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Mini Review

A Minireview: Usefulness of Transporter-Targeted Prodrugs in Enhancing Membrane Permeability

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ABSTRACT

Orally administered drugs are categorized into 4 classes depending on the solubility and permeability in a Biopharmaceutics Classification System. Prodrug derivatization is one of feasible approaches in modifying the physicochemical properties such as low solubility and low permeability without changing the *in vivo* pharmacological action of the parent drug. In this article, prodrug-targeted solute carrier (SLC) transporters were searched randomly by PubMed. Collected SLC transporters are amino acid transporter 1, bile acid transporter, carnitine transporter 2, glucose transporter 1, peptide transporter 1, vitamin C transporter 1, and multivitamin transporter. The usefulness of transporter-targeted prodrugs was evaluated in terms of membrane permeability, stability under acidic condition, and conversion to the parent drug. Among prodrugs collected, peptide transporter-targeted prodrugs exhibited the highest number, and some prodrugs such as valaciclovir and valganciclovir are clinically available. ATP-binding cassette efflux transporter, P-glycoprotein (P-gp), reduces the intestinal absorption of lipophilic P-gp substrate drugs, and SLC transporter-targeted prodrugs of P-gp substrate drugs circumvented the P-gp-mediated efflux transport. Thus, SLC transporter-targeted prodrug derivatization seems to be feasible approach to increase the oral bioavailability by overcoming various unwanted physicochemical properties of orally administered drugs, although the effect of food on prodrug absorption should be taken into consideration.

Introduction

In a Biopharmaceutics Classification System (BCS), orally administered drugs are categorized into 4 classes depending on the solubility and permeability. BCS class I drugs exhibit high solubility and high permeability, class II drugs low solubility and high permeability, class III drugs high solubility and low permeability, and class IV drugs low solubility and low permeability.[1] Among these drugs, class I drugs alone can be absorbed efficiently and steadily with less interindividual variations. According to a Biopharmaceutics Drug Disposition Classification System, BCS class I drugs are thought to be absorbed mostly by passive diffusion with a minimal effect of transporters including the influx solute carrier (SLC) and ATP-binding cassette (ABC) efflux transporters. For BCS classes II-IV drugs, transporters contribute to their intestinal absorption predominantly as follows: ABC efflux transporters, especially P-glycoprotein (P-gp, *ABCB1*), contribute to BCS class II drugs, SLC transporters contribute to class III drugs, and both SLC and ABC transporters contribute to class IV drugs.[2] P-gp is abundantly expressed in the middle and distal small intestine and limits the absorption of structurally and pharmacologically unrelated lipophilic P-gp substrate drugs depending on their absorption sites in the intestine.[3,4] The low membrane permeability of BCS class III drugs would be due to the low transport capacity of SLC transporters, in addition to the first-pass metabolism in the intestine. The expression sites of transporters are mostly site specific, and the expression levels of transporters are limited.[5-7] Accordingly, the transporter-mediated transport is saturable depending on the luminal concentrations of solutes.

Prodrug derivatization is one of feasible approaches in modifying the solubility and permeability without changing the *in vivo* pharmacological action of drugs. Prodrugs are defined as pharmacologically inactive chemical derivatives of a drug molecule that requires a transformation chemically and enzymatically within the body to release the active drug, and prodrugs are designed to overcome pharmaceutical and pharmacokinetically based problems associated with the parent drug molecule that would

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otherwise limit the clinical usefulness of the drug.[8] It is reported that, in recent years, almost 10% of the global marketed medications are prodrugs, 20% of all small molecular medicines approved between 2000 and 2008 were prodrugs, and over 30% of drugs approved at 2008 were prodrugs.[8,9] In this minireview, prodrug-targeted SLC transporters were searched randomly by PubMed research engine. By selecting an appropriate SLC transporter as a targeting transporter, the low solubility, the low permeability, and therefore the low oral bioavailability of parent drugs could be improved.

Amino Acid Transporter

Amino acids are transported by multiple transporters with overlapping substrate specificities, and Na^+-independent neutral amino acid transporter, LAT1 (SLC7A5), transports L-type large neutral amino acids with branched and aromatic side chains such as leucine (Leu), isoleucine (Ile), phenylalanine (Phe), methionine (Met), tyrosine (Tyr), histidine, tryptophan (Trp), and valine (Val). LAT2 (*SLC7A6*) has also broad substrate specificities and transports L-isomers of neutral alpha-amino acids such as Tyr, Phe, Trp, threonine, asparagine, Ile, cysteine, serine (Ser), Leu, Val, and glutamine (Gln) with a high affinity and histidine, alanine (Ala), Met, and glycine (Gly) with a low affinity.[10,11] LAT1 and LAT2 transport also several exogenously synthesized drugs such as L-dopa, alpha-methyldopa, melphalan, and gabapentin.[12] LAT1 protein is abundant in the colon, and its abundance markedly decreased at the level of jejunum and ileum. In contrast, LAT2 exhibits relative homogeneous presence across the digestive tract in human and rat intestine.[13] When these LAT substrate drugs were taken with foods, the oral bioavailability is significantly reduced.[14]

Quinidine

Quinidine is known as a typical substrate and inhibitor of P-gp and used as an antiarrhythmic agent. Quinidine is classified as a BCS class I drug with high solubility and high permeability. However, the intestinal absorption of quinidine from the distal small intestine expressing P-gp abundantly is low because quinidine is recognized as a substrate for P-gp at the low luminal concentration of quinidine.[3,4] To overcome such P-gp-mediated efflux transport, the usefulness of amino acid transporter-targeted prodrug of quinidine was investigated by using Val ester of quinidine (Val-quinidine).[15] Quinidine increased 2-fold the uptake of ritonavir, a P-gp substrate, in MDCK1 cells transfected with MDR1 (MDCK-MDR1) cells. In contrast, Val-quinidine did not alter the ritonavir uptake. The efflux transport in a basolateral-to-apical direction of quinidine in MDCK1-MDR1 cells was 3-fold greater than the influx transport in a apical-to-basolateral direction. In contrast, the transport rate of Val-quinidine was comparable between the influx and efflux directions. These results indicated that Val-quinidine is not a P-gp substrate, different from quinidine. In contrast, the uptake rate of glycine-sarcosine (Gly-Sar), a typical substrate for peptide transporter and various amino acid model substrates, was reduced in the presence of Val-quinidine, indicating that Val-quinidine is a substrate and inhibitor for amino acid transporter. Furthermore, the transport characteristic of Ile ester prodrug of quinidine (Ile-quinidine) was investigated from the viewpoint whether amino acid ester prodrug of quinidine can circumvent P-gp-mediated cellular efflux.[16] Ile-quinidine did not alter the uptake of erythromycin, a P-gp substrate, in MDCK-MDR1 cells. In addition, Ile-quinidine exhibited only a 1.3-fold difference between the influx and efflux transport rates in MDCK-MDR1 cell monolayer, indicating that Ile-quinidine exhibits quite low affinity toward P-gp. Study on chemical and enzymatical hydrolysis of Ile-quinidine resulted in the low conversion of quinidine during the transport. In competitive inhibition studies, Ile-quinidine was recognized by multiple amino acid transporters including LAT1, LAT2, and cationic amino acid transporter.

Bile Acid Transporter

Multiple transporters including Na^+/taurocholate cotransporting polypeptide (NTCP, *SLC10A1*), several organic anion transporting polypeptides (OATPs) such as OATP1A2 (*SLCO1A2*), OATP1B1 (*SLCO1B1*), OATP1B3 (*SLCO1B3*), and OATP4A1 (*SLCO4A1*) and multidrug resistance protein 3 (MRP3, *ABCC3*) at the sinusoidal membrane of hepatocytes, bile salt export pump (BSEP, *ABCB11*) at the bile canalicular membrane of hepatocytes, and the apical Na^+-dependent bile salt transporter (ASBT, *SLC10A2*) at the apical membrane of enterocytes are involved in the enterohepatic recirculation of bile acids. NTCP and OATPs transport bile acids into hepatocytes from blood circulation, MRP3 and BSEP, and bile salt export pump transport bile acids into blood circulation and bile juice, respectively, from hepatocytes, and ASBT transports bile acids into enterocytes from intestinal lumen. It is reported that trihydroxy bile acids such as cholate, a primary bile acid, are better transported than dihydoxy bile acids such as chenodeoxycholate, a primary bile acid, and deoxycholate, a secondary bile acid in the ileum of the small intestine.[17] ASBT is abundantly expressed in the distal segment of the small intestine (ileum), compared to proximal segment.[7,18]

Acyclovir

Acyclovir (ACV) is absorbed by multiple transporters including nucleoside transporters and partly by noncarrier-mediated diffusion in the intestine.[19] ACV is categorized as a BCS class III drug when ACV is administered at a dose of 400 mg and as a BCS class IV drug at a dose of 800 mg, due to the low permeability and limited water solubility of ACV (solubility is 2.3 mg/mL in water).[20] To enhance the low oral bioavailability of ACV, prodrugs synthesized to target SLC transporters are as follows: 5′-amino acid ester prodrugs,[21-23] beta-glucoside-conjugated prodrug,[24] dipeptide ester prodrugs,[25,26] and bile acid—conjugated prodrugs.[27] Bile acid—conjugated prodrugs of ACV were synthesized using 4 bile acids, chenodeoxycholate (CDCA), deoxycholate, cholate, and ursodeoxycholate and Val as a linker. Among them, ACV valchenodeoxycholate (ACV-Val-CDCA) exhibited the highest affinity toward ASBT, and ACV-Val-CDCA was hydrolyzed and released ACV. The cellular uptake of ACV from ACV-Val-CDCA in COS cells transfected with ASBT (COS-ASBT cells) resulted in a 16-fold greater than that from ACV. In COS-ASBT cells, the enhanced permeability was found to be due to ASBT-mediated uptake and increased passive permeability. Oral bioavailability of ACV was increased 2-fold by administering ACV-Val-CDCA compared to ACV in rats.

Gabapentin

Gabapentin, an LAT substrate drug having a similar structure to gamma-amino butyric acid, is a broad-spectrum antiepileptic drug. Gabapentin exhibits dose-dependent absorption kinetics and dose-independent disposition kinetics. The inhibitor of LAT, 2-aminobicyclo-(2,2,1)-heptane-2-carboxylic acid, inhibited the intestinal absorption of gabapentin *in vivo*.[28] The oral bioavailability of gabapentin, estimated by urinary excretion of unchanged form, was approximately 58% of dose after single dosing of 200 mg in healthy subjects.[29] The high doses of gabapentin are required in the treatment of neuropatic pain, therefore, the usefulness of bile acid—targeted prodrug of gabapentin was examined in increasing the saturable oral absorption of gabapentin.[30] Among 5 synthesized conjugates, 2 monoanionic gabapentin conjugates, CDCA-alpha-benzyl-glu-gapapentin methyl ester (I)