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The role of organic anion transport protein 1a4 in drug delivery and diseases: a review

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Abstract

OATP1A4 is an important member of the family of organic anion transporting polypeptides (OATPs), which is generally thought to mediate cellular uptake of endogenous and exogenous substances, such as bile acids, drugs and environmental toxins. Recent studies have found that Oatp1a4 plays an important role in drug passage through the blood-brain barrier and is expected to be an important target for drugs used to treat central diseases. Oatp1a4 has also been associated with various diseases such as cholestasis. differences in Oatp1a4 across age and sex have also become an area of concern for precision drug administration. Therefore, this paper presents a systematic review of Oatp1a4 expression in drug transport and various physiopathological states.

Keywords: organic anion transporting polypeptides; OATP1A4; cholestasis; drug delivery.

Practical Application: Important for precise clinical use of drugs.

1 Introduction

Currently, foods have gained more attention in terms of their health support and disease-controlling ability(Kesika et al., 2022). Moreover, the study of organic anion transporters is becoming more and more important (Ji et al., 2022; Tan et al., 2022; Tao et al., 2023). Membrane transporters play an important role in the absorption, distribution and elimination of endogenous and xenobiotics, such as bile acids and drugs. Organic anion transporting polypeptides (OATPs) are a class of membrane transporters belonging to the solute carrier (SLC) family that mediate the uptake of a large number of substrates including bile acids, hormones and many drugs (Hagenbuch & Stieger, 2013). OATPs have been found to be expressed in several human organs including liver, kidney, brain and intestine (Gong et al., 2011; Hagenbuch & Stieger, 2013). In terms of clinical relevance, OATPs proteins often serve as key transport vehicles for drugs across the blood-brain barrier. On the other hand, the expression level of OATPs varies significantly across multiple disease states (Kim, 2003; Shitara et al., 2003). In recent years, much progress has been made in the identification of endogenous substrates of OATPs and their role in drug transport (Hagenbuch & Meier, 2004). Organic anion transport protein 1a4 (Oatp1a4) (Figure 1) is the prototypical member of the Oatp family of highly homologous transport proteins that are highly expressed in the liver, cerebrum (Imai et al., 2013), and skeletal myofibres (Sakamoto et al., 2008). The important role of Oatp1a4 in the passage of drugs through the blood-brain barrier has attracted increasing attention. In addition to this, Oatp1a4 has been associated with a variety of diseases. Therefore, this paper systematically reviewed the expression of Oatp1a4 in drug administration, cholestasis and other pathological states and its differences across gender and age. The aim is to bring more attention to the role of Oatp1a4 in the precise clinical administration of medications.

2 OATP1A4 in physiological state

Organic anion transporting polypeptides (Oatps) play an important role in transporting endogenous substances and xenobiotics to the liver and have been implicated in drug-drug interactions. Many factors, such as gender, age and diet, may influence their expression, leading to altered drug disposition, efficacy and toxicity. Organic anion transport protein 1a4 (Oatp1a4) is the prototypical member of the Oatp family of highly homologous transport proteins that are highly expressed in the liver, cerebrum (Imai et al., 2013), and skeletal myofibres (Sakamoto et al., 2008), while its placental expression is low (St-Pierre et al., 2004). In mouse livers, Oatp1a4 is female-predominant. Hepatic Oatp1a4 mRNA levels were decreased by both androgens and male-pattern growth hormone administration (Cheng et al., 2006). This sex-specific difference is also reflected in the functional expression of blood-brain barrier Oatp1a4 (Brzica et al., 2018). And, Oatp1a4 mRNA expression is age-dependent. It was hardly detectable in fetal rat livers, low at birth, Subsequently, rapidly increased after weaning (21 d), and reached the peak at 60 d, and then remained stable during the age between 60-180 d, at last decreased at elderly (540 and/or 800 d) (Hou et al., 2014). In clinical practice thyroid dysfunction varies with age and asymptomatic manifestations of hyperthyroidism are frequently observed in the elderly. In the hyperthyroid state, the expression of Oatp1a4 is downregulated (Engels et al., 2015). In terms of diet, high sucrose diet could reduce gene expressions of Oatp1a4 (Zagorova et al., 2015). Calorie restriction (CR) is one of the most effective anti-aging interventions in mammals. CR could increase the female-predominantly expressed Oatp1a4 (Fu & Klaassen, 2014). Maternal consumption of a high-fat diet during pregnancy and lactation also increases the mRNA expression of Oatp1a4 (Tanaka et al., 2018). Inosine induces a decrease in Oatp1a4 expression levels through activation of xanthine oxidase

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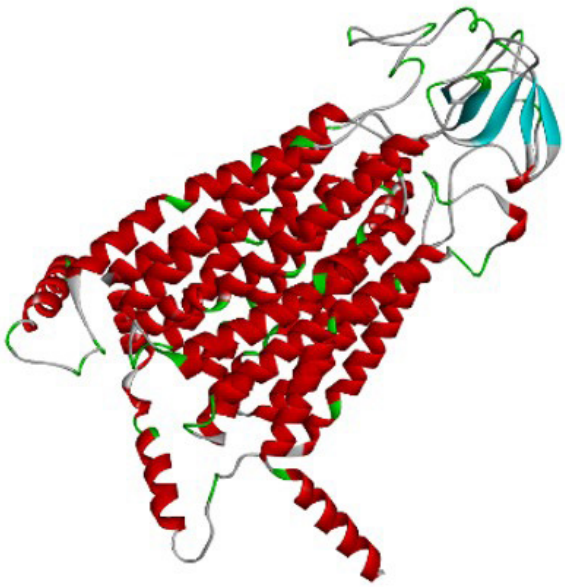

Figure 1. The theoretical 3D structures of OATP1A4 from AlphaFold v2.0, a protein structure database (Jumper et al., 2021).

induced oxidative stress, as confirmed by experiments in rats fed inosine (Tsujimoto et al., 2013).

3 OATP1A4 and drug delivery

3.1 Role of OATP1A4 in the blood-brain barrier

The physical and biochemical properties of the blood-brain barrier (BBB) make the treatment of central nervous system disorders extremely difficult because drug delivery to the central nervous system (CNS) is greatly limited by BBB. In contrast, drug delivery to CNS can be achieved by targeting drug uptake transporters such as Oatp1a4, which is also thought to be a strategy that could improve drug delivery to the brain. It has been demonstrated that the transport activity of Oatp1a4 in the BBB is directly regulated by TGF-β/ALK1 signaling, and this pathway could be a target for controlling the CNS delivery of OATP substrate drugs. (Abdullahi et al., 2018), and activation of activin receptor-like kinase (ALK)-1 using bone morphogenetic protein (BMP)-9 increased the expression of Oatp1a4 protein in rat brain microvessels in vivo (Abdullahi et al., 2017a). Hence, targeting Oatp1a4 regulation represents an opportunity to control Oatp1a4 functional expression for the purpose of delivering therapeutics to the CNS (Abdullahi et al., 2017b). The human ortholog of Oatp1a4 is OATP1A2. It has been shown that OATP1A2 could be regulated by transforming growth factor-β/activator receptor-like kinase 1 signaling in humans (Ronaldson et al., 2021). Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors), as transport substrates for Oatp1a4 improve functional neurological outcomes in patients, and Oatp1a4 statin uptake is higher in the cerebral cortex relative to the hippocampus and cerebellum (Betterton et al., 2022). Pitavastatin, rosuvastatin, pravastatin, taurolite, digoxin, ochratoxin A and [d-penicillamine (2,5)]-enkephalin are currently identified as substrates of Oatp1a4, which mediates the brain-blood and blood-brain transport of these drugs across the blood-brain barrier (Ose et al., 2010). There is growing evidence that bumetanide also affects brain disorders, including autism, neonatal seizures, and epilepsy; however, the low brain levels of bumetanide after systemic administration severely limit its clinical use in the treatment of brain disorders. In vivo experiments have shown that restricted passive diffusion and active efflux transport, mediated by Oat3 as well as the organic anion transporting peptide (Oatp) Oatp1a4 and multidrug resistance protein 4, explain the extremely low brain concentrations achieved after systemic administration of bumetanide (Römermann et al., 2017). Pain is a major symptom associated with inflammation, and inhibition of inflammatory pain by the anti-inflammatory drug diclofenac attenuates these changes in Oatp1a4 functional expression, suggesting that peripheral inflammation can modulate BBB transporters (Ronaldson et al., 2011).

3.2 Role of OATP1A4 in the blood retinal barrier and blood-arachnoid barrier

Oatp1a4 is also expressed on the blood retinal barrier (BRB) and is a major determinant in controlling the entry of anionic drugs into the retina. Immunoblotting and immunohistochemical analysis showed that Oatp1a4 is localized to the apical membrane of the retinal pigment epithelium (Akanuma et al., 2013). Recent studies have shown that Oatp1a4 is involved in the transport of nutrients including riboflavin, L-ornithine, β-alanine and L-histidine in the blood to the retina, and pravastatin in the BRB (Kubo et al., 2018). In addition, there is evidence that Oatp1a4 plays a role in drug clearance at the blood-arachnoid barrier (BAB) and may play an important role in cerebrospinal fluid (CSF) detoxification in vivo by limiting the distribution of organic anions in the brain and spinal cord (Yaguchi et al., 2019).

3.3 Role of OATP1A4 in hepatic metabolism

It is well known that the liver is the primary organ of drug metabolism and organic anion transporting peptides (Oatps) are involved in hepatic transport of a variety of organic anion compounds and drugs. The function of Oatp1a4 dominates the region around the central hepatic vein (CV) in the rat liver lobules and can affect the distribution of substrates such as sulfanilamide-101, digoxin, quinine, d-verapamil, 17beta-estradiol-d-17beta-glucuronide in the liver (Akanuma et al., 2019). It has been shown that Oatp1a4 plays a major role in the hepatic accumulation of cardiac glycosides (Takano et al., 2018) and berberine (Chen et al., 2015) in mice. Oatp1a4 plays a major role in the hepatic uptake of beta-lactam antibiotics in humans, and probably corresponds functionally to OATP1B3 in rat liver (Nakakariya et al., 2008). Eprosartan is an angiotensin II receptor antagonist used clinically for the treatment of hypertension and heart failure. It is transported by multiple Oatps (at least Oatp1a1 and Oatp1a4)/Mrp2 in rats and at least OATP1B1/MRP2 in humans (Sun et al., 2014). Adverse effects of statins are usually the result of drug-drug interactions, and inhibition of the Oatp1a4 and Oatp1b2 transporters in rats by the bacteriostatic agent fusidic acid (FA) may attenuate hepatic uptake of statins, leading to increased blood and tissue

concentrations that exhibit musculoskeletal toxicity (Eng et al., 2016). Pregnenolone-16alpha-carbonitrile (PCN) regulates the expression of some transporters, namely, Oatp1a4 and Mrp3 in liver via a PXR-mediated mechanism (Cheng & Klaassen, 2006).

3.4 Role of OATP1A4 in drug metabolism

The liver plays an important role in the in vivo metabolism of drugs, and hepatic transporters contribute to the absorption and excretion of drugs by the liver. Dexamethasone (DEX) treatment of hepatocytes increased the expression of CYP3A1/2, Oatp1a4 and Mrp2 and decreased the expression of Ntcp (Turncliff et al., 2004). Hepatotoxicity of methotrexate was increased during human treatment with dexamethasone, and analysis of methotrexate transporter expression in the liver showed upregulation of Mrp2, Oatp1a4, and Oat2 and downregulation of Mrp3, resulting in reduced biliary elimination and leading to increased hepatotoxicity of the drug in combination with DEX (Fuksa et al., 2010). Perfluorooctanoic acid (PFOA) and perfluorodecanoic acid (PFDA) have been detected in wildlife and humans worldwide. Both play a central role in the down-regulation of Oatp1a1, 1a4, 1b2 (Cheng & Klaassen, 2008). Perinatal exposure to polybrominated diphenyl ethers (PBDEs) resulted in increased expression of the hepatic efflux transporters Mdr1 (multidrug resistance), Mrp2 (multidrug resistance-associated protein) and Mrp3, and the influx transporter Oatp1a4 mRNA (Szabo et al., 2009). Patients with nonalcoholic steatohepatitis (NASH) may ingest both Pravastatin and herbs containing Evodiamine, which upregulates the expression of Oatp1a1, Oatp1a4, and Oatp1b2 decreasing systemic exposure to pravastatin (Liang et al., 2022). The regulation of Oatp1a4 by some natural products or traditional drugs has also been reported. For example, monoammonium glycyrrhizinate (MAG) increases the expression of Oatp1a4 and decreases the expression of Mrp2 (Zhou et al., 2016). Silymarin inhibits protein expression of Oatp1b2 and Oatp1a4 in NASH animals (Lynch et al., 2021). Imperatorin, Isoimperatorin, and Angelica dahurica extract can significantly downregulate the expression of Oatp1a1, Oatp1a4, and Oatp1b2 of liver in mice (Wang et al., 2020).

4 OATP1A4 and diseases

4.1 OATP1A4 and cholestasis

Cholestasis is caused by interruption of bile flow and is associated with a variety of liver diseases, and organic anion transporting polypeptides are thought to have an important function in bile acid (BA) transport. Uptake of conjugated BA by the liver may be affected by down-regulation of OATP1A1 and up-regulation of OATP1A4 (Slijepcevic et al., 2015). Oatp1a4 is upregulated in the liver and downregulated in the intestine after bile duct ligation (BDL) in rats (Giroux et al., 2022), this seems to indicate that Oatp1a4 is associated with cholestasis. However, in another experiment using 7-day BDL-induced liver dysfunction rats, it was found that the mRNA expression of Oatp1a4 in the liver of BDL rats decreased to 84.8% of that of normal rats (Horiuchi et al., 2009). This difference in results may be caused by the experimental period. Under lipopolysaccharide (LPS)-induced inflammatory conditions, lymphocyte deficiency altered basal and inflammatory IL-6 mRNA expression, and B-cell deletion also attenuated Oatp1a4 mRNA in LPS-treated mice, suggesting that IL-6 signaling may play a critical role (Bodeman et al., 2013). Reverse regulation of Mrp2 and 3 is thought to represent an adaptive response to cholestatic injury in hepatocytes, and downregulation of periportal Ntcp and induction of Oatp1a4 and Oatp1b2 in BDL and LPS-treated rat livers may be adaptive mechanisms for reducing cholestatic injury in hepatocytes with profound downregulation of Bsep and Mrp2 (Donner et al., 2007). Mice deficient in ATP11C are characterized by conjugated hyperbilirubinemia and nonconjugated hyperbilirubinemia, and the basal bile salt uptake transporters OATP1B2, OATP1A1, OATP1A4, and Ntcp are almost absent in central hepatocytes of ATP11C-deficient livers with features very similar to those of Rotor syndrome, suggesting that deletion of OATP expression potentially predisposes to Rotor syndrome (de Waart et al., 2016). Transmembrane protein 30A (TMEM30A) is a β-subunit essential for the function of ATP11C, and the expression and membrane localization of ATP11C were significantly reduced in Tmem30a LKO mice, which correlated with impaired expression and localization of BS transporters, such as OATP1A4, OATP1B2, NTCP, BSEP, and MRP2, suggesting that TMEM30A deficiency can lead to intrahepatic cholestasis in mice by impairing the expression and localization of BS transporters and associated nuclear receptors (Liu et al., 2017). Alpha-naphthyl isothiocyanate (ANIT) is a hepatotoxic agent that causes acute intrahepatic cholestasis in rodents. In an experiment on the effect of Dioscin on ANIT-induced cholestasis, it was found that co-treatment of ANIT with Dioscin prevented adaptive downregulation of Oatp1a1, 1b2 and promoted upregulation of Oatp1a4, multidrug resistance-associated protein (Mrp)2 and bile salt export pump (Bsep), suggesting that Dioscin may prevent hepatic transporters by restoring expression to prevent impairment of liver function (A. Zhang et al., 2016). Pyrazinamide (PZA), a first-line drug for the treatment of tuberculosis, causes severe hepatotoxicity, with a 2-fold increase in serum levels of both ALT and AST, a 10-fold increase in total bile acids in serum, and significantly altered mRNA and protein expression of bile acid synthesis and transporters in PZA-treated rats, with FXR, Bsep, Mrp2, Mdr2, Ostα/β Oatp1a1, Oatp1b2, and Cyp8b1 were decreased, whereas Mrp3, Ntcp, Oatp1a4, and Cyp7a1 were increased (Guo et al., 2016). In estrogen-induced cholestasis, ethinylestradiol significantly increased cholestasis markers, decreased bile bile acid excretion, downregulated hepatocyte transporters (Ntcp/Oatp1b2/Oatp1a4/Mrp2), and upregulated Mrp3 (Muchova et al., 2015). Yinchenhao Decoction (YCHD) is a famous traditional Chinese formula used for treating cholestasis. The cholestatic effect of YCHD was shown to be related to its modulating effect on the expression of metabolic enzymes and transporters in cholestatic liver. YCHD significantly increased the expression of UGT1A1, bile salt export pump, MRP2 and OATP1A4 in cholestatic rats, which had a great ameliorating effect on cholestasis (Yi et al., 2018). In an experiment using Oatp1a4-deficient mice to investigate the physiological role of Oatp1a4 in BA homeostasis, female Oatp1a4-deficient mice showed no significant alterations in BA concentrations in serum or liver, whereas male Oatp1a4 null mice showed significant alterations in BA homeostasis, including increased concentrations of deoxycholic acid (DCA) in serum, liver, and

intestinal contents. Loss of Oatp1a4 function did not reduce BA accumulation in serum or liver of bile duct ligated mice, suggesting that Oatp1a4 is unlikely to be an uptake transporter of BA, but plays an important role in secondary BA metabolism in male mice (Zhang et al., 2013).

4.2 OATP1A4 and liver diseases

The liver plays an important role in the detoxification process of foreign bodies. Hepatobiliary transporters contribute to the process of foreign body uptake and elimination by the liver. The expression of these transporters may be regulated in the presence of liver failure. For example, in the Long-Evans Cinnamon (LEC) rat hepatitis model, decreased hepatic expression of three sinusoidal organic anion transporters, Ntcp, Oatp1a1 and Oatp1a4, was found (Chiba et al., 2007). Progressive loss of mRNA for transporters such as Ntcp, Bsep, Mrp2, Oatp1/Oatp1a1, Oatp2/Oatp1a4 and Oatp4/Oatp1b2 was found at 20 and 32 weeks of hepatocarcinogenesis in rats (Monte et al., 2005). Plasma bilirubin levels are increased in rat models and in patients with alcoholic liver disease (ALD). The constructive androgen receptor (CAR) is a known xenobiotic receptor that induces bilirubin detoxification and transport, and the CAR agonist phenobarbital (PB) downregulates bilirubin levels in the serum of ALD patients, while selectively upregulating the expression levels of OATP1A1, OATP1A4, UGT1A1 and MRP2 (Wang et al., 2017). After hepatic ischemia-reperfusion (IR) injury, mRNA expression of hepatic transporter Oatp1a1, Oatp1a4, Oatp1b2, Ntcp, Mdr2 and Bsep decreased, while Mdr1b expression increased (Tanaka et al., 2006). Chronic high-fat diets are a key factor in obesity, and progressive obesity can subsequently lead to liver damage, kidney damage, and intestinal atrophy. Transporters expressed in the liver, kidney and intestine play an important role in the deposition of nutrients and drugs. In HFD-fed mice, the relative expression of Oat2 was increased 4.08-fold and the protein expression of Oat2 was upregulated at 24 weeks, while the mRNA expression of the uptake transporters Oct1, Oatp1b2 and Oatp1a4 was decreased by 79%, 61% and 19%, respectively (Lu et al., 2019).

4.3 OATP1A4 and other diseases

Autosomal dominant polycystic kidney disease (ADPKD), a common form of hereditary polycystic kidney disease (PKD), is a major cause of renal failure, and increased bile acids in the liver of rats with polycystic kidney (PCK) are associated with decreased protein expression of Mrp2 and Oatp1a4 in the liver (Bezençon et al., 2019). Protein expression of Oatp1a4 is significantly decreased in the brains of Alzheimer's disease (AD) mice (Wen et al., 2021). Cerebral hypoxia/reoxygenation stress (H/R) is a component of multiple diseases, and in rat brain microvessels, Oatp1a4 expression is significantly increased under H/R conditions (Thompson et al., 2014). Elevated systemic levels of cytokines in rheumatoid arthritis (RA) can alter the expression of metabolic enzymes and transporters. mRNA levels of intestinal Cyp3a1 and hepatic Cyp2c6, Cyp2c7, Cyp3a1, Oatp1a1, Oatp1b2, Oatp1a4 and Mrp2 were significantly decreased in rats with collagen-induced arthritis (CIA) (Lin et al., 2017).

5 Conclusions

Oatp1a4 is an important Organic anion transporting polypeptides which is known to play an important role in the transport of many drugs and endogenous substances, such as bile acids. Oatp1a4 is highly expressed in the liver and brain and has significant age and sex differences, which are important for individualized drug effectiveness and safety. And significantly altered expression of Oatp1a4 has been found in a variety of diseases. However, the regulatory mechanisms of Oatp1a4 are still poorly understood and more studies are needed to elucidate them.

Ethical statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest statement:

The authors declare no conflict of interest in preparing this article.

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