediating resistance of cancer cells to various cytotoxic anticancer drugs. Studies in Mdr1a/1b double-null mice demonstrate that Mdr1 at intestinal and blood brain barriers critically protects against xenobiotics. Many therapeutically important drugs have been identified as Mdr1 substrates, such as vinblastine, paclitaxel, doxorubicin, etoposide, verapamil, digoxin, and cyclosporin A. Mdr1 inhibitors have been developed to overcome drug resistance of cancer cells; however, side effects of Mdr1 inhibition is a major obstacle to application of Mdr1 inhibitors in cancer chemotherapy. Studies in both Eisai and TR-hyperbilirubinemic rats, which carry natural Mrp2 mutations, indicate that Mrp2 is responsible for the intestinal efflux of certain glucuronide metabolites (e.g., E3040, a novel thromboxane synthase inhibitor). Bcrp transports heme compounds and confers resistance to anticancer drugs (e.g., anthracyclines, mitoxantrone, and camptothecins). Abcg5 and Abcg8 knockout mice have elevated blood levels of phytosterols and accumulate phytosterols in brain Selected

dietaryplant sterols disturb cholesterol homeostasis by affecting two critical regulatory pathways of lipid metabolism. Thus, Abcg5 and Abcg8 play a key role in protecting against disruption of cholesterol homeostasis by dietary plant sterols.

Basolateral Efflux Transporters in Intestine[14]: Mrp3 has been shown to be able to transport certain bile acids; however, results from Mrp3-null mice showed that Mrp3 is not essential for intestinal reabsorption of bile acids. Instead, Osta and Ostb form heterodimers and transport major bile acids Thus, Osta and Ostb are the putative bile acid transporters responsible for effluxing the reabsorbed bile acids back into the blood; nevertheless, the exact function of Ost in enterohepatic circulation of bile acids needs to be confirmed in knockout mice. Additionally, Abca1 is a cholesterol efflux transporter enriched on the basolateral membrane of enterocytes. Studies of Abca1 null mice showed that Abca1 is essential for intestinal absorption and whole-body metabolism of cholesterol Additionally, the bidirectional nucleoside transporter Ent1 is proposed to be responsible for pumping the absorbed nucleosides back into blood; however, no in vivo data have been reported.

Transporters In Liver[15,16]

In liver, uptake transporters play a key role in hepatic uptake and clearance of xenobiotics absorbed by the intestine, a process contributing to hepatic first pass. Uptake transporters expressed highly on the basolateral membrane of hepatocytes include the liver specific bile acid transporter Na taurocholate cotransporting polypeptide (Ntcp, Slc10a1), liver-specific Oatp1b (OATP1B1 and 1B3 in humans and Oatp1b2 in rodents), Oatp1a (Oatp1a1 and 1a4 in rodents and OATP1A2 in human cholangiocytes), Oct1 (Slc22a1), organic anion transporter 2 (Oat2, Slc22a7), and Ent1 (Fig. 2). ATP8b1 is an aminophospholipid flippase localized to the apical membrane of hepatocytes and cholangiocytes. Canalicular transporters are responsible for biliary excretion of chemicals. Transporters expressed highly on the canalicular membrane include Mrp2, Bcrp, multidrug and toxin extrusion 1 (Mate1, Slc47a1), bile salt export pump (Bsep, Abcb11), Mdr2 (Abcb4), Abcg5, Abcg8, and ATP7b. Efflux transporters Mrp3, Mrp6 (Abcc6), and Abca1 are present at high levels on the basolateral membrane of hepatocytes, responsible for efflux of substrates back into the blood, a process called 'retro-transport'. The common names of uptake (left side) and efflux (right side) xenobiotic transporters enriched in hepatocytes are shown with arrowheads pointing to the direction of xenobiotic transport. Gene names in lower case representmouse genes. Human orthologs (in all capital) of these mouse genes have been identified (with the

same names unless otherwise indicated). Compared to mice, humans and rats have similar expression patterns for all genes shown except that humans and mice have higher levels of MRP3/Mrp3 than rats in liver.

Basolateral Uptake Transporters in Liver[17]

Uptake studies demonstrate that a major portion of bile acid uptake by hepatocytes is Na dependent, and the liver-specific Ntcp transports all major bile acids (mainly conjugated bile acids) in a Na dependent manner. Thus, Ntcp is considered a major transporter responsible for hepatic uptake of bile acids. Nevertheless, Oatps are proposed to be responsible for the Na independent portion of uptake of bile acids into hepatocytes. Oatps transport a wide variety of amphipathic organic compounds, such as bile acids, steroid conjugates, thyroid hormones, anionic oligopeptides, drugs, toxins, and other xenobiotics However, different from MRPefflux transporters, the Oatp1a subfamily in rodents generally does not have orthologs in humans. Nevertheless, the rodentliver-specific basolateral uptake transporter Oatp1b2 (Slco1b2), previously known as Lst-1 or Oatp4, has the human orthologs OATP1B1 and OATP1B3. In vitro studies show that phalloidin, a toxic bicyclic peptide from the toxic mushroom Amanita phalloides, is a specific substrate for rat Oatp1b2 as well as human OATP1B1 and OATP1B3. Consistent with the in vitro studies, our in vivo study shows that Oatp1b2-null mice are completely resistant to phalloidin induced hepatotoxicity; in contrast, Oatp1b2-null and wild type mice are similarly susceptible to hepatotoxicity induced by amanitin, a structurally similar bicyclic peptide responsible for the oral toxicity of Amanita phalloides in humans. Interestingly, in vitro studies indicate that the bile acid transporter Ntcp transports a-amanitin. Thus, Oatp1b2 and OATP1B1/1B3 appear to have unique substrate specificity and physiological functions in liver, and the bile acid transporter Ntcp may also be responsible for hepatic uptake of certain xenobiotics.

Apical Flippase in Liver[18]

Flippases are located in the membrane helping the movement of phospholipid molecules between the two leaflets that compose the plasma membrane. The flippase ATP8b1 translocates aminophospholipids from the outer to the inner leaflet of the apical membrane of hepatocytes and cholangiocytes. Humans with mutations in ATP8B1 develop type-1 progressive familial intrahepatic cholestasis (PFIC1). Interestingly, PFIC1 patients have hepatic downregulation of BSEP, which may partially explain the similar phenotypes between PFIC1 and PFIC2

(mutation in BSEP). ATP8b1-mutant mice have decreased biliary secretion of bile acids but increased biliary secretion of phosphatidylserine, cholesterol, and ectoenzymes

Basolateral Efflux Transporters in Liver[19]

Mrp3 has been shown to transport bile acids in vitro. After bile duct ligation, Mrp3-null mice have lower blood levels of bilirubin glucuronides and higher hepatic levels of bile acids

relative to wild-type mice, indicating important roles of Mrp3 in retro-transporting bilirubin glucuronides and bile acids. Our previous studies showed that chemical induction of hepatic Mrp3 in rats markedly shifted the disposition of acetaminophen from biliary to urinary excretion. Conversely, Mrp3-null mice have markedly increased biliary excretion and decreased urinary excretion of acetaminophen and morphine glucuronides. Thus, Mrp3 appears to play a key role in retro-transporting glucuronides from liver into blood and thus increasing their urinary excretion. Mrp4 (Abcc4) is expressed highest in kidney and transports various substrates such as steroid glucuronides, folates, cAMP, cGMP, bile acids, and prostaglandins. Although the basal expression is low in liver, Mrp4 is induced in Mrp2-null mice and mice with cholestasis. After bile duct ligation, Mrp4-null mice have intrahepatic accumulation of bile acids and more severe liver injury, indicating an important role of Mrp4 as a backup system to transport bile acids out of liver back into blood. Mutations of the MRP6 (ABCC6) gene are implicated in the etiology of pseudoxanthoma elasticum and its vascular complications in humans. Mrp6-null mice develop mineralization of connective tissues, a phenotype similar to that in humans. Mrp6 transports small peptides such as the endothelin receptor antagonist BQ123. Interestingly, although Mrp6 mRNA and protein are expressed highest in liver, Mrp6- null mice do not have liver disease. It has been proposed that the complex disease pseudoxanthoma elasticum may be due to a metabolic disorder at the environment genome interface. Mice with hepatocyte-specific knockout of Abca1 have markedly decreased blood levels of total and high-density lipoproteins (HDL) cholesterol relative to wild type mice, and Abca1-null hepatocytes lost apoA I dependent capacity of effluxing cholesterol and phospholipid, demonstrating a critical role of hepatic Abca1 in effluxing lipid into blood and in maintaining the circulation of mature HDL particles

Transporters In Kidney[20,2,22]

Kidney plays a key role in urinary secretion and reabsorption of endogenous chemicals and/or xenobiotics, and is thus very rich in transporters (Fig. 3). Proximal tubules are the major site of secretion and reabsorption, where

basolateral uptake transporters Oat1(Slc22a6), Oat3 (Slc22a8), Oct1, Oct2 (Slc22a2), and Oatp4c1 (Slco4c1) are responsible for transporting organic anions and cations from blood into tubular cells, whereas apical efflux transporters Mrp2, Mrp4, Mate1, Bcrp, and Mdr1 transport these organic anions and cations into urine for urinary secretion. On the apical membrane of proximal tubules, uptake transporters Oatp1a1, 1a4, 1a6, 2a1, 2b1, 3a1, Oat2 (Slc22a7), Oat5 (Slc22a10), urate transporter 1 (Urat1, Slc22a12), Octn1, Octn2 (Slc22a5), Cnt1, Pept2 (Slc15a2), Asbt, and type II Na -Pi cotransporter (Npt2, Slc34a1)

The common names of xenobiotic transporters responsible for secretion (left side) and reabsorption (right side) in proximal tubule epithelial cells are shown with arrowheads pointing to the direction of xenobiotic transport. Gene names in lower case represent mouse genes (with the exception of Oat-k1/k2 which represent rat genes). All human orthologs (in all capital) of these mouse genes except some Oatps and Oat-k1/k2 have been identified (with the same names unless otherwise indicated). Compared to mice and rats, humans have similar expression patterns for most genes shown except that humans have much lower levels of BCRP and PEPT2 than rats and mice in kidney. reabsorb chemicals filtered through glomeruli back into tubule cells, whereas basolateral efflux transporters Osta, Ostb, Mrp1 (Abcc1), Mrp3, Mrp5 (Abcc5), Mrp6, Ent1, and Ent2 transport these reabsorbed chemicals back into the blood.

Basolateral Uptake Transporters in Kidney[23]

Oat1 and Oat3 are localized on the basolateral membrane, responsible for tubular uptake in renal proximal tubules. Despite the lack of morphological changes in Oat1-null and Oat3-null mice, there are considerable alterations in renal uptake and/or secretion of organic anions in these two knockout mice. In Oat1-null mice, loss of renal uptake of furosemide results in impaired diuretic responsiveness to this drug, and several endogenous organic anions display higher plasma concentrations and/or lower urinary concentrations (e.g. 3-hydroxyisobutyrate, 3-hydroxybutyrate, 4-hydroxyphenyllactate, benzoate, 2-hydroxy-3-methylvalerate, 3-hydroxypropionate, and N-acetylaspartate), suggesting the physiological role of Oat1 in transporting these compounds. Additionally, OAT1 has been implicated in renal uptake of 2,4-dichlorophenoxyacetate, an anionic herbicide, in humans. In Oat3-null mice, renal uptake of taurocholate, estrone sulfate, and para-aminohippurate are greatly decreased. Oct1 and Oct2 are localized to the basolateral membrane of proximal tubules, responsible for renal uptake of cationic compounds, and they have largely overlapping substrate specificities. Consequently,

knockout of either Oct1 or Oct2 has minimal effect on urinary excretion of cationic chemicalshowever, knockout of both Oct1 and Oct2 completely abolished renal secretion of tetraethylammonium and substantially increases its blood concentration. Currently, Oatp4c1 is the only member of the Oatp family found to be expressed on the basolateral membrane of proximal tubules in humans and rodents. Oatp4c1 transports cardiac glycosides, thyroid hormone, cAMP, and methotrexate in vitro. Thus, Oatp4c1 may be important in transporting these chemicals into tubules.

Transporters in Brain[24]

Mdr1 (P-glycoprotein), expressed highly in the endothelial cells of brain capillaries, is a key component of the blood-brain barrier against xenobiotic insult to the brain. In the choroid plexus, Mrp1, Mrp4, and Pept2 are highly expressed. Mrp1 transports conjugated organic anions (e.g., leukotriene C4 and GSH S-conjugates of prostaglandin A2) and cytotoxic hydrophobic peptides (de Jong et al., 2001). Mrp1 protects the choroid plexus epithelium and contributes to the blood-cerebrospinal fluid barrier. In addition to choroid plexus, Mrp4 is also expressed in the apical membrane of endothelial cells of brain capillaries; Mrp4-null mice treated with the anticancer drug topotecan have increased levels of topotecan in the brain. Pept2-null mice have a marked decrease in uptake of dipeptides into choroid plexus. Additionally, Oat3 is moderately expressed in choroid plexus, and Oat3-null mice have a marked decrease in uptake of fluorescein in choroid plexus. In the brain, ethanol consumption decreases the expression of Ent1, which transports adenosine as well as nucleosides and nucleoside analogs. Ent1-null mice have decreased hypnotic and ataxic responses to ethanol and increased consumption of alcohol compared to their wild type littermates; such phenotype is attenuated by an adenosine receptor agonist, indicating an important role of Ent1 in regulating adenosine signaling and ethanol consumption/behaviors in the brain. Human OATP1C1 (SLCO1C1) and mouse Oatp1c1 proteins share 83.5% homology. Oatp1c1 has a high affinity and specificity for thyroxine (T4) and is expressed predominantly in capillaries throughout the brain. Thus, Oatp1c1 is proposed to be essential for transport of T(4) across the blood-brain barrier. The monocarboxylate transporter 8 (MCT8, SLC16A2) is a high-affinity transporter for the active hormone T3. Men with mutations in MCT8 have severe, X-linked, psychomotor retardation and high serum T3 levels. A similar phenotype is replicated in Mct8-null mice, which have lower T3 in brain but higher T3 in liver,

resulting in a decrease in serum cholesterol and an increase in alkaline phosphatase. Thus, chemicals affecting the expression/function of Oatp1c1 and Mct8 may alter thyroid hormone homeostasis and mental development.

Transporters in Testes[25]

Mrp1 and Mrp9 are highly expressed in testes. Mrp1-null mice are susceptible to testicular damage induced by the anticancer drug etoposide phosphate. Currently, the physiological function of the testisspecific Mrp9 remains unknown. The third organic cation/ carnitine transporter Octn3 is almost exclusively expressed in testis the physiological importance of Octn3 in the testis awaits further investigation. Additionally, members of the Oatp super family (Oatp6b1, Oatp6c1, and Oatp6d1) are exclusively expressed in testes they are thought to be responsible for testicular uptake of dehydroepiandrosterone and its sulfates, precursors of in vivo androgen and, thus, estrogen biosynthesis.

Transporters in Placenta[26]

Placental transporters play important roles in handling of xenobiotics across the maternal-fetal interface. In a study of placental expression of transporters, 16 transporters, namely Mdr1a and 1b, Mrp1 and 5, Oct3 and Octn1, Oatp1a5 (Slco1a5) and Oatp4a1 (Slco4a1), Dmt1, zinc transporter 1 (Znt1, Slc30a1), Atp7a, Atp7b, prostaglandin transporter, Abcg8, Ent1, and Ent2, are expressed in placenta at concentrations similar to or higher than in maternal liver and kidney in rats. Additionally, Bcrp is highly expressed in human placenta and has been implicated as a placental survival factor (E. After intravenous administration of P-glycoprotein substrate drugs to the pregnant dams, Mdr1a/1b double-null fetuses have marked higher levels of digoxin, saquinavir, or paclitaxel than wildtype fetuses, indicating an essential role of Mdr1 in limiting fetal penetration of various potentially harmful or therapeutic compounds. Znt1 null mice die in utero, which cannot be rescued by manipulating maternal levels of zinc, indicating a key role of Znt1 in transplacental transporting maternal zinc into the embryonic environment.

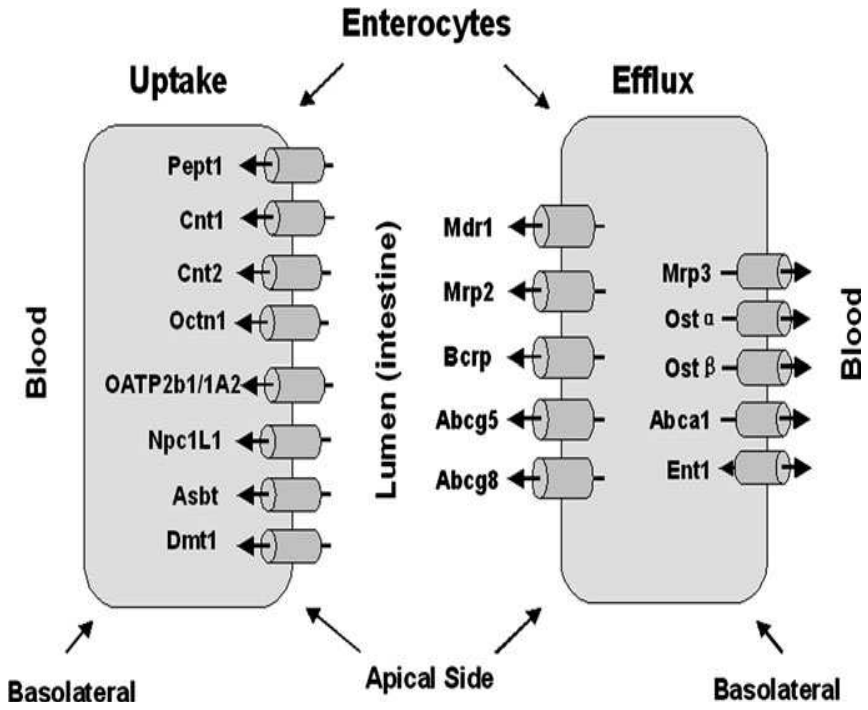


FIG. 1. Intestinal transporters.

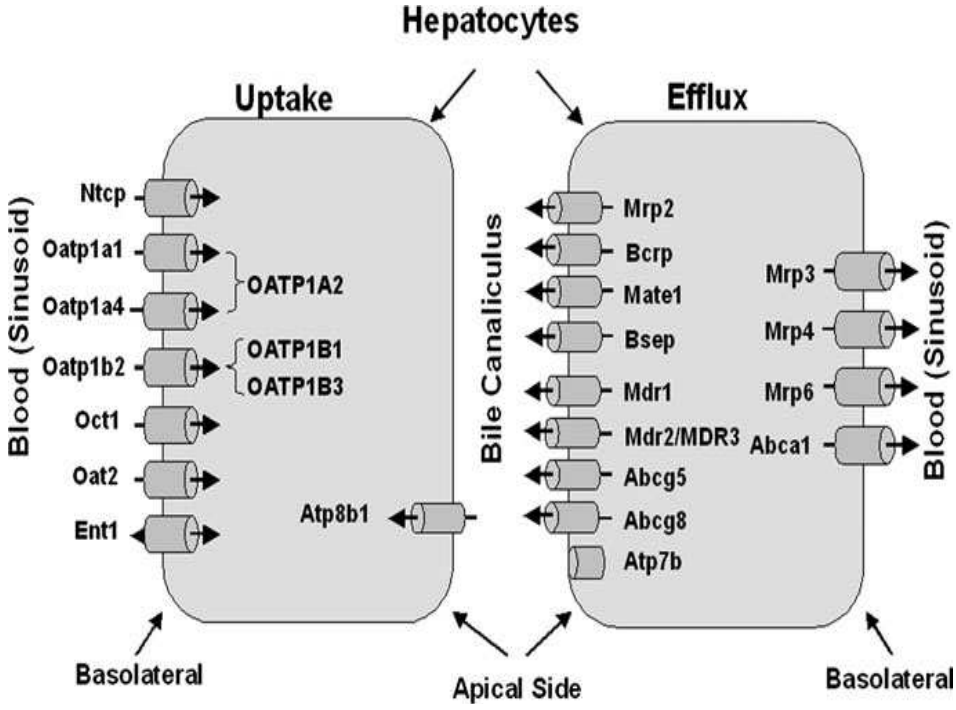


FIG. 2. Hepatic transporters.

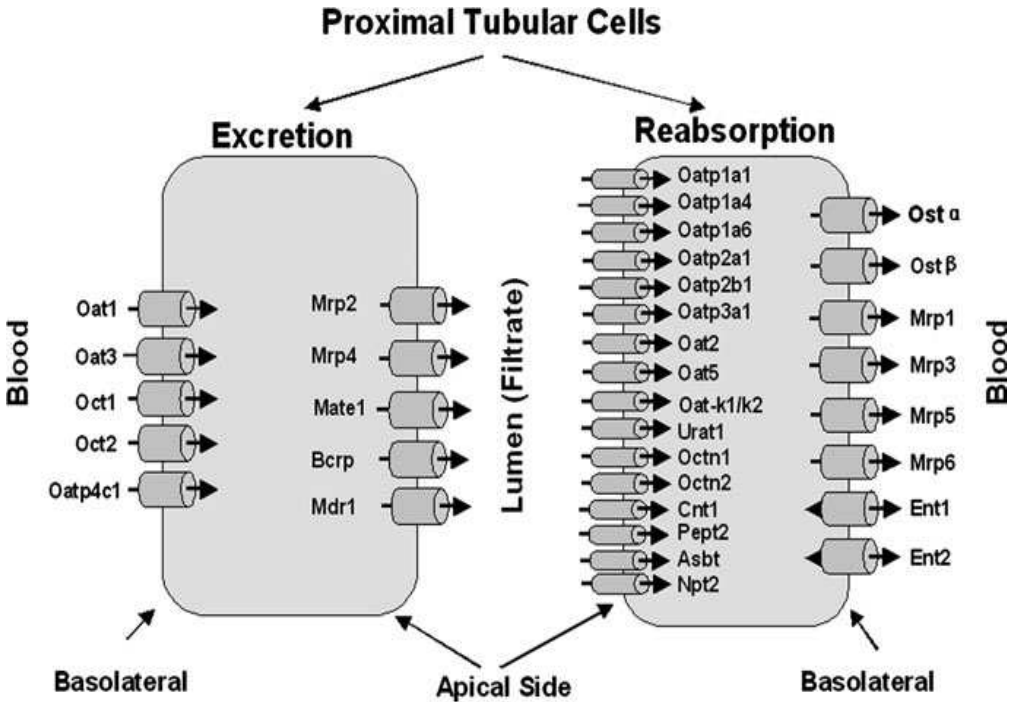


FIG. 3. Renal transporters

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