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Editorial

Organic Anion Transporting Polypeptides (OATPs)

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Editorial

Orally administered drugs need to pass through the intestinal wall and enter the portal blood before they reach the systemic circulation. Membrane transporters [influx and efflux] play a vital role in defining the rate and extent of intestinal absorption of drugs, as well as the hepatic drug clearance for both first-pass and elimination [1-4]. Moreover, renal membrane transporters determine the amount of drug excreted via the kidneys, while the distribution of drugs to their sites of action [brain, eye etc.] is influenced by the transporters at the blood-tissue borders. These membrane transporters are either localized on the apical or the basolateral side of the membrane and are classified in two categories [i] influx [uptake into cell] and [ii] efflux [out of cell] [5-7]. Chemistry of these transporters along with metabolic reactions [Phase I and II] may be considered as a requirement for chronological navigation of the basolateral and apical membranes [1,8-10].

Organic Anion Transporting Polypeptides [OATPs] are the plasma membrane transporters involved in cellular uptake of amphipathic drugs in tissues such as the intestine, liver and kidneys [11]. Several molecules/ substrates, such as bile salts, steroid conjugates, thyroid hormones, anionic oligopeptides, anti-cancer drugs, anti-retroviral drugs, and other therapeutic moieties traverse via OATPs. These transporters based on their localization [apical and basolateral] in tissues, such as brain, liver or kidneys, may affect the pharmacokinetics and efficacy of drugs transported through them. The absorption of drugs in the GI tract is facilitated by OATPs which are localized on the apical side of intestinal enterocytes. Hepatic OATPs expressed on the basolateral side of hepatocytes help in transport of drugs from blood into hepatocytes. Physico-chemical characteristics of the drug molecule can affect its systemic clearance if the drug molecule gets transported via hepatic or renal OATPs. Hepatic OATPs can further affect or limit the volume of distribution of drugs which are distributed mainly via the liver or enterohepatic circulation. Also, elimination of drugs in urine can be significantly enhanced or diminished by renal OATPs. Expression of OATPs on the Blood-Brain Barrier [BBB] may also alter the CNS distribution of drug therapeutics [11-14].

Table 1: Human OATP transporters, their gene names, tissue distribution, substrates and inhibitors [16-21].

OATP	Gene Name	Tissue Distribution	Substrates	Inhibitors
OATP1A2	SLCO1A2	Brain, kidney, liver, Intestine	Fexofenadine, levofloxacin, pitavastatin, rocuronium, rosuvastatin, saquinavir, Thyroxin	Grapefruit juice, orange juice, apple juice, naringin, hesperidin, rifampicin, rifamycin SV
OATP1B1	SLCO1B1	Liver	Atorvastatin, atrasentan, benzylpenicillin, bosentan, caspofungin, cerivastatin, enalapril, fluvastatin, irinotecan(SN-38metabolite), methotrexate, olmesartan, pitavastatin, pravastatin, repaglinide, rifampicin, rosuvastatin, simvastatin acid, temocapril, troglitazone sulphate, valsartan, nilotinib, vandetanib, pazopanib	Cyclosporine, gemfibrozil, gemfibrozil-O-glucuronide, rifampicin, rifamycin SV, clarithromycin, erythromycin, roxithromycin, telithromycin, indinavir, ritonavir, saquinavir, pazopanib, nilotinib

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OATP1B3	SLCO1B3	Liver	Bosentan, digoxin, docetaxel, enalapril, fexofenadine, fluvastatin, methotrexate, olmesartan, paclitaxel, pitavastatin, rifampicin, rosuvastatin, telmisartan, thyroxine, valsartan, canertinib, nilotinib, vandetanib, pazopanib	Cyclosporine, rifampicin, rifamycin SV, clarithromycin, erythromycin, roxithromycin, telithromycin, vandetanib
OATP1C1	SLCO1C1	Brain, testis, ciliary body	Thyroxine	
OATP2A1	SLCO2A1	Ubiquitous	Latanoprost	Diclofenac, furosemid, 4,4'-Diisothiocyano-2,2'-stilbenedisulfonic acid (DIDS), niflumic acid
OATP2B1	SLCO2B1	Liver, placenta, intestine, heart, skin	Atorvastatin, benzylpenicillin, fexofenadine, fluvastatin, glibenclamide, pravastatin, rosuvastatin	Cyclosporine, gemfibrozil
OATP3A1	SLCO3A1	Ubiquitous	Benzylpenicillin, thyroxine, vasopressin	-
OATP4A1	SLCO4A1	Ubiquitous	Benzylpenicillin, thyroxine	-
OATP4C1	SLCO4C1	Kidney	Digoxin, methotrexate, sitagliptin, thyroxine	-
OATP5A1	SLCO5A1	Unknown	-	-
OATP6A1	SLCO6A1	Testis	-	-

Human OATPs include 11 members and are encoded by the genes of Solute Carrier Organic Anion transporter [SLCO] super family [11]. OATPs are known to contain 12 transmembrane domains based on hydropathy analysis. A recent computational study suggests that the transport mechanism of substrates via OATPs is through a positively charged central pore in a so-called rocker-switch type mechanism. The uptake mechanism via OATPs is known to be independent of potassium, chloride and sodium gradients, membrane potential and ATP levels. As per published literature, cellular uptake via OATPs take place by electro neutral exchange, wherein the organic anions get attached to the efflux of neutralizing anions, such as glutathione or glutathione-S-conjugates and bicarbonate, although, the nature of the neutralizing anions for human OATPs still remains unknown [15]. A comprehensive list for Human OATP transporters, their gene names, tissue distribution, substrates and inhibitors has been provided in (Table 1).

Recent findings have shown critical involvement of OATPs in the absorption and disposition of a large number of drug therapeutics. The roles of OATPs has been highly scrutinized and widely recognized in Drug-Drug Interactions [DDIs], as well as in elucidating pharmacokinetic inter-individual variability of various drug molecules. Genetic variation in OATP-encoding genes and inhibition of OATP function has clinically significant consequences on drug therapy. In recent years, these transporters have been regarded as crucial molecular targets for potential DDIs. These transporters, in conjunction with the metabolizing enzymes and efflux proteins, may eventually determine the total flux or loss of the therapeutic agents. Better understanding of OATPs would help in determining the disposition of drug molecules and predict potential adverse drug reactions associated with transporter mediated DDIs.

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