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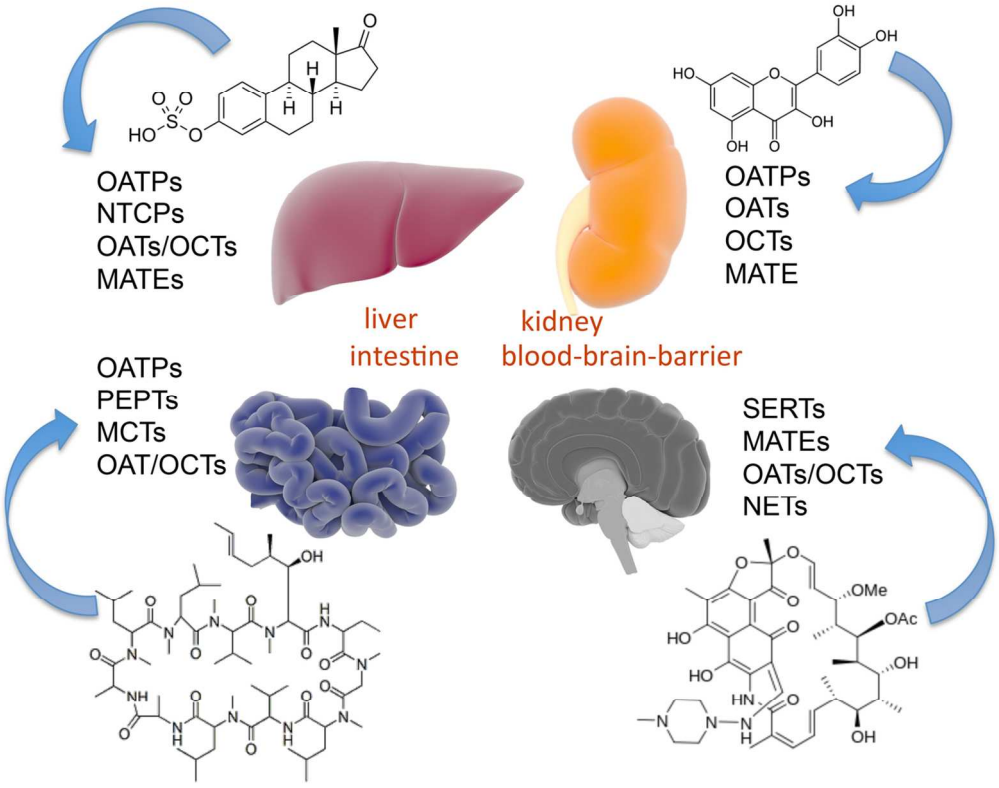

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Insights into Solute Carriers: Physiological Functions and Implications in Disease and Pharmacokinetics

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The importance of solute carrier (SLC) transporters in human physiology and disease has gained increasing attention in recent years. SLCs compose the largest family of transporters and there is growing evidence of their implication in health and in several pathologies, suggesting strong interest for these transporters as novel targets for drug discovery. Since SLCs transport a broad range of endogenous and exogenous compounds including drugs, they are the basis of important drug-drug interactions, causing potential drug toxicity or lack of efficacy. This review compiles recent knowledge on the natural occurrence of the main SCL families in human organs and tissues, highlighting their biological function and dysfunction in disease. Additionally, SLC implications in pharmacokinetics and drug-drug interactions are reviewed; concepts that can be useful in drug design.

1. Introduction

The field of transport biology has steadily grown over the past decade and is now recognized as playing an important role in the manifestation and treatment of disease. Solute carriers (SLCs) are membrane transport proteins crucial for the control of several physiological functions, including nutrient and xenobiotic uptake, organic and inorganic ion transport and waste removal [1]. In general, the SLC transporter family consists of proteins with a molecular mass in the range of 40-90 kD containing 300-800 amino acid residues [2] differentially expressed at apical or basolateral epithelial membranes of major organs, and whose coordinated function is essential to maintain homeostasis [3].

The SLC gene series comprises 52 families in humans with a total of 395 transporter genes [4]. A list of these genes can be found at the HUGO Gene Nomenclature Committee (HGNC) website (see www.genenames.org/genefamilies/SLC). Hedinger et al. in 2004 [5] published for the first time a revision of the different types of mammalian transport systems belonging to the SLC series and their role in physiology, pathology and therapeutics. As a result the scientific community became more aware of SLC transporter potential and increased research interest has been focused on the role of SLCs in health and disease.

The SLC gene series encodes passive transporters, ion-coupled transporters and exchangers [6]. A transporter is included in a specific SLC family if it shows at least 20–25% amino acid sequence identity to other members of the family. The nomenclature of these transporters usually begins with the symbol SLC followed by a number (e.g., SLC1, solute carrier family 1), then followed by a letter that corresponds to the subfamily (e.g., SLC1A) followed by a number that characterizes the specific transporter (e.g., SLC1A2) [7]. SLCO nomenclature is used to identify solute carrier organic anion transporter genes.

Until recently researchers mainly concentrated their efforts on the study of five SLC transporters, in particular SLC22A6 (also known as OAT1 or NKT), SLC22A8 (also known as OAT3 or ROCT), SLC22A2 (also known as OCT2), SLCO1B1 (also known as OATP1B1) and SLCO1B3 (also known as OATP1B3) due to their recognized impact in drug absorption, distribution, metabolism and excretion [8]. The potential importance of SLC transporters in drug pharmacokinetics has led Regulatory Authorities to require such information during the drug approval process [7]. Nevertheless, the majority of the SLC proteins are still not well characterized, nor have their physiological roles been completely elucidated. This review is a challenging task due to the extensive list of SLC members and their complexity, ranging from transporters that interact with a limited type of substrates in a very selective way, such as amino acid transporters in the SLC7 family, to members that transport a wide variety of chemical entities, as seen with the OATs. In the same family of transporters the degree of specificity can differ and there is overlap in substrate specificity among different SLC families [4]. Detailed knowledge

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of SLC function will be useful in medicine, genetics, biology and drug development [9].

In this review we focus on recent knowledge of the biological functions of the SCL transporter family in the organs and tissues where they are mainly expressed and their implication for several pathological conditions. Additionally, we further describe their role in pharmacokinetics and list the main compounds reported to inhibit their function that may hint to new approaches in drug design and the development of novel therapeutics.

2. SLCs – Biological functions and tissue distribution

The role of SLC transporters in human physiology is a growing area of research due to their recognized importance on body homeostasis [4]. SLCs transport amino acids and oligopeptides, glucose and other sugars, inorganic and organic cations and anions, bile salts, acetyl coenzyme A, essential metals, biogenic amines, neurotransmitters, vitamins, fatty acids and lipids, nucleosides, ammonium, choline, thyroid hormone and urea. Whereas transporters exist for all endogenous substrates, it is likely that exogenous compounds such as drugs, non-essential metals and many other environmental toxicants are able use several SLCs thereby enabling absorption or extrusion of these molecules from cells [9].

Membrane transporters are widely expressed throughout the body. Numerous SLC transporters have been identified in the intestine, liver, kidney [10] and blood brain barrier (BBB) [11]. Interestingly, while some research has been conducted focusing on the role of SLC transporters in the liver and kidney, less is known about their importance in the intestine, the main organ responsible for nutrient and drug uptake [12]. A list of the main mammalian SLC transporters is included in Table 1, ordered by organ, together with referenced drug substrates for each transporter.

Since SCL transporter activity can be used for beneficial or detrimental effects, detailed knowledge of their physiological functions, substrate specificity and mechanisms of action is essential.

2.1 SLCs in the liver

The liver is a major detoxification organ responsible for a number of functions such as: removing and excreting body wastes and hormones as well as drugs and other xenobiotics, synthesizing plasma proteins, producing immune factors, producing bile, excretion of bilirubin, storing vitamins, minerals and sugars, and processing nutrients absorbed from the digestive tract. In coordination with metabolizing enzymes, SLC transporters are important determinants of drug metabolism and drug clearance by the liver [13].

In the basolateral (sinusoidal) membrane of human hepatocytes, several members of the SLC family were identified including organic anion transporting polypeptides OATP1B1 (SLC21A6), OATP1B3 (SLC21A8) and OATP2B1 (SLC21A9), OATP1A2 (SLCO1A2), sodium taurocholate cotransporting polypeptide, NTCP (SLC10A1), organic anion transporter OAT2 (SLC22A7) and the organic cation transporter OCT1 (SLC22A1). OATP1B1 and OATP1B3 are transporters exclusively expressed on the hepatocyte [14-16].

These SLC transporters have a large range of endogenous substrates such as conjugated bilirubin, estradiol-17β-glucuronide, thyroxin, cholate, and taurocholate. In the liver, OATPs and NTCP uptake bile acids, thus helping to maintain a circulating pool of bile acids, an important factor for bile flow and the control of cholesterol levels. Furthermore, OATPs are responsible for the uptake of thyroid hormones [14]. The genes encoding for OATP1B1 and OATP1B3 are polymorphic; these transporters are involved in bilirubin clearance and the presence of polymorphisms is associated with hyperbilirubinaemia and jaundice [4]. Mutations on these transporter genes can lead to hyperbilirubinaemia associated with Rotor's syndrome [17]. MATE1 is also expressed in the liver [18].

2.2 SLCs in the kidney

The kidney represents an important route for the elimination of metabolic products and xenobiotics, as well as for the maintenance of essential compounds, regulating water volume and ionic equilibria in the body.

The proximal tubule of the kidney is involved with the handling of uremic toxins (e.g., indoxyl sulfate), environmental toxins (e.g., mercury, aristolochic acid), metabolites (e.g. uric acid), dietary compounds and signaling molecules. These processes rely on several multispecific transporters of the solute carrier superfamily, OAT and OCT subfamilies [19]. The sodium-potassium-chloride cotransporter NKCC2 (SLC12A1) is present in the ascending limb of the loop of Henle. This cotransporter is responsible for the reabsorption of sodium from the lumen filtrate; mutations of SLC12A1 are associated with Bartter's syndrome, causing hypercalciuria and blood volume reduction [20]. The renal distal tubule expresses TSC (SLC12A3), the sodium-chloride cotransporter and mutations in this transporter have been identified as causing an inherited disease, Gitelman's syndrome. This syndrome causes hypokalaemic alkalosis and electrolyte disorders [21]. OAT1 (SLC22A6), OAT3 (SLC22A8), sodium-phosphate cotransporter 1 (NTP1; SLC17A1), NPT4 (SLC17A3), UTB (SLC14A1) and UTA (SLC14A2) are all expressed in the kidney and have been demonstrated to facilitate urea secretion [4]. The sodium-glucose co-transporter 2, SGLT2 (*SLC5A2*) SGLT2 is the major cotransporter involved in glucose reabsorption in the kidney [22].

Recently new families of SLC transporters have been identified in the kidney, such as the multidrug and toxin extrusion transporters MATE1 (SLC47A1) and MATE2K (SLC47A2) and the organic anion transporter OATP4C1 (SLCO4C1) [23].

Studies of transporter polymorphisms raised the possibility that multiple SNPs of SLC transporters in basolateral (e.g., OAT1 and OAT3) and apical (e.g., URAT1, OAT4) membranes may alter the passage of drugs, toxins, and metabolites from blood to urine. These polymorphisms may be the basis of differences in drug response and toxicity [19].

2.3 SLCs in the intestine

In the intestine, various SLC members play an important role in nutrient and xenobiotic absorption. Glucose absorption is facilitated by two apical enterocyte transporters, SGLT2 (SLC5A2), a low affinity and high capacity transporter and SGLT1 (SLC5A1), a high affinity and low capacity transporter [24]. The apical sodium-dependent bile acid transporter (ASBT) is responsible for the reabsorption of bile acids from the lumen of the intestine; OATP2B1 transports organic anions and OCTN2 transports organic cations [25]. PEPT1, PEPT2, PHT1 (SLC15A family) transports small peptides; OAT and OCT (SLC22A family) transport organic anion and cation transporters, respectively; CNT and ENT (SLC28A and 29A family) as well as CNT1/2 (concentrative nucleoside transporters 1/2) transport nucleosides; PMAT (SLC29 family) transports monoamines and MCT (SLC16A family) transports monocarboxylic acids [12]. The serotonin transporter (SERT) was also identified in the intestine [25].

2.4 SLCs in the BBB

The blood brain barrier (BBB) controls the entrance and exit of substances between the blood and the central nervous system (CNS), effectively protecting the CNS against exogenous substances [26].

Several transporter proteins allow the movement of vital substances in and out of the brain, such as glucose, essential amino acids, and precursors for neurotransmitters. The BBB contains several SLC transporters such as the acidic sugar transporter AST (SLC7A5), OATP2B1 (SLC21A9), OCT3 (SLC22A3) and anion exchangers EDM4 (SLC26A1) and DTDST (SLC26A2), both transporting sulfates and charged inorganic molecules. Sulfates are used to synthesize sulfated proteoglycans in the brain that modulate neuronal function [11, 27]. THTRI (SLC19A3) is a thiamine (vitamin B3) transporter at the BBB. Mutations in this transporter are associated with biotin responsive basal ganglia disease [28]. MCT13 (*SLC6A13)* is a neurotransmitter transporter of physiological substrates that includes gamma-aminobutyric acid (GABA). GABA is the main inhibitory neurotransmitter in the mammalian central nervous system. Its principal function is to reduce neuronal excitability throughout the nervous system. In humans, GABA is also directly involved in the maintenance of muscle tone [29].

MATE2 (SLC47A2) is a multidrug and toxin extrusion transporter initially identified in the kidney and recently identified at the BBB [4]. It transports organic cations and may have a key role in the entrance of amines into the CNS. LAT1 (SLC3A2/ SLC7A5) is a L-type amino acid transporter 1 and RFC (SLC19A1) is a folate transporter [30].

Vesicular monoamine transporters (PACAP38) are involved in the transport of neurotransmitters into synaptic cells and acts as neuroprotectants, enzyme activity regulators and as activators of neural stem cells [31].

Members of the SLC family control the concentration of neurotransmitters such as glutamate and serotonin in synapses, thereby regulating downstream neurosignaling pathways that are activated or inhibited *via* membrane receptors [32]. Modulation of serotonergic signaling occurs, in part, by uptake of the transmitter by the serotonin transporter (SERT) [33].

3. SLCs in human disease

Many genes in the SLC superfamily are involved in inherited disorders and other human diseases (4, 7, 9). The abnormal function of SLCs due to mutations or genetic variants is implicated in diseases such as autism, diabetes, cancer, psychiatric disorders and neurodevelopmental disorders [34]. Human genetic studies have clarified the roles of more-recently identified SLC transporters in both rare and common diseases, suggesting a wealth of new therapeutic opportunities [4]. Mutations in SLC members can lead to differential drug response among individuals (pharmacogenetics). For instance, the intracellular concentrations of the antidiabetic drug metformin are affected by genetic variations in OCT1 [32].

Therefore several SLC transporters are being exploited as drug targets, including the glucose transporters (SLC5 family), neurotransmitter transporters (SLC6 family), intestinal bile acid transporters (SLC10 family) and cation-Cl-cotransporters (SLC12 family). The intestinal oligopeptide transporter PEPT1 (SLC15A1) and the various SLC transporters at the BBB have been investigated as promising drug delivery systems [7]. Several classes of marketed drugs target well-known SLC transporters, such as anticancer and antirheumatic agents, antivirals, statins and histamine H2 receptor antagonists [8]. SLCs are being used as drug targets for a wide range of diseases and disorders such as major depression [35], hypercholesterolemia [34], deficit and hyperactivity disorder ADHD and hypertension [34]. SLCs are especially important as targets in cancer treatment [36].

As a recent SLC drug modulator example, we mention sodium-glucose co-transporter 2 (SGLT2) inhibitors that represent a novel therapeutic approach in the management of type 2 diabetes mellitus; they act on the kidneys to decrease the renal threshold for glucose and increase urinary glucose excretion. Canagliflozin is an orally active, reversible, selective SGLT2 inhibitor [22].

The website Centerwatch.com "Drugs in Clinical Trials Database" allows access to drugs under clinical trials where one can find novel SLC drug targets currently under study.

3.1 SLCs in CNS disorders

The SLC6 family is the most exploited family for the treatment of CNS-disorders. The specific targeting of SLC6 family transporters have led to great improvements in the treatment of psychiatric disorders such as major depression, general anxiety disorders and obsessive compulsive disorder [35]. The most commonly utilized transporter is SERT (SLC6A4), the target for serotonin reuptake inhibitors (SSRIs), where polymorphisms in this transporter are implicated with interindividual variability of SSRI efficacy [37]. The synaptic vesicular glycoprotein2- family of proteins SV2A, SV2B and SV2C show a high degree of sequence homology to the SLC22 family and have been used as a drug target in the treatment of

epilepsy via drugs such as levetiracetam and racetam analogs [38]. Tiagabine is used as an anticonvulsant acting at the GABA transporter-1 [39].

The SLC18- family of vesicular monoamine transporters (VMAT) may be useful in the treatment of Parkinson disease via drugs directly targeting these transporters, such as reserpine [40]. Reserpine has also been suggested as a possible treatment of cocaine addition, although with contradictory results [34].

The norepinephrine transporter (NET/SLC6A2) regulates norepinephrine at the neuronal level to regulate downstream adrenergic pathways associated with behavior. Drugs like d-methylphenidate inhibit NET activity to increase adrenergic signaling in attention-deficit hyperactivity disorder (ADHD) [32].

3.2 SLCs in cardiovascular disease

SLC transporters have also been involved in the treatment of cardiovascular disease. The prototypic uricosuric agent, probenecid, prevents reabsorption of uric acid in the proximal tubule of the nephron by specifically inhibiting SLC22 family transporters in patients with hyperuricemia [39]. Probenecid decreases blood pressure in knockout compared to wild type mice and this effect is explained by altered clearance via OAT transport. OAT3 inhibitors, such as the experimental compound eosin-Y, have also been demonstrated to reduce blood pressure in mice [41].

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors, popularly known as statins, are currently used for the treatment of hypercholesterolemia and prevention of cardiovascular disease [42]. The pharmacokinetics of the great majority of members of this class are rate limited by uptake via OATP transporters from the blood to the hepatocyte, where they pharmacologically act [43].

3.3 SLCs in cancer

Augmented levels of nutrient transporter proteins are typical in aggressive and highly malignant tumors. As malignant cells are more dependent on accelerated nutrient import, these up-regulated transporters could be appropriate targets for selective anti-cancer therapies [36].

There has been increasing studies showing that OATPs may play an important role in the biology of various cancers. De novo expression of OATPs, like OATP1B1 and OATP1B3, normally exclusively expressed in liver, has been identified in a variety of cancers (breast, colon, pancreas, stomach, prostate, bone, and ovarian) [44].

Multiple factors (e.g. hormones, proinflammatory cytokines, drugs) can affect the distribution, expression and activity of OATPs, leading to an altered accumulation of OATP substrates and related food-drug and drug-drug interactions. Changes in the distribution and expression of OATPs in malignant tissues may be related to the pathological process of cancer, while the modulation epigenetic mechanism also contribute to their distribution patterns [45, 46]. Recent reports demonstrate that some OATPs are up- or down regulated in several cancers and that OATP expression might affect cancer development. On the basis of the findings summarized in this review, we propose that OATPs could be valuable targets for anticancer therapy [47].

Three families carry out the transport of nucleosides and nucleotides: SLC28, with three members, functions in Na-coupled nucleoside transport and thus is a potentially important pharmacological target; SLC29, with four members, mediates (along with the SLC28 transporters) uptake of natural nucleosides (among them adenosine) — these members are major routes of entry for a variety of nucleoside analogues used in anticancer therapies [9, 48].

The glucose family of transporters, namely GLUT1-5 and SGLT1-3 are also being tested as potential drug targets, namely with the drug glufosfamide in clinical trials for pancreatic cancer [49].

Inhibitory molecules for the L-type amino acid transporter 1 (LAT1) have been demonstrated to diminish tumor progression in several cancer types [50].

4. SLC drug modulators and their impact in pharmacokinetics

Members of several SLC and SLCO families, such as the SLC21 family (organic anion transporters), SLC22 (organic cation/anion/zwitterion transporters), and SLC47 (multidrug and toxin extrusion transporters), are highly abundant in the intestine, liver and kidney, major organs that regulate drug absorption, distribution, metabolism, and elimination (ADME). As many available drugs are substrates or inhibitors (Table 1; Figure 1) for these transporters, it is therefore expected that many types of DDIs may occur, leading to increased or decreased drug serum levels. DDI can cause profound clinical effects, either by reducing or enhancing toxicity or therapeutic efficacy of drugs. In Figure 1, the structures of estrone-3-sulphate, quercetin, cyclosporine and rifampicin, representative inhibitors of SLC activity, are depicted.

In this section we briefly describe DDIs in the intestine, liver and kidney. As SLCs are expressed in several, DDIs can affect more than one target. For example, the organic ion transporter 1 (OCT1/SLC22A1) transports anti-cancer and anti-viral drugs into the liver and kidney and may, therefore, mediate drug-drug interactions [32].

4.1 SLC drug modulation in the intestine

Orally administered drugs must pass through the gut wall mucosa before reaching the capillaries that lead to the portal vein. Major uptake transporters responsible for xenobiotic transport in the intestine include the SLC superfamily. Additionaly, many dietary and herbal products in the intestine such as grapefruit, orange and apple juices and green tea can also interact with SLCs [12].

There are several described DDI interactions due to OAPT in the intestine. In a clinical trial, aliskiren suffered a 61% reduction in area under the curve, (AUC) and 81% reduction in

maximum concentration (Cmax) when administered together with grapefruit juice, an OATP inhibitor [51]. In another clinical study fexofenadine also suffered a 63% reduction in AUC when administered together with grapefruit juice [52]. Sirolimus and everolimus (OATP inhibitors) reduced estrone-3 sulphate uptake in human transfected cells [53].

4.2 SLC drug modulation in the liver

Because liver clears most drugs and other xenobiotics, it determines the efficacy and toxicity associated with drug exposure. During the last decades, drug-induced liver injury has been the most frequent cause of safety-related drug marketing withdrawals in the US [54]. Dronedarone, fosinopril, lapatinib, rapamycin, and zafirlukast are examples of drugs causing hyperbilirubinemia, and to some extent liver hepatotoxicity [55].

Several drugs may inhibit liver OATP transporters, (e.g. cyclosporine) causing pharmacokinetic drug–drug interactions. Additionally, genetic variability in genes encoding OATP transporters can led to significant inter-individual discrepancies in pharmacokinetics. For example, a single nucleotide polymorphism (c.T521C, p.Val174Ala) in the *SLCO1B1* gene encoding OATP1B1 decreases the ability of OATP1B1 to transport simvastatin from the portal circulation into the liver, resulting in significantly increased plasma concentrations of simvastatin acid and an enhanced risk of simvastatin-induced myopathy. *SLCO1B1* polymorphism also affects the pharmacokinetics of many other, but not all (fluvastatin), statins and that of the antidiabetic drug repaglinide, the antihistamine fexofenadine and the endothelin A receptor antagonist atrasentan [39, 56].

Probenecid and verapamil-inhibitable accumulation of the OATP substrate E3S and of the OCT1 substrate TEA were clearly detected in cultured human hepatocytes [15].

4.3 SLC drug modulation in the kidney

The tubular secretion of drugs is facilitated by members of the SLC transporter family, which both import and export substrates depending on concentration gradients. Molecular mechanisms of renal injury have been intensively studied and elucidated in recent years [57]. Drug-induced nephrotoxicity is responsible for about 20% of hospital admissions due to acute renal failure. The susceptibility of drug-induced renal injury varies depending on drug class and is associated with several risk factors, including age (e.g., children, elderly), female sex, pre-existing renal impairment, underlying disease or concomitant medications [58].

The tyrosine kinase inhibitor (TKI) imatinib has been identified as a potent, noncompetitive inhibitor of OCT2, and its use appears to protect patients from cisplatin-induced nephrotoxicity by preventing platinum accumulation into the kidney [59].

Both diclofenac and its major metabolite acyl-β-D-glucuronide are eliminated in urine and were studied as substrates of different human drug transporters in vitro. Diclofenac and its metabolite were identified as substrates of OATs [60], and is an example where drug substrates and metabolites can competitively use the same transporters. Interruption of transporter functions could lead to DDIs resulting in the increase of plasma exposure of the substrate and the metabolite.

Imatinib, nilotinib, gefitinib and erlotinib inhibit MATE1 and MATE2 mediated metformin transport, suggesting that this transporter-mediated DDI with TKIs may affect the disposition, efficacy and toxicity of metformin and possibly of other drugs that are substrates for these export proteins [18].

5. Conclusions and future perspectives

An International Transporter Consortium (ITC), consisting of industrial, regulatory, and academic scientists with expertise in drug metabolism, transport, and pharmacokinetics, was formed in 2007 to further explore the role of drug transporters in pharmacotherapy and adverse drug reactions. The first ITC report provided an overview of principal transporters involved in drug pharmacokinetics, examples of various technologies responsible for transporter-related DDIs, and criteria for the development of clinical studies of transporter DDIs [61]. Since then much research has been done targeting membrane transporters, and more recently a major focus has been directed to the less studied SLC transporter family, as increasing knowledge shows SLC transporters to be involved in adverse drug reactions and disease states. A better understanding of SLC metabolic pathways, physiological role and morphogenesis is crucial for the development of this promising field [8]. Although a high number of genes encode for solute carriers, only 12 SLCs are being used as therapeutic agents [39]. Regulatory Authorities have issued recent DDI guidances where an increased emphasis has been given to transporter based DDI evaluations [62, 63].

The potential rational design for drugs targeting SLC is multifarious. SLCs can be used as drug delivery systems as they represent significant entrance pathways in several cells/organs. For example, the majority of beta-lactam antibiotic drugs demonstrate PEPT carrier mediated transport characteristics. Understanding the nature of PEPT1 and the structural requirements of drug transport by PEPT1 led to a strategic development of prodrugs [12]. The same applies to the delivery of antineoplasic agents in cancer [64].

Another approach would be to develop SLC specific inhibitors like the TKI imatinib, a noncompetitive inhibitor of OCT2, which protects patients from cisplatin-induced nephrotoxicity by preventing platinum accumulation in the kidney [59]. Conscious drug design towards SLCs seems a promising avenue that would bring significant advances in the treatment of several pathologies including cardiovascular disorders, CNS diseases and cancer.

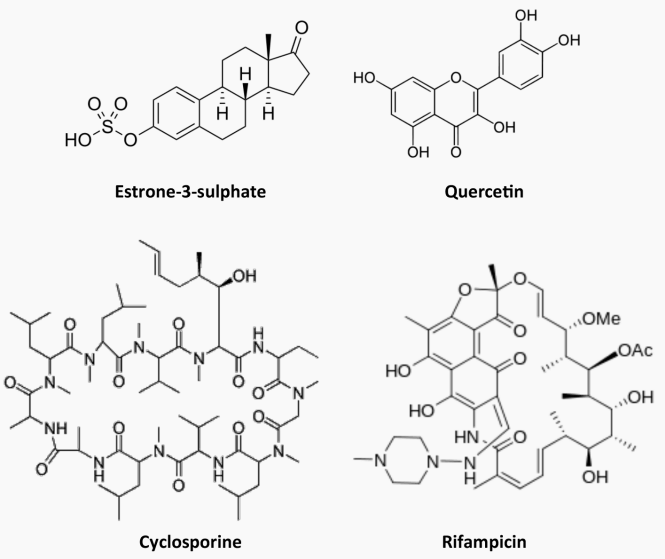

Fig. 1 – Chemical structure of well-known SLC-inhibitors.

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Table 1 – SLCs distribution by organ and reported drug substrates and inhibitors.

Organ	SLC	Substrates	Inhibitor
Liver	OATP1B1	acyl-β-D-glucuronide diclofenac [60] asunaprevir [66] atorvastatin [67, 68] atrasentan [69] benzylpenicilin [70] berberine [71] bosetan [72] caspofungin [73] cerivastatin [74] clopidogrel [75] docetaxel [76] enalapril [77] eprosartan [79] fexofenadine [81] fluvastatin [83, 84] glibenclamide [85, 86] lopinavir [85] methotrexate [88] nateglinide [85] olmersartan [90] paclitaxel [44] pitavastatin [54] pitavastatin [89] pravastatin [92] repaglinide [85] rifampicin [66, 93] rosuvastatin [88] rosuvastatin [89, 94] simeprevir [85] torasemide [85] valsartan [95]	carfilzomib [65] dronedarone hydrochloride [65] flavin adenine dinucleotide [65] fosinopril sodium [65] gliquidone [65] lapatinibe [65] N-O didansylL-tyrosine [65] rapamycin [65] sirolimus [65] zafirlukast [65] trametinib [65] flavonoids (quercetin and kaempferol) [78] estrone-3-sulphate [80] budenoside [82] rifampicin [82] cyclosporine [82] clarithromycin [87] glibenclamide [86] rifampicin [89] gemfibrozil [84] telithromycin [91] roxithromycin [91] erythromycin [91]
	OATP1B3	asunaprevir [66] atorvastatin [43, 68] atrasentan [85] bosetan [96] dioscin [97] docetaxel [76] enalapril [98] erythromycin [99] fexofenadine [100] fluvastatin [84] glibenclamide [85, 86] imatinib [101] methotrexate [44] nateglinide [85] olmesartan [102] paclitaxel [44] pitavastatin [89]	carfilzomib [65] clarithromycin [87] cyclosporine [82] dronedarone hydrochloride [65] estrone-3-sulphate [80] flavin adenine dinucleotide [65] flavonoids (quercetin and kaempferol) fosinopril sodium [65] gemfibrozil [84] glibenclamide [86] gliquidone [65] lapatinibe [65] N-O didansylL-tyrosine [65] rapamycin [65] rifampicin [82] rifampicin [89] sirolimus [65]

		pravastatin [103] repaglinide [85] rifampicin [66] rosuvastatin [89, 94] simeprevir [85] telmisartan [104] torasemide [85] valsartan [85]	trametinib [65] zafirlukast [65]
	OATP2B1	acyl-β-D-glucuronide diclofenac [60] asunaprevir [66] atorvastatin [43, 68] benzylpenicillin [70] fexofenadine [106] fluvastatin [84] glibenclamide [86] montelukast [107] pitavastatin [108] pravastatin [109] rifampicin [66] rosuvastatin [94]	asunaprevir [105] budenoside [82] cyclosporin [78, 82] daclatasavir [105] estrone-3-sulphate [80] flavonoids (quercetin and kaempferol) [78] gemfibrozil [84] glibenclamide [86] naringin [78] quinidine [78] rifampicin [82] simeprevir [105] sofosbuvir [105]
	OATP1A2	aliskiren [110] atenolol [52] celiprolol [52] ciprofloxacin [52] docetaxel [76] erythromycin [99] fexofenadine [52, 113] imatinib [113, 114] methotrexate [113] pitavastatin [115] rosuvastatin [116] saquinavir [117] talinolol [52]	azithromycin [111] clarithromycin [111] cyclosporin [78] estrone-3-sulphate [80] flavonoids (quercetin and kaempferol) [78] nariginin [112] quinidine [78]
	NTCP	atorvastatin [43] rosuvastatin [91]	cyclosporine [118] diclofenac [118] estrone-3-sulphate [80] flavonoids (quercetin and kaempferol) [78] lumiracoxib [118] myrcludex B [118] sodium taurocholate [118]
	OAT2	erythromycin [119]	cimetidine [120]

		methotrexate [119]	
	OAT7	pravastatin [121]	
	OCT1	debrisoquine [122] metformin [43] monocrotaline [122] O-desmethyltramadol [122] tropiset [122]	camptothecin [123] verapamil [112]
	MATE		cephalexin [120] cetirizine [124] cimetidine [120] cobicistat [120] indinavir [124] ritonavir [124] thrimethropin [120]
Kidney	OAT1	acyl-β-D-glucuronide diclofenac [60] olmesartan [102]	
	OAT3	acyl-β-D-glucuronide diclofenac [60] adefovir [126] benzylpenicillin [126]	diclofenac [125] mulberrin [125] quercetin [125] telmisartan [125]
	OAT4	acyl-β-D-glucuronide diclofenac [60] diuretics [127]	
	OCT1	amisulpride [128] metformin [43] sulpiride [128]	cyclosporine [78] naringin [78] quinidine [78]
	OCT2	amisulpride [128] metformin [43] sulpiride [128]	dolutegravir [120] flavonoids (quercetin and kaempferol) [78]
	OCT3	metformin [43]	cimetidine [120]
	MATE	acyclovir [124] captopril [124] cisplatin [124] metformin [43] quinine [124]	cephalexin [124] cetirizine [124] cimetidine [120] cobicistat [120] indinavir [120] ritonavir [124] thrimethropin [120]
	SGLT2	canagliflozin [22] phlorizin [130]	phlorizin [129]
	NPT		nonsteroidal anti-inflammatory drugs [131] pravastatin [131]

	OATP1A2	aliskiren [110] atenolol [52] celiprolol [52] ciprofloxacin [52] docetaxel [76] erythromycin [99] fexofenadine [52, 113] imatinib [113, 114] methotrexate [113] pitavastatin [115] rosuvastatin [116] saquinavir [117] talinolol [52]	
Intestine	OATP 2B1	acyl-β-D-glucuronide diclofenac [60] asunaprevir [66] atorvastatin [43, 68] benzylpenicillin [70] fexofenadine [106] fluvastatin [84] glibenclamide [86] montelukast [108] pitavastatin [115] pravastatin [109] rifampicin [66] rosuvastatin [94]	budenoside [82] cyclosporine [82] estrone-3-sulphate [80] rifampicin [82]
	PEPT1	amoxicillin [132] glycylsarcosine [132] valacyclovir [133] valganciclovir [133]	Gly-Sar [12] JBP485 [12] lisinopril [12]
	PEPT2	angiotensin-converting enzyme inhibitors [134] β-lactam antibiotics [134]	glycylsarcosine [135]
	OAT	acyl-β-D-glucuronide diclofenac [60] olmesartan [102]	diclofenac [125] mulberrin [125] quercetin [125] telmisartan [125]
	OATP1A2		azithromycin [111] clarithromycin [111] cyclosporine [78] estrone-3-sulphate [80] flavonoids (quercetin and kaempferol) [78] naringin [78] quinidine [78]
	OCT	acyclovir [12] memantine [12] metformin [12]	cyclosporin [125] naringin [125] quinidine [125]

		ranitidine [12] tetraethylammonium [12] zalcitabine [12]	
	CNT	2′,3′-dideoxyinosine [136] 5-fluoro-2′-deoxyuridine [136] 5-fluorouridine [137] 5-fluorouridine [136] arabinosylcytosine [136] cladribine [136] diethyldithiocarbamate [136] fludarabine [136] gemcitabine [137] gemcitabine [136] melarsoprol [136] pentamidine [136] ribavirin [137] zalcitabine [136] zebularine [136]	
	PMAT	dilazep [138] tetraethylammonium [139]	cimetidine [12] decynium-22 [12] desipramine [12] fluoxetine [12] GBR12935 [12] quinidine [12] quinine [12] rhodamine123 [12] verapamil [12]
	MCT	benzoic acid [12] β-hydroxybutyrate [12] carbenicillin indanyl sodium [12] foscarnet [12] mevolonic acid [12] p-aminohippuric acid [12] phenethicillin [12] propicillin [12] salicylic acid [12]	statins [80]
	OCTN2	imatimib [101]	
BBB	OATP2B1	acyl-β-D-glucuronide diclofenac [60] asunaprevir [66] atorvastatin [43, 68] benzylpenicillin [70] fexofenadine [106] fluvastatin [84] glibenclamide [86] montelukast [108] pitavastatin [115] pravastatin [109] rifampicin [66] rosuvastatin [94]	estrone-3-sulphate [121]

	OAT		probenecid [140]
	OCT1		cyclosporin [78] naringin [78] quinidine [78]
	OCT3	metformin [43]	
		fenfluramine [116] 3,4-methylenedioxymethamphetamine [142]	citalopram [141] desipramine [141] fluoxetine [141]
	MATE	acyclovir [124] captopril [124] cisplatin [124] metformin [43] quinine [124]	cephalexin [124] cetirizine [124] cimetidine [120] cobicistat [120] indinavir [124] ritonavir [120] thrimethropin [120]
	NET	tricyclic antidepressants [117] selective serotonine reuptake inhibitors [143]	citalopram [141] desipramine [141] fluoxetine [141]
	PEPT1		Gly-Sar [12] JBP485 [12] lisinopril [12]
	LAT1	boronophenylalanine [144]	